CholGate

Computerized Clinical Decision Support for Primary and Secondary Prevention of Cardiovascular Disease
The work in this thesis was conducted at the Department of Medical Informatics, ErasmusMC University Medical Centre Rotterdam, The Netherlands.

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CholGate - Computerized clinical decision support for primary and secondary prevention of cardiovascular disease
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CholGate

Computerized clinical decision support for primary and secondary prevention of cardiovascular disease

CholGate
Computerondersteunde besluitvorming op het gebied van primaire en secundaire preventie van hartvaatziekten

Proefschrift

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
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Table of Contents

1 Introduction ................................................................................................................................. 7

2 Cross sectional analysis of guidelines on cardiovascular disease risk factors: going to meet the inconsistencies ............................................................................................................. 15

3 Identification of the four “conventional” cardiovascular disease risk factors by Dutch General Practitioners .................................................................................................................. 29

4 Management of hypertension and hypercholesterolaemia in primary care in the Netherlands ................................................................................................................................. 47

5 Differences between statins on clinical endpoints. A population based cohort study ................................................................................................................................. 69

6 CholGate – An integrated clinical decision support system for primary and secondary prevention in cardiovascular disease ........................................................................................................ 87

7 CholGate, the effect of alerting versus on-demand computer based decision support on treatment of dyslipidaemia by general practitioners - A randomized trial ................................................................................................................... 101

8 General Discussion .................................................................................................................. 119

Summary ....................................................................................................................................... 129

Samevatting ................................................................................................................................... 137

Acknowledgements ...................................................................................................................... 145

CV ................................................................................................................................................ 149
Introduction

Evidence based medicine

The practice of modern medicine should be based on evidence. Yearly researchers deliver new publications that increase insight in current medicine and often urge to a substantial change in medical practice. The rate at which researchers provide new insights and evidence into medicine is staggering. During the year 2004 alone, 54 576 new articles have been published just in the domain of cardiovascular disease (CVD)\(^1\). Although systematic reviews provide evidence to help physician making decisions about health care\(^2\), staying up to date with all the new evidence is hardly feasible for a busy physician, resulting in delays in implementing new knowledge into practice. This knowledge gap might lead to suboptimal care and unnecessary health care expenditure\(^3\)\(^4\). To assist practitioners in keeping up to date and dealing with specific clinical conditions, various organisations develop guidelines. Guidelines condense the available evidence and translate that evidence to concrete recommendations for action – these guidelines could provide needed support to implement best practice according to the latest evidence\(^6\)\(^7\).

The Dutch College of General Practitioners’ guidelines

Guidelines are defined as “systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances”\(^8\). In the Netherlands, the Dutch College of General Practitioners (DCGP) develops evidence based guidelines to assist general practitioners in dealing with specific clinical conditions in a primary care setting, including recommendations for CVD risk factor management. A number of studies have shown that the availability of guidelines does not necessarily lead to the use of these guidelines by physicians. Even when authoritative guidelines are available, changing the behaviour of physicians has proved to be difficult\(^6\)\(^7\). For example, adherence to the DCGP cholesterol guideline in primary practice is low, mainly due to the complexity of the guideline and interruption of the workflow process of the general practitioner\(^9\). These issues are by no means limited to only cholesterol guidelines; other investigators also report that barriers to
implement guidelines into practice include complexity of the guideline algorithms, difficulties in changing practice routines, the amount of time needed to and difficulty in remembering preventive tasks\textsuperscript{10-12}. Various authors have shown that integrating a clinical decision support system into the electronic health record of a physician is an effective strategy to introduce guidelines into daily practice\textsuperscript{13, 14}.

**Clinical decision support systems**

Clinical decision support systems (CDSSs) are information systems that aim to optimize physicians' clinical decision making. Several studies have shown that CDSS can facilitate change in physician behaviour\textsuperscript{15, 16}. Guidelines frequently simplify complicated algorithms; a complex risk function, for example, is reduced to a graphical table that can readily be understood and used by the reader. Simplifying complex algorithms into graphical tables, however, might lead to a limited performance of the underlying data calculation models. CDSS obviate the need for this simplification as these systems can easily calculate the complex algorithms. Therefore, where previously users were required to make interpolations for complex treatment decisions, CDSS can now assist users in coming to evidence based decisions. To get to the point of effective CDSS, however, is not as simple as constructing an algorithm.

As the complexity of a CDSS increases so, does the need for relevant patient data that the system uses to guide practice. This data must have meaning for the system. For example, the letters “CHOL” recorded in a system might clearly mean Cholesterol to a human user. To a computer, however, “CHOL” means nothing until some form of structure and meaning has been given to these letters. This is achieved by structuring and coding of data. Coded data relies on widely used coding schemes to record data. In The Netherlands general practitioners generally use the International Classification for Primary Care (ICPC) for coding diagnoses and the Anatomical Therapeutical Classification (ATC)\textsuperscript{17} for coding medication. Structuring data is achieved by organizing data in a way that it allows an automatic interpretation. For example using the letters “CHOL” in the previous example means nothing until the system can translate it into a meaning: i.e. “CHOL” means cholesterol. A system that is integrated with an electronic patient record, therefore, is highly dependant on the structure and quality of data that is
captured by a user.

**General practice and the state of CDSS in the Netherlands**

General practitioners (GPs) function as gatekeepers in the Dutch healthcare system. Most patients will first visit a GP with a health-related problem. In addition, more than 95% of GPs in the Netherlands have adopted an electronic health record into daily care entering patient data during patient encounters\(^{18,19}\). This leads to opportunities to study various CDSS in primary care. Various success factors for the implementation of a CDSS into daily practice have been described. These factors include providing support as part of the clinician’s workflow, providing decisions at the point of care, providing recommendations rather than just assessments, and providing computerized decision support\(^ {16,20}\).

Apart from taking into account success factors, the designer of a CDSS has the choice between different methods of introducing CDSS in daily practice. Two methods of introducing CDSS in daily practice have been studied: on-demand mode and alerting mode. Using the first method, the on-demand mode (also referred to as order entry mode), the user decides when decision support is needed and then activates the CDSS. In a randomized trial Van Wijk et al., using the on-demand method, assessed the impact on the volume of test ordering, of the decision support system BloodLink, on the volume of test ordering, and determined the compliance of Dutch general practitioners to the recommendations for test ordering as defined in the guidelines of the Dutch College of General Practitioners\(^ {14}\). Through the effect of BloodLink on the test ordering behaviour of the GPs the authors demonstrated the effective introduction of guidelines into daily practice using an on-demand CDSS: a physician had to activate the decision support system to get specific support during a relevant patient encounter. This method, therefore, implicitly requires the physician’s awareness of the need for specific support in a specific clinical situation. For example if a patient presents with minor respiratory complaints and simultaneously is known with various cardiovascular risk factors the physician needs to be aware of the encounter’s different aspects. Firstly the patient requires treatment for his or her respiratory complaints. Secondly, the patient’s visit provides an opportunity for possible primary prevention given the patient’s cardiovascular risk factors.
In a second method of implementing CDSS, the so called alerting or critiquing mode, the user is alerted when advice is available on a patient. The Asthmacritic study used alerting and critiquing, to implement guidelines into primary care\textsuperscript{21}. In this study a CDSS was integrated into the EHR, providing a physician with comments on a patient’s status according to the DGCP guidelines’ recommendations on asthma and chronic obstructive pulmonary disease. Providing alerts, however, demands a tight integration with the host EHR - the systems can alert a physician that an extra action needs to be taken during a patient encounter only if sufficient data are available. For example, taking the previously mentioned example of the patient with respiratory complaints with cardiovascular risk factors; the CDSS based on data available in the electronic record alert the physician that prevention is necessary.

Both methods of providing decision support have advantages and disadvantages. On-demand or Order entry systems, can be argued, are less obtrusive, less complicated due the lower integration level into the EHR, and only provide support when activated. However, these systems can lead to lost opportunities for care. The main advantage of alerting systems is the ability to make users aware of the need for actions. However, the tight integration into the EHR and possible inopportune alerting places extra demands on developers.

Although it is known that both systems are effective in providing decision support in various settings\textsuperscript{16}, no direct comparison of the two methods has been made. We constructed CholGate, a CDSS to aid in the management of primary and secondary prevention of CVD to study these different strategies.

**Outline of thesis**

To compare the methods of providing decision support we needed a domain where there would be frequent difficult decision making. It is known that cardiovascular disease (CVD) is the leading cause of mortality in industrialized countries\textsuperscript{22}. Coronary heart disease and stroke are the principle components of CVD. Risk factors for developing CVD include smoking, male gender, diabetes mellitus, hypertension, haemostatic factors, family history of CVD, age, and abnormal blood lipids\textsuperscript{23}. Evidence exists that managing CVD risk factors in primary care plays an important role in decreasing the morbidity and mortality due to cardiovascular disease\textsuperscript{24-26}. 
Additionally, drug treatment for elevated cholesterol among patients with an increased risk for cardiovascular disease leads to a decreased morbidity and mortality. The management of CVD risk factors is generally referred to as primary and secondary prevention of CVD. Primary prevention aims to lower the incidence of the event, in other words, prevent the occurrence of CVD. Secondary prevention aims at reducing more and severe occurrences of CVD after the onset of initial CVD. The general practitioner is in a large part responsible for effective primary and secondary prevention of CVD. However, the treatment decisions in the current DCGP guidelines on primary and secondary prevention are complex, and spread over different guidelines. This thesis lists the research that was performed in order to compare the two methodologies of providing decision support.

In Chapter 2 we address the question: “Do the practice guidelines of the Dutch College of General Practitioners allow the identification of clear and unambiguous recommendations with respect to the management of CVD risk factors in primary care?”

In Chapter 3 we focus on: “To what extent do general practitioners monitor the four conventional risk factors, and the associated measurements for cardiovascular risk factors in relation to the time of first clinical presence of CVD?”

In Chapter 4 we ask ourselves: “To what extent do Dutch general practitioners adhere to the recommendations for treatment and monitoring hypertension and hypercholesterolemia as defined in the guidelines of the Dutch College of General Practitioners?”

Evidence-based medicine requires that guidelines be revised in the light of the available randomized clinical trials. New trials that first appear in medical journals are read by physicians, and may subsequently result in revision of guidelines. Adoption of recent knowledge into daily practice could therefore precede dissemination of revised guidelines. In Chapter 5, we analyze statin prescription by Dutch GP’s and compare the risk of cardiovascular and cerebrovascular
events between atorvastatin users and other statin users in daily general practice.

In Chapter 6 we describe the system design of CholGate, a system to improve both primary and secondary prevention of CVD. Taking advantage of the use of electronic health records (EHR) by Dutch general practitioners, CholGate is integrated within the EHR to provide decision support in the clinician’s workflow. Firstly, we discuss the underlying knowledge base of the system. Secondly, we highlight issues in gathering relevant patient data to identify patients at risk. Thirdly, we discuss the system’s user interface and workflow impact, and, finally, we focus on special considerations in implementing the system.

In Chapter 7 we address the following question by means of a randomized controlled trail: “Does providing alerts give better result in primary care than on-demand decision support?”
References


Cross sectional analysis of guidelines on cardiovascular disease risk factors: going to meet the inconsistencies

Jacobus T van Wyk, Marc A M van Wijk, Peter W Moorman, Johan van der Lei

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Medical Decision Making. 2006 Jan-Feb;26(1):57-62
Abstract

**Objective:** To identify the possible inconsistency of statements among the practice guidelines of the Dutch College of General Practitioners (DCGP) with respect to the management of risk factors for cardiovascular disease (CVD).

**Methods:** Cross sectional analysis of all electronically available DCGP practice guidelines dealing with CVD risk factor management for statement inconsistencies and reference inconsistencies.

**Results:** Six DCGP out of 74 electronically available guidelines had either CVD or CVD risk factors as subject of the guideline. Eight statement inconsistencies were found and for each statement inconsistency a reference inconsistency was present.

**Conclusions:** Given that inconsistencies were found, we recommend that organizations that maintain a set of guidelines update the guidelines using a cross sectional analysis of guidelines. Inconsistencies between guidelines might lead to physicians being unintentionally non-compliant with guideline recommendations.
Introduction

Cardiovascular disease (CVD) is the leading cause of mortality in industrialized countries. Risk factors for developing CVD include smoking, male gender, diabetes mellitus, hypertension, haemostatic factors, family history of CVD, age, and abnormal blood lipids. Evidence exists that managing CVD risk factors in primary care plays an important role in decreasing the morbidity and mortality due to cardiovascular disease. However, getting evidence into practice is one of the major challenges of modern medicine. To deal with the rapidly expanding amount of medical knowledge, guidelines are viewed increasingly as a mechanism for distributing knowledge to practitioners. Guidelines are defined as “systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances.” In the Netherlands, the Dutch College of General Practitioners (DCGP) develops evidence based guidelines to assist general practitioners in dealing with specific clinical conditions in a primary care setting, including recommendations for CVD risk factor management. All guidelines are published both in “Huisarts en Wetenschap”, the scientific journal of the DCGP, and on the internet.

A number of studies have shown that the availability of guidelines does not necessarily lead to the use of these guidelines by physicians. Even when authoritative guidelines are available, changing the behaviour of physicians has proved to be difficult. For example, adherence to the DCGP cholesterol guideline in primary practice is low, mainly due to the complexity of the guideline and interruption of the workflow process of the general practitioner. Several studies using different strategies of guideline implementation have shown varying degrees of success. A number of studies showed an effective strategy for guideline implementation is integrating guideline based decision support systems (DSS) into the electronic medical record (EMR). The objective of the systems is to help the physicians in making guideline based healthcare decisions at the point of care.

In order to implement a guideline in a DSS, developers need to formalize the statements of the guideline. However, with respect to the management of chronic diseases, more than one guideline can be applicable. In addition patients may have more than one disease. If a
statement in one guideline is inconsistent with a statement in another guideline the developer is confronted with ambiguous recommendations. It means that the developer will not be able to formalize the guidelines appropriately. Therefore, to determine whether guidelines provide a consistent base for the development of a DSS, developers have to perform a careful analysis on consistency of guidelines.\footnote{17}

The objective of this study is to identify the possible inconsistency of statements among the practice guidelines of the DCGP with respect to the management of CVD risk factors. We want to determine whether these guidelines provide a consistent base for the development of a decision support system for the management of CVD risk factors.

**Methods**

We define *statements* as actions suggested in guidelines to be performed by the physician in the clinical management process.

To identify possible inconsistencies among guidelines with respect to the management of CVD, we analyzed all clinical practice guidelines of the DCGP available on 1 September 2002.\footnote{7} Guidelines with CVD or diabetes mellitus, blood lipids, hypertension, smoking, and haemostatic factors as the subject of the guideline were selected for analysis.

All guidelines adhered to a common structure. This structure consisted of 3 sections with subsections: Introduction and background, diagnosis and evaluation, and treatment. Apart from the first section "Introduction and Background", the guideline sections corresponded to the subjective, objective, assessment, and plan (SOAP) methodology for problem orientated patient recording.\footnote{18,19} The second section, "Diagnosis and evaluation", included screening and history taking, physical examination, special investigations, and evaluation which corresponded to the subjective, objective, and assessment components of the SOAP methodology. The third section, "Treatment", corresponded to the plan component of the SOAP methodology (Figure 1).

To identify inconsistencies among the selected guidelines we compared statements that contained similar actions. To avoid mismatching of statements among the guidelines, we veri-
fied that *statements* were comparable with respect to the distinctive components of the clinical management process. For example, a screening test in one guideline cannot be compared to a therapy effectiveness test in another guideline. That is, we identified whether *statements* applied to the same clinical scenario in dealing with a patient in order to avoid mismatching statements with different clinical endpoints. A *statement inconsistency* refers to the situation in which a statement in one guideline recommends a certain action in a specific scenario, whereas the comparable statement in another guideline does not recommend the same action for that scenario or recommend a different action to the same scenario. To gain insight into whether guideline authors compared statements in related guidelines, we determined for each statement inconsistency whether cross references were present between the guidelines.

**Results**

The DCGP published 74 guidelines up to 1 September 2002. Six guidelines of the 74 electronically available guidelines satisfied the selection criteria of CVD or diabetes mellitus, blood lipids, and hypertension as subject of the guideline. The angina pectoris\[^{20}\], peripheral arterial disease\[^{21}\], and transient ischaemic attack (TIA)\[^{22}\] guidelines satisfied the selection criterion of CVD as subject of the guideline. For blood lipids, diabetes mellitus and hypertension\[^{23-25}\] separate guidelines existed. No guidelines dealt with smoking, age or haemostatic factors as subject of the guideline.

In the six identified guidelines, we found a total of eight statement inconsistencies: two in the subjective component, two in the objective component and four in the plan component. The diabetes mellitus and cholesterol guidelines showed the highest number of statement inconsistencies. For each of the statement inconsistencies, a reference inconsistency was present. Table 1 shows all statement inconsistencies.

**Discussion**

The objective of this study was to identify the possible inconsistency of statements among the practice guidelines of the DCGP with respect to the management of CVD risk factors. We
wanted to determine whether these guidelines provide a consistent base for the development of a decision support system for the management of cardiovascular disease risk factors.

Most statements in the selected guidelines were consistent. However, we identified eight statement inconsistencies. Formalization of guidelines requires consistency of guideline statements. When viewing the guidelines as an integral part of the overall risk management of CVD the significance of inconsistencies becomes apparent. For example, in our analysis we found that the cholesterol guideline stated explicitly that triglyceride testing should not be done, even in the case of patients suffering from diabetes mellitus. However, the diabetes mellitus guideline states that a diabetic should have a triglyceride value determined yearly. Guidelines are defined as “systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances”. Our focus was to find directly contradictory statements that would be irreconcilable in implementing a DSS. The clinical relevance of the contradictions remains open for debate. For example, one guideline (diabetes) recommends treating diabetic patients with cholesterol abnormalities with statins, and only after treatment is not successful the GP should refer the patient. Another guideline (cholesterol) recommends for the same population immediate referral to a specialist. From the patient outcome perspective, the difference might not be large. From designing a DSS, however, these constitute different recommendations; if these statements between guidelines are inconsistent, appropriate assistance through a DSS will not be possible.

If authoritative organisations develop guidelines, clinicians will rely on those guidelines, and may consider consistency to be implicit. Furthermore, if guideline issuing organisations aim to improve compliance to guidelines, consistency among the guidelines of that same organisation is a prerequisite. Even if general practitioners intend to adhere to guidelines, they will not succeed to adhering to more than one guideline simultaneously if a patient suffers from more than one disease and the guidelines are inconsistent. This urges the guideline developing organisations to carefully review previously released guidelines for statement inconsistencies between guidelines during the process of updating guidelines or drafting new guidelines. Given that inconsistencies were found, we recommend that organizations that maintain a set of
guidelines provide physicians with a list of known inconsistencies among those guidelines.

A few mechanisms might cause inconsistencies among the DCGP guidelines. Firstly, although the available scientific evidence plays an important role, the DCGP acknowledges that the guidelines are, to a varying degree, dependent on subjective opinions of individuals involved in the creation of that guideline. Each guideline is based on arguments of the individual members of the taskforce and subsequent reviewers. However, for each guideline different general practitioners participate in the taskforce. The process of developing guidelines, therefore, does not guarantee consistency.

Secondly, the timeframe in which guidelines are developed and revised might be another cause of inconsistencies. For example, the hypertension and peripheral arterial disease guidelines that the cholesterol guideline refers to were revised after the revision of the cholesterol guideline.

Thirdly, as new evidence becomes available, the DCGP issues new guidelines and revises existing guidelines. Therefore, corresponding statements in different guidelines can be based on different evidence. This is an inherent limitation to the current paper-based guideline development and revision process. The fact that for all statement inconsistencies a reference inconsistency exists is another example of the limitation of the DCGP paper-based guidelines development process. Given that guidelines are electronically available, guideline developers might hyperlink corresponding statements in recently issued or revised guidelines to statements in previously issued guidelines enabling the updating of existing guidelines with new evidence. Linking statements facilitates the review process with respect to inconsistencies in related guidelines facilitating the formalization of these guidelines for use in a DSS, and leading to consistent cross referencing.

The fact that all guidelines adhere to a common structure consisting of sections, and being translatable to the SOAP methodology could be important for developers of DSS. If physicians apply the SOAP methodology entering patient data, decision support based on the corresponding section of guidelines could be linked to the distinctive components of the clinical management process, enabling the physician to integrate the guideline into the patient’s
Currently various groups are working on modelling guidelines to be computer interpretable\textsuperscript{27-29,30}. However, none of these groups explicitly require consistency among guidelines. We believe that consistency between guidelines is a prerequisite in the development of computer interpretable guidelines. Adherence to guidelines does not solely rely on the implementation strategy chosen for the guideline, but on consistency of the guidelines themselves as well. Recently Shiffman \textit{et al} published a checklist of 18 points for guidelines structure\textsuperscript{31}. However, this checklist does not mention the cross consistency in statements and the cross consistency in referencing of related guidelines; issues that in our opinion should be added to the checklist for guideline structure. Modelling of guidelines to be computer interpretable should start with a careful analysis and updating of guidelines on consistency by guideline developers. This will assist the subsequent implementation of several guidelines into DSS by system developers, as well as clarifying the management of a single patient with multiple chronic diseases by physicians. A cross guideline consistency enables the physician to integrate across relevant guidelines into the patient’s management process. Further research is necessary to assess the feasibility of this approach.

We believe that the strength in our study lies in the fact that we performed the first cross sectional analysis of all CVD risk factor statements in all relevant guidelines issued by the DCGP. Our approach might also be applicable on guidelines for managing CVD risk factors developed by other organizations.
Figure 1. The DCGP guideline sections and subsections with the corresponding components of the problem orientated patient recording methodology (Subjective, Objective, Assessment, and Plan)

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Subjective</th>
<th>Objective</th>
<th>Assessment</th>
<th>Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Introduction and Background</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b) Diagnosis and evaluation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Special Investigations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c) Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 1. Statement inconsistencies in the DCGP guidelines in distinctive SOAP components of the problem orientated patient recording methodology with respect to risk factors for cardiovascular diseases in similar clinical scenarios

<table>
<thead>
<tr>
<th>General statement in SOAP components</th>
<th>Angina⁸²</th>
<th>Diabetes⁸⁴</th>
<th>Cholesterol⁹³</th>
<th>Hypertension⁹²</th>
<th>TIA* ²²</th>
<th>PAD† ²¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subjective</strong></td>
<td>A general practitioner should note cardiovascular family history</td>
<td>Subjective</td>
<td>Subjective</td>
<td>Subjective</td>
<td>Subjective</td>
<td>Subjective</td>
</tr>
<tr>
<td></td>
<td>First degree family members younger than 60 years of age</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Note heart failure as cardiovascular condition</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Objective</strong></td>
<td>Determine a triglyceride (TG) values</td>
<td>Subjective</td>
<td>Subjective</td>
<td>Subjective</td>
<td>Subjective</td>
<td>Subjective</td>
</tr>
<tr>
<td></td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
</tr>
<tr>
<td></td>
<td>Perform a cholesterol test in all patients with angina pectoris</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
</tr>
<tr>
<td></td>
<td>Any type II diabetic should get a cholesterol test</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
</tr>
<tr>
<td></td>
<td>Any male aged 18-70 or female aged 18-75 should get a cholesterol test if cardiovascular disease</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
</tr>
<tr>
<td></td>
<td>Patients with hypertension and cardiovascular disease should get a cholesterol test</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
</tr>
<tr>
<td></td>
<td>Patient younger than 65 with TIA should get a cholesterol test</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
</tr>
<tr>
<td></td>
<td>Patients with PAD should get a cholesterol test</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
</tr>
<tr>
<td><strong>Plan</strong></td>
<td>Lose weight if body mass index (BMI) is above threshold</td>
<td>Subjective</td>
<td>Subjective</td>
<td>Subjective</td>
<td>Subjective</td>
<td>Subjective</td>
</tr>
<tr>
<td></td>
<td>BMI threshold &gt; 25 kg/m²</td>
<td>BMI threshold &gt; 27 kg/m²</td>
<td>BMI threshold &gt; 27 kg/m²</td>
<td>BMI threshold &gt; 27 kg/m²</td>
<td>BMI threshold &gt; 27 kg/m²</td>
<td>BMI threshold &gt; 27 kg/m²</td>
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<td></td>
<td>No statement</td>
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<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
</tr>
<tr>
<td></td>
<td>Treat with a statin in primary prevention</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
</tr>
<tr>
<td></td>
<td>BMI threshold &gt; 27 kg/m²</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
</tr>
<tr>
<td></td>
<td>Refer if cholesterol &gt; 8 mmol/l</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
</tr>
<tr>
<td></td>
<td>Refer if cholesterol &gt; 9 mmol/l</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
</tr>
<tr>
<td></td>
<td>Refrain from treating patient but refer to specialist if incidental TG value &gt; 4 and patient is diabetic</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
<td>No statement</td>
</tr>
</tbody>
</table>

* TIA - transient ischemic attack † PAD - Peripheral arterial disease
References


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Jacobus T van Wyk, Marc AM van Wijk, Miriam CJM Sturkenboom, Peter W Moorman, Johan van der Lei

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Abstract

**Background:** Detecting and managing the four major conventional risk factors – smoking, hypertension, diabetes mellitus, and hypercholesterolemia is pivotal in the primary and secondary prevention of cardiovascular disease (CVD).

**Objective:** To assess the preventive activities of general practitioners regarding the four conventional risk factors, and the associated measurements for cardiovascular risk factors by general practitioners in relation to the time of first clinical presence of CVD.

**Setting:** Large longitudinal general practice research database (IPCI) in the Netherlands from September 1999 to August 2003.

**Participants and methods:** Patients older than 18 with newly diagnosed CVD with at least one year of valid history before and after first clinical diagnosis of CVD. Details on conventional risk factors and associated measurements for the four cardiovascular risk factors were assessed in relation to the first clinical diagnosis of CVD.

**Results:** In total 157,716 patients met the inclusion criteria. Of the 2,594 patients with newly diagnosed CVD, at least one of the four investigated risk factors was observed in 76% of females and 73% of males. In 40% of cases no risk factor was recorded before the date of first CVD. In 16% of cases no associated measurements were present before the first CVD diagnosis.

**Conclusion:** In daily practice general practitioners seem to focus on secondary prevention of CVD. Intervention strategies that aim to influence general practitioners’ case finding behaviour should focus on increasing the awareness of physicians in performing risk factor associated measurements in patients eligible for primary prevention of CVD. Further research will have to show the feasibility and effectiveness of such intervention strategies.
Introduction

In the Netherlands, the Dutch College of General Practice (DCGP) develops evidence-based guidelines to assist general practitioners (GPs) in dealing with specific clinical conditions, including recommendations for preventive activities regarding cardiovascular disease (CVD) risk factor management. These guidelines correspond to internationally developed guidelines on the prevention of atherosclerotic disease. Recent studies emphasize the value of detection of the so-called four conventional or major risk factors for CVD: Smoking, hypertension, diabetes mellitus, and hypercholesterolemia. Managing these four risk factors plays an important role in the primary and secondary prevention of cardiovascular disease. All international guidelines on the prevention of atherosclerotic disease emphasize the need to manage these four major risk factors.

However, a number of researchers have argued that although authoritative guidelines are available, both primary and secondary prevention of CVD are sub-optimally performed. Little is known about GPs’ preventive activities regarding major risk factors and associated measurements for cardiovascular risk factors in relation to the first clinical presence of CVD.

In this study we assess the preventive activities of GPs regarding the four conventional risk factors and associated measurements for these risk factors in patients eligible for primary or secondary prevention of CVD in relation to the time of first clinical presence of CVD.

Methods

Setting

We conducted a retrospective cohort study in the Integrated Primary Care Information (IPCI) database. IPCI is a longitudinal GP research database, which contains information from computer-based patient records of GPs in The Netherlands. Within The Netherlands, patients are registered at single GP and the record for each individual patient contains all medical information on that patient. The database contains information on approximately 500,000 patients. The computer records contain information on patient demographics, symptoms (free text),
diagnoses (using the International Classification for Primary Care (ICPC)), episodes, referrals, laboratory values, measurements (e.g. BP, cholesterol levels), drug prescriptions with their ICPC-coded indications, and hospitalizations. Summaries of the hospital discharge letters or information from specialists are available in a free text format. To maximize completeness of the data, GPs who participate in the IPCI project are not allowed to use paper-based records. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for epidemiological research.

Source population and CVD study cohort

The source population comprised all subjects of 18 years and older, with at least one year of valid database history. This means that the patient was registered for at least one year with the GP and the GP should participate in the IPCI project for at least one year. All subjects were followed from the latest of the following dates: one year of valid history, age 18, or start of the study period (September 1999) until death, transferral out of practice, last data draw down or end of the study period (August 2003), whichever came first.

The CVD study cohort comprised all subjects with a first recorded diagnosis of clinical atherosclerotic disease, defined as clinical coronary heart disease (angina pectoris, myocardial infarction), transient ischaemic attacks (TIA), ischaemic cerebrovascular attacks, and peripheral arterial disease. Because our study focused on preventive activities of GPs in relation to the time of first clinical presence of the predefined atherosclerotic disease, we excluded all patients with less than one year of follow-up after the first event.

Definition of the risk factors hypertension, diabetes mellitus, hypercholesterolemia, and smoking, and associated measurements

We evaluated the so called modifiable conventional or major risk factors for developing atherosclerotic disease. The guidelines of the DCGP dealing with primary and secondary prevention of CVD focus on smoking, hypertension, diabetes, and hypercholesterolemia as modifiable risk factors. These guidelines are familiar to and considered authoritative by Dutch GP's. Because our objective was to assess preventive activities of Dutch GP's in daily practice
we restricted ourselves to these so called four conventional risk factors. The Dutch guidelines on prevention of CVD correspond to widely accepted international guidelines on prevention of CVD (i.e. National Cholesterol Education Program's Adult Treatment Panel III guideline, the European guidelines on prevention of coronary heart disease, guidelines of the American College of Physicians, and guidelines of the American Heart Association/American College of Cardiology) 

Patients were considered to suffer from the risk factor hypertension if they had an ICPC coded diagnosis of hypertension by the GP or a specialist, or if they were treated with antihypertensive drugs (thiazides, beta-blockers, calcium channel blockers, ACE-inhibitors, or angiotensin-II antagonists), while excluding prescriptions for angina pectoris or heart failure.

The risk factor diabetes mellitus was identified by an ICPC coded diagnosis of diabetes by the GP or a specialist, or if treatment was present with insulin or oral antidiabetics.

Because the ICPC classification does not distinguish between the various lipid abnormalities, patients were considered to have the risk factor hypercholesterolemia in the presence of a total cholesterol value greater than 5 mmol/l (1999 DCGP cholesterol guideline). For all conditions we determined the date of first presence in the record and assumed that these conditions were chronic.

Information on the risk factor smoking was obtained from the medical records and information on active smoking as well as non-smoking was considered.

Associated measurements were measurements used to determine the presence of a risk factor. For smoking the measurement was a question regarding smoking status. For hypertension the associated measurement was the recording of BP value. For diabetes it was the presence of a glucose measurement. For hypercholesterolemia it was the presence of a serum cholesterol test.

**Preventative activities of General Practitioners**

We established whether any patient in our CVD cohort had hypertension, hypercholesterolemia, diabetes, or smoked. We calculated prevalences at the end of the observation period. Subsequently we assessed whether the diagnosis in the patient record of these risk factors
occurred before the first recorded diagnosis of clinical atherosclerotic disease, on the same day that clinical atherosclerotic disease was recorded, or after the recording of clinical atherosclerotic disease.

We established whether any patient in our CVD cohort had a cholesterol measurement, a BP measurement, a glucose test, or a noted enquiry on smoking status. We calculated prevalences at the end of the observation period. Subsequently we assessed whether the measurements were performed before the first recorded diagnosis of clinical atherosclerotic disease, on the same day that clinical atherosclerotic disease was recorded, or after the recording of clinical atherosclerotic disease.

**Statistical Methods**

Categorical data are presented as percentages, and continuous data are presented as means (SDs). Where applicable, frequencies were analyzed using χ² tests, and continuous variables were analyzed by Mann-Whitney U tests. We used SPSS version 11 (SPSS Inc, Chicago, IL) for analyzing data. We considered comparisons significant at P<0.05.

**Results**

Of the 157 716 patients who met the inclusion criteria in the source population, a first recorded diagnosis of clinical atherosclerotic disease occurred in 2594 patients (52.7% male, 47.3% female) during the study period. At the end of the observation period of all patients with newly diagnosed CVD, 40.7 % had recorded hypertension, 41.7 % had recorded hypercholesterolemia, 16.5% had diabetes mellitus and 28.2% had been or were smokers. At the end of the observation period 74.4% of newly diagnosed CVD patients had at least one of the four risk factors.

Table 1 shows the number of associated measurements for conventional risk factors and risk factors by gender.

Table 2 shows when individual risk factors were recorded in relation to the first diagnosis of CVD. As shown in table 2, of the 732 patients who smoked, 62% were known to smoke before the CVD event (the primary prevention window), 19% were recorded as smokers on the same day that CVD was diagnosed, and 19% were recorded as smokers after the first CVD event.
Table 3 shows the cumulative number of risk factors present per patient related to the time of first CVD diagnosis. The total number of risk factors present per patient increased on or after the date of first CVD diagnosis, the percentage of patients with no risk factors decreased from 39.7% to 25.6%.

Table 4 shows the first entry of associated measurements for cardiovascular risk calculation related to the time of first CVD diagnosis. Of all new CVD patients, 957 (36.9%) patients had a measurement for smoking. When measurements were related to the first diagnosis of CVD, 61.8% were before the first diagnosis of CVD, 20.2% were on the same day as the diagnosis, and 18.1% were after the diagnosis.

Table 5 shows the total number of associated measurements for cardiovascular risk factors per patient related to the time of first CVD diagnosis. In 15.9% of cases no measurements were present before the first CVD diagnosis. The percentage of patients with no associated measurements decreased on or after the date of first CVD diagnosis to 2.4%. Only 18.2% of patients had all associated measurements performed after the first diagnosis of CVD.

**Discussion**

**Statement of principal findings**

The aim of this study was to assess the identification of the 4 conventional risk factors, and associated measurements by GPs in patients eligible for primary or secondary prevention of CVD. The prevalence of conventional risk factors in our data set corresponds to previously published data on conventional risk factors. All the 2594 patients in our study were required to have at least one year of observation before the first CVD event was diagnosed – time during which they were eligible for primary prevention. In approximately 60% of patients the risk factor was known before the first diagnosis of CVD, however only a fraction (10%) of patients had all risk factor measurements before the first diagnosis of CVD. More than half of patients had one or no risk factor measurement before the first diagnosis of CVD. We believe benefit can be gained for patients at risk of CVD by screening for risk factors in an earlier stage.

A comparison of when risk factors were present in relation to the date of CVD diagnosis
showed that - if a risk factor was present - diabetes, hypertension, and hypercholesterolemia were diagnosed in greater numbers (75-79%) than smoking (62%) before the first recorded diagnosis of CVD. Of patients with smoking and hypertension, 19% and 5% respectively had the first entry of the risk factor on the date of CVD diagnosis. In 40% of patients no risk factor was present before the first recorded diagnosis of CVD. However, on the day of CVD diagnosis, the number of patients without a risk factor decreased by 6%, and by a further 9% after the CVD diagnosis. We conclude that GPs tend to complete their screening for risk factors when confronted with a new CVD event. In the light of the evidence on reducing the number of CVD events by early identification and management of risk factors, much is to be gained in influencing the GPs’ case finding behaviour in primary prevention of CVD 27-30.

Only BP measurements were recorded in the majority of new CVD patients. Measurements for cholesterol, smoking and glucose were recorded in 50 to 60% of patients. Physicians frequently recorded measurements on or after the first recorded diagnosis of CVD. This indicates that the confrontation with the CVD event triggered the physician to assess additional risk factors. The DCGP guidelines recommend cholesterol, glucose, BP and smoking status measurements in all patients with CVD. The fact that only BP measurements were performed in most patients with CVD indicates that GPs show moderate compliance with DCGP guidelines’ recommendations regarding secondary prevention of CVD. Of all patients, 15.9% had no risk factor measurements in their records before the first recorded diagnosis of CVD. This could explain why approximately 40% of all the patients who developed CVD, did not have a risk factor present before the first diagnosis of CVD. For primary prevention to be successful, case finding of risk factors by performing associated measurements is a prerequisite.

**Strengths and weaknesses of the study**

Our study benefits from the fact that it was done in an observational database, reflecting GPs’ actions without any intervention by the researchers. GPs are not forced to adhere to study protocols and are free to record what they want. That our study reflects prevalence found by other groups, makes our findings generalizable 9,10. As is noted by other authors, a weakness of observational data is that these reflect what GPs chose to capture in their records 31. This
can lead to an underestimate of risk factor identification and measurements in our study. The prevalence of smoking shown in our work is an example of the difficulties in determining the risk status of individuals purely from observational data. The prevalence of smokers in our study was less, compared to the known Dutch prevalence 32. This can be partly explained by smokers hiding their smoking status from physicians, resulting in a lower than expected smoking prevalence observed in general practice 33, and GPs not recording normal values (i.e. “non smoker”).

**Strengths and weaknesses in relation to other studies, discussing important differences in results**

Khot et al showed that the four conventional risk factors are related to the development of CVD 9. Our data confirm this in an observational setting. As mentioned before our study might underestimate the number of risk factors in CVD (71-75% with at least one risk factor and CVD vs. 85-90% in Khot et al). This can partly be explained by the difficulty in obtaining complete data in an observational setting. In addition, our data indicate that the records of patients without CVD but with a risk factor present show few associated measurements for cardiovascular risk calculation.

We do not know of other studies which looked at the timeframe of risk factor diagnosis in relation to the first diagnosis of any clinical atherosclerotic disease, nor any that evaluated when the first associated measurements for risk profile estimation were performed in relation to the first CVD diagnosis. One study in similar observational setting looking at risk factor management in CVD, found that the management of these risk factors was poor 31. A Dutch study showed that in a selected population under-screening and under-treatment of patients eligible for primary or secondary prevention of CVD is common 34. The identification of risk factors based on abnormal values of associated measurements for cardiovascular risk calculation, precedes the adequate management of risk factors. Our study shows that the insufficient attention to performing associated measurements for cardiovascular risk calculation hampers effective primary prevention.

With respect to the management of the four conventional risk factors, the Dutch
guidelines on prevention of CVD correspond to international guidelines. The main focus of the guidelines is the early detection and management of these four modifiable risk factors.

Our definition of hypercholesterolemia is a blood cholesterol value greater than 5 mmol/l. This value is used in the Netherlands to define abnormal high blood cholesterol; in the presence of atherosclerotic disease it warrants medical treatment. This differs from other international guidelines that emphasize LDL cholesterol testing as an important indicator of abnormal lipid values. However since all international guidelines emphasize the early detection of abnormal blood lipid values, we do not believe that this will make our results less generalizable; we believe that GP’s threshold for early detection is low, irrespective of which blood lipid value is used.

In the Netherlands the DCGP guidelines are viewed as authoritative. However, having authoritative guidelines available does not directly translate into compliance to guidelines. Different strategies of guideline implementation have shown varying degrees of success in improving compliance. A number of studies showed an effective strategy for guidelines implementation is integrating guideline based decision support systems (DSS), into the electronic medical record (EMR). The objective of the systems is to help the practitioners in making guideline based healthcare decisions at the point of care, therefore increasing adherence to guidelines, and indirectly, favourably influencing patient outcomes – the main aim of evidence based medicine. The availability of enough relevant data, however, is a prerequisite for any decision support system to give proper support.

The majority of GPs in The Netherlands have replaced their traditional paper-based patient records with computer-based patient records, the physicians entering patient data themselves in the computer during patient encounters. The use of electronic patient records creates new opportunities for the implementation of decision support systems; integration of decision support facilities with electronic patient records provides a natural way to support clinical practice.

Our study shows that concerning CVD management, data regarding risk factors are available, but frequently too “late”. The essence of primary prevention is the identification of risk
factors by performing associated measurements in patients at risk of atherosclerotic disease preceding the event. Giving GP’s the tools to identify patients eligible for primary prevention, might invite them to perform associated measurement for cardiovascular risk calculation in a much earlier stage. Therefore unlike previous efforts in decision support systems we argue that the focus should not be on the rules and algorithms that guide these systems - this is contained in evidence based medicine itself - but rather on increasing the awareness of physicians in obtaining the relevant data. Giving effective feedback on the values in relation to cardiovascular risk might lead to better case finding of patients. Further research will have to show whether this approach is feasible and effective.

Conclusion

In daily practice GPs seem to focus on secondary prevention of CVD. Intervention strategies that aim to influence GP’s case finding behaviour should focus on increasing the awareness of physicians in performing associated measurements in patients eligible for primary prevention of CVD. Further research will have to show the feasibility and effectiveness of such intervention strategies.
Table 1: Associated measurements and prevalence of conventional risk factors for CVD one year after first diagnosis of CVD

<table>
<thead>
<tr>
<th>Measurements and risk factors, n(%)</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean(SD)</td>
<td>69.9</td>
<td>65.4</td>
</tr>
<tr>
<td>Smoking measurement</td>
<td>372</td>
<td>585</td>
</tr>
<tr>
<td>Smoking</td>
<td>293</td>
<td>439</td>
</tr>
<tr>
<td>Glucose measurement</td>
<td>830</td>
<td>808</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>206</td>
<td>222</td>
</tr>
<tr>
<td>BP measurement</td>
<td>1165</td>
<td>1298</td>
</tr>
<tr>
<td>Hypertension</td>
<td>568</td>
<td>489</td>
</tr>
<tr>
<td>Cholesterol measurement</td>
<td>604</td>
<td>737</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>521</td>
<td>560</td>
</tr>
<tr>
<td>No. of Risk Factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>297</td>
<td>367</td>
</tr>
<tr>
<td>1</td>
<td>434</td>
<td>479</td>
</tr>
<tr>
<td>2</td>
<td>340</td>
<td>381</td>
</tr>
<tr>
<td>3</td>
<td>122</td>
<td>119</td>
</tr>
<tr>
<td>4</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>Total number of patients, n (%)</td>
<td>1220</td>
<td>1374</td>
</tr>
<tr>
<td>With at least one risk factor</td>
<td>923</td>
<td>1007</td>
</tr>
</tbody>
</table>

* Risk factor prevalence differences between men and women in CVD subgroups statistically significant at P<.001 unless otherwise noted
† Risk factor prevalence differences between men and women in CVD subgroups statistically significant at P<.05
‡ Risk factor prevalence differences between men and women in CVD subgroups nonsignificant
### Table 2: Timing of individual risk factor diagnosis in relation to first diagnosis of a CVD event (n=2594)

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Patients with risk factor</th>
<th>Risk factors related to the time of first diagnosis of CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Before</td>
</tr>
<tr>
<td>Smoking</td>
<td>732</td>
<td>454</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>428</td>
<td>334</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1057</td>
<td>837</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>1081</td>
<td>812</td>
</tr>
</tbody>
</table>

### Table 3: Presence of cumulative number of the four risk factors as noted by the GP in relation to first diagnosis of a CVD event (n=2594)

<table>
<thead>
<tr>
<th>Cumulative no. of risk factors per patients</th>
<th>Before</th>
<th>On the same day of diagnosis</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n (%)</td>
<td>n</td>
</tr>
<tr>
<td>0</td>
<td>1031 (39.7)</td>
<td>893 (34.4)</td>
<td>664 (25.6)</td>
</tr>
<tr>
<td>1</td>
<td>880 (33.9)</td>
<td>951 (36.7)</td>
<td>913 (35.2)</td>
</tr>
<tr>
<td>2</td>
<td>518 (20.0)</td>
<td>566 (21.8)</td>
<td>721 (27.8)</td>
</tr>
<tr>
<td>3</td>
<td>139 (5.4)</td>
<td>156 (6.0)</td>
<td>241 (9.3)</td>
</tr>
<tr>
<td>4</td>
<td>26 (1.0)</td>
<td>28 (1.1)</td>
<td>55 (2.1)</td>
</tr>
</tbody>
</table>
### Table 4 Timing of associated measurements for individual risk factor in relation to first diagnosis of a CVD event (n=2594)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Patients with measurement</th>
<th>Measurements related to the time of first diagnosis of CVD</th>
<th>Before</th>
<th>On the same day of diagnosis</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Smoking</td>
<td>957</td>
<td>591 (61.8)</td>
<td>193 (20.1)</td>
<td>173 (18.1)</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>1602</td>
<td>804 (50.2)</td>
<td>525 (32.8)</td>
<td>273 (17.0)</td>
<td></td>
</tr>
<tr>
<td>BP</td>
<td>2463</td>
<td>2059 (83.6)</td>
<td>241 (9.8)</td>
<td>163 (6.6)</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>1341</td>
<td>966 (72.0)</td>
<td>29 (2.2)</td>
<td>346 (25.8)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 5 Presence of cumulative number of associated measurements for the four risk factors as noted by the GP in relation to first diagnosis of a CVD event (n=2594)

<table>
<thead>
<tr>
<th>Cumulative no. of measurements per patient</th>
<th>Measurements related to the time of first diagnosis of CVD</th>
<th>Before</th>
<th>On the same day of diagnosis</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>0</td>
<td>412 (15.9)</td>
<td>155 (6.0)</td>
<td>62 (2.4)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1000 (38.6)</td>
<td>729 (28.1)</td>
<td>503 (19.4)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>374 (14.4)</td>
<td>744 (28.7)</td>
<td>699 (26.9)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>560 (21.6)</td>
<td>673 (25.9)</td>
<td>858 (33.1)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>248 (9.6)</td>
<td>293 (11.3)</td>
<td>472 (18.2)</td>
<td></td>
</tr>
</tbody>
</table>

|                                           | n     | %     | 2594 (100.0) | n     | %     | 2594 (100.0) | n     | %     | 2594 (100.0) |
Chapter 3

References


Identification of “Conventional” Risk Factors


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Management of hypertension and hypercholesterolaemia in primary care in the Netherlands

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Abstract

**Objective**: Screening, treatment and monitoring guidelines for hypertension and hypercholesterolaemia have been developed to assist physicians in providing evidence-based healthcare. We conducted a retrospective study to assess the management of patients with these single or combined conditions.

**Research design and methods**: This was a retrospective cohort study conducted using data from the Integrated Primary Care Information (IPCI) project based in the Netherlands. Management of hypertension and hypercholesterolaemia was assessed from 2000–2003 by measuring the numbers of patients screened for these conditions, treated pharmacologically, and monitored for treatment success.

**Results**: Approximately 11%, 3% and 10% of participants were eligible for screening for hypertension alone, hypercholesterolaemia alone and both conditions, respectively. Blood pressure screening was high in patients eligible for both blood pressure and cholesterol screening (>85%), whereas cholesterol screening was low (<56%). Among patients newly identified with hypertension or hypercholesterolaemia who were eligible for pharmacotherapy, 29% and 43%, respectively, were not treated within one year of diagnosis. Undertreatment was significantly lower in patients with both conditions (24% and 37% for antihypertensive and lipid-lowering treatment, respectively, and 28% were not treated for both). Among newly treated patients, in the first year of treatment there was no record of a blood pressure or cholesterol assessment, for 35% and 72%, respectively.

**Conclusion**: Management was sub-optimal in patients with hypertension or hypercholesterolaemia as well as in those with both of these conditions. The results of this study are likely to be widely applicable, particularly to other European and industrialised countries that have similar free-access health care systems to the Netherlands.
Chapter 4

Introduction

Hypertension and hypercholesterolaemia are common, modifiable risk factors for cardiovascular disease (CVD), which is a leading cause of morbidity and mortality in industrialised countries. The level of cardiovascular (CV) risk associated with concurrent hypertension and hypercholesterolaemia is far greater than the risk associated with either condition in isolation. Long-term treatment of hypertension may substantially reduce the risk of myocardial infarction and stroke; long-term use of lipid-lowering medications reduces the risk of coronary heart disease (CHD). Despite abundant evidence of the risks associated with hypertension and hypercholesterolaemia, and the proven efficacy of available treatments for these conditions, there is considerable underdiagnosis and undertreatment of these conditions.

The majority of previous studies have not addressed the overall management of hypertension and hypercholesterolaemia, and instead have focused on one aspect, such as screening or treatment. Furthermore, many of these studies have not assessed the concomitant management of patients with both conditions. Moreover, studies examining the undertreatment of hypercholesterolaemia often have been based on selected secondary prevention populations or have been based on self-reported information. Previous studies in the Netherlands did not distinguish between undertreatment due to lack of prescribing or undertreatment due to lack of persistence in taking medications.

We conducted a retrospective study using a database containing general practitioner (GP) medical records. Our aims were to assess the extent of screening for, and pharmacological treatment of, hypertension and hypercholesterolaemia, and the extent of blood pressure (BP) and cholesterol monitoring in patients initiating treatment for one or both of these conditions. We then compared these findings with the recommendations of the national guidelines for hypertension and cholesterol management. Furthermore, we assessed the impact of the presence of concomitant hypertension and hypercholesterolaemia, versus either condition alone, on the management of these conditions.
Patients and Methods

Database and study population

Patient data were retrieved from the Integrated Primary Care Information (IPCI) project. The IPCI is a GP research database, containing longitudinal computer-based patient records (more than 500,000 patients in total) from 150 GPs in the Netherlands. The electronic records contain coded and anonymous data on patient demographics, symptoms (in free text), diagnoses by GPs and specialists (using the International Classification for Primary Care), referrals, laboratory findings, clinical assessments, hospitalisations, and prescribed medications (including indications and dosage regimens). The IPCI system complies with the European Union guidelines on the use of medical data for research and has been proven valid for pharmacoepidemiological research. The study was approved by the Scientific and Ethical Advisory Board of the IPCI project.

The study population comprised subjects aged ≥16 years, who had been registered for at least 1 year with their GP and whose GP had participated in the IPCI project for at least 1 year. The study period was from January 2000 to September 2003. Patients were followed until their death, transfer from the GP’s practice, or until the end of the study period.

Screening

Patient eligibility for, and the prevalence of, BP and cholesterol screening were assessed as of January 1, 2000 and January 1, 2002. Patient eligibility for screening was determined according to the 1999 Dutch College of General Practitioners (DCGP) clinical guidelines (Table 1). Recommendations of current DCGP cholesterol guidelines include the screening of individuals with familial hypercholesterolaemia. However, since this condition could not be assessed reliably for all subjects, it was not included in the analyses. Patients were considered to have had their cholesterol level screened if they had a previous record of at least one total cholesterol or total cholesterol/high-density lipoprotein (HDL) ratio measurement, a prescrip-
tion for statin treatment, or a diagnosis of hypercholesterolaemia.

**Identification of hypertension and hypercholesterolaemia**

Hypertension was defined as: a recorded diagnosis by the patient’s GP or specialist; ≥2 BP measurements >160/95 mm Hg (in accordance with the 1999 DCGP guidelines); or antihypertensive pharmacotherapy (thiazide, β-blocker, calcium channel blocker, angiotensin-converting enzyme inhibitor, or angiotensin II antagonist).

Hypercholesterolaemia was defined as: a recorded diagnosis by the patient’s GP or specialist; total cholesterol >5 mmol/L (193 mg/dL); or treatment with a statin. The prevalence of hypertension alone, hypercholesterolaemia alone, and concurrent hypertension and hypercholesterolaemia, was determined on January 1 of 2000, 2001, and 2002.

Newly identified patients had no recorded evidence of hypertension and hypercholesterolaemia in their history. The earliest date that one of the hypertension criteria was identified was considered as the index date for the onset of hypertension. Newly identified patients with hypercholesterolaemia were determined in a similar manner. Among these cohorts, subgroups were identified as: patients who were known to have hypertension at the first diagnosis of hypercholesterolaemia, patients who had hypercholesterolaemia at the first diagnosis of hypertension, and patients who were identified with hypercholesterolaemia and hypertension within a period of 30 days.

**Pharmacological treatment**

Only individuals with at least 1 year of follow-up data after the onset of hypertension or hypercholesterolaemia were included in the evaluation of treatment. At the index date, we assessed whether the patient was eligible for treatment, and if the patient was prescribed pharmacological treatment within 1 year after the index date. The 1999 DCGP guidelines, which use the Framingham risk function to estimate CV risk, were used to determine treatment eligibility (Table 1). The presence of concomitant CVD was determined from coded diagnoses. Risk factors for CVD were obtained from patients’ medical records and CV risk profiles. In the absence of total cholesterol/HDL ratios, which are necessary to calculate the Framingham risk
score, gender and age-specific reference values were imputed. Also, since the thresholds for treatment eligibility in the Dutch guidelines omit left ventricular hypertrophy, this condition was not considered in this calculation.

The number of patients eligible for treatment at the index date, the proportion who received treatment within 1 year, and the proportion monitored for BP and cholesterol during the first year following treatment initiation, were estimated.

**Statistical analysis**

Descriptive statistical analyses were performed with SPSS version 11 (SPSS Inc., Chicago, IL, USA). Patient characteristics were summarised by mean and standard deviation (SD) for continuous variables and by percentage for categorical variables. Prevalences were summarised by mean and 95% confidence intervals (CI). Chi-square tests were used to assess differences in the treatment and monitoring rates of patients with and without prevalent concomitant conditions.

**Results**

The source population with 1 year of valid history comprised 250,210 subjects aged ≥16 years (mean age 42.6 years, 50.6% female).

**Screening**

Overall, the proportion of the population who were eligible for BP screening as of January 1, 2000 and January 1, 2002 was slightly above 20% (Table 2). Fewer patients (approximately 13%) were eligible for cholesterol screening. The BP screening rate for patients who were eligible for both cholesterol and BP screening was considerably higher than in those patients eligible for BP screening alone (86.2% vs 50.8% in 2000). Also, the rate of cholesterol screening was higher in patients eligible for both types of screening compared with those eligible for cholesterol screening alone (50.2% vs 38.0% in 2000).

Despite little change in the proportion of patients who were eligible for screening from 2000 to 2002, the proportion of patients who were screened increased slightly over this time.
period (Table 2).

### Prevalence

The prevalence of concomitant hypertension and hypercholesterolaemia increased from 6.5% in 2000 to 8.1% in 2002 (Fig. 1).

### Pharmacological treatment

We identified 8495 new patients with hypertension and 10,451 new patients with hypercholesterolaemia. Among these patients, there were 964 in whom hypertension and hypercholesterolaemia were identified within a period of 30 days. Clinical and demographic characteristics at the index date are presented in Table 3. It is noteworthy that 23.6% of newly identified patients with hypertension were known to have existing hypercholesterolaemia, and 45.9% of newly identified patients with hypercholesterolaemia were known to have existing hypertension. The estimated 10-year risk of CHD was, on average, 10.5%, 14.7%, and 12.9% among patients with newly identified hypertension, hypercholesterolaemia, and both conditions newly identified, respectively.

The numbers of patients who were eligible for antihypertensive or lipid-lowering pharmacotherapy based on the 1999 guidelines (Table 1) and the proportions of these patients who received treatment within 1 year of diagnosis are shown in Table 4. Overall, undertreatment was substantial, with 28.7% and 43.1% of treatment-eligible patients not receiving treatment for hypertension and hypercholesterolaemia, respectively (Fig. 2A, 2B). Moreover, 27.9% of treatment-eligible patients who were identified with both hypertension and hypercholesterolaemia within 30 days did not receive treatment for both conditions (Fig 2C). Undertreatment rates for patients with prevalent concomitant hypertension and hypercholesterolaemia were significantly lower than undertreatment rates in persons with a single condition ($p < 0.001$) (Table 4).

### Monitoring during initial treatment

Overall, 90% of the patients had at least one visit to their GP during the first year of treatment. Approximately 65% of patients treated for hypertension had a BP measurement recorded in their first year of treatment. Only 27.6% of patients treated for hypercholesterolaemia,
irrespective of the type of statin used, had a cholesterol level measurement recorded during their first year of treatment (Table 4; Fig 2A, 2B). Among patients taking simvastatin (the only drug for which cholesterol monitoring is recommended [Table 1]) 25.4% had one or more recorded cholesterol measurements for this time period. Among patients newly identified with both hypertension and hypercholesterolaemia and who were treated for both conditions, only 16.7% had both their BP and cholesterol recorded (Figure 2C). Blood pressure and cholesterol monitoring rates did not differ significantly between patients with one condition only versus patients with both conditions (Table 4).

**Discussion**

This study demonstrates that the management of hypertension and hypercholesterolaemia is far from optimal across the entire management process (screening, treatment, and treatment monitoring) in primary care in the Netherlands. The prevalence of these conditions, as well as the prevalence of concomitant hypertension and hypercholesterolaemia is substantial and increased between 2000 and 2002. Furthermore, we observed that these two CV risk factors commonly coexisted. The reasons for this increase in the prevalence of hypertension and hypercholesterolaemia are uncertain, but could be related to increased screening for these conditions and ageing of the population.

Many patients who were eligible for BP and cholesterol screening were not screened. For example, by 2002 almost 30% of those eligible did not have their BP screened, and over 45% of those eligible failed to have their cholesterol levels screened. These observations are surprising considering the extent of information regarding CV risk factors and events that was available in the patients' medical records. However, the small increase in screening from 2000 to 2002 and the increased levels of screening of patients with concomitant hypertension and hypercholesterolaemia (compared with those with just one of these conditions) indicates one area of improvement. Nevertheless, the reasons for this poor performance should be identified and addressed.

Among treatment-eligible patients with newly identified hypertension or hypercholesterola-
laemia, many did not receive pharmacotherapy for their condition within 1 year of their initial diagnosis (hypertension 29%; hypercholesterolaemia 43%). Monitoring rates among those initiating antihypertensive or lipid-lowering pharmacotherapy were also low (65% and 28%, respectively). The presence of concomitant hypertension or hypercholesterolaemia in these patients resulted in a small improvement in the rate of treatment but had no significant effect on monitoring rates. Among patients newly identified with both hypertension and hypercholesterolaemia who were eligible for treatment, 28% did not receive pharmacotherapy for both conditions. In those initiating treatment for both conditions, only 17% had both their BP and cholesterol measured during the first year of treatment.

Since GPs participating in IPCI are not allowed to maintain additional paper records, the low treatment and monitoring rates that we have observed here are likely to represent an accurate view of the state of management of hypertension and hypercholesterolaemia in the Netherlands.

Our study used the 160/95 mm Hg cut-off points of the 1999 DCGP guidelines\textsuperscript{16} to define hypertension. In the 2003 DCGP hypertension guidelines\textsuperscript{18}, the cut off point was lowered to 140/90 mm Hg (Table 1), in accordance with World Health Organization/International Society of Hypertension (WHO/ISH) recommendations\textsuperscript{24}. Therefore, whilst our assessment of patient management was based on the guidelines that were in place at the time of the study, the actual prevalence of hypertension and concomitant hypertension and hypercholesterolaemia using the current definition (140/90 mm Hg)\textsuperscript{18} was higher in this population (Fig. 1). This suggests that there were many patients who potentially could have benefitted from pharmacotherapy but who were not recognised as being in need of treatment.

Despite a generally high acceptance rate of the DCGP guidelines among GPs\textsuperscript{19}, low adherence to these guidelines has previously been recognised. Grol et al\textsuperscript{25} found that many of the DCGP recommendations were followed in only 61% of clinical decisions. Aside from the issue of cost-effectiveness, which forms part of the DCGP cholesterol guidelines, there are a number of barriers that may prevent physicians from adhering to guidelines. These barriers may relate to a general lack of familiarity, awareness or agreement with the guidelines, or a lack of outcome
expectancy, self-efficacy, or motivation. We expect that our results are influenced by all of these factors, but that certain aspects are more pertinent. For example, hypertension guidelines generally are easier to implement, because of the less invasive nature of the procedures involved, which may improve adherence. Efforts to facilitate the implementation of guideline recommendations, particularly those for hypercholesterolaemia, are required urgently.

Previous studies conducted in a variety of locations and settings have assessed the extent of undertreatment of hypertension, hypercholesterolaemia or both conditions, and our results point to the same conclusion: undertreatment is extensive, even in patients who have both conditions and are therefore at increased risk for developing CVD. For example, similarly high rates of undertreatment of hypertension (30% for females and 47% for males) have been observed in a Dutch population-based survey conducted between 1987 and 1995 among individuals aged 20–59 years of age. In our study, 31% of treatment-eligible patients over the same age range were undertreated. This level of undertreatment for hypertension at the 160/90 mm Hg threshold is greater than that observed in the US in a survey completed in 1994 (22%), but less than that seen in surveys conducted in Canada (1986–92; 38%), England (1998;48%), Italy (1998;46%), Spain (1990; 54%), Sweden (1999; 51%) and Germany (1997–99; 59%).

Recent studies conducted in the United Kingdom (UK), have indicated that secondary prevention patients who are at high risk of further CVD events often do not have their cholesterol levels recorded (17% in a small study [n=300] and 51.7% for a much larger study [n=89,422]) among patients who had their cholesterol level recorded only half were receiving statin therapy. Furthermore, evidence from a range of studies conducted in both primary and secondary prevention populations suggests that patient receiving statin therapy are rarely titrated to the doses required to attain lipid treatment goals.

The treatment rates for hypercholesterolaemia in the present study are much higher than the results of the MORGEN (Monitoring Project on Risk Factors for Chronic Diseases) study, a 1987–1997 Dutch population-based, cross-sectional study of individuals aged 20-59 years. In the MORGEN study, 32% of individuals who were eligible for treatment (accounting for 5.5% of the total population with suboptimal cholesterol levels) were aware of their high cholesterol
levels, and only 16.3% of these treatment-eligible individuals were treated. Our higher treatment rates (60.9% when restricted to the same age range as the MORGEN study) might point to an improvement in cholesterol management with time. Mantel-Teeuwisse15 observed a comparable increase in treatment rates with time, from 10% (1987–1992) to 45.9% (1998–2002). This increase in treatment rates for hypercholesterolaemia has been reported in studies in across Europe and in Australia7, 14, 35, 37, 38. A slight increase in the use of antihypertensive medications was also reported between 1995–6 and 1999–2000 across 15 European countries8. However, unlike the results for hypercholesterolaemia, this increased utilization of antihypertensives was not associated with a decrease in the prevalence of hypertension8.

Blood pressure monitoring is recommended by the DCGP guidelines in patients starting antihypertensive therapy16,18. However, in this study, the rate of BP monitoring (65%) was lower than the 81% rate found in a similar observational setting in the United States41.

The DCGP guidelines also advise that cholesterol should be tested 3 months after initiating treatment with simvastatin17. For statins other than simvastatin, cholesterol monitoring is not an explicit recommendation of the DCGP guidelines17. However, the rate of cholesterol monitoring in patients on simvastatin treatment was very low and was similar to the rate of monitoring among patients treated with other types of statins. Most current international guidelines recommend the monitoring of hepatotoxicity in patients administered statin therapy, but not of cholesterol levels. This is inconsistent with the approach advocated regarding the monitoring of BP during antihypertensive treatment. As acknowledged in the DCGP cholesterol guidelines, persistence with therapeutic regimens is essential for successful treatment. Monitoring of laboratory levels is an effective way of ensuring patient adherence to treatment, and it is likely that the lack of follow-up cholesterol measurements could have a negative impact on persistence with lipid-lowering treatment and the attainment of therapeutic goals. The low recorded monitoring rates observed in patients with both hypertension and hypercholesterolaemia suggest that there may be many missed opportunities to assess the status of these conditions and to provide appropriate follow-up care.
Limitations and validity

Our study benefits from the fact that it used an observational database, which reflects the GP’s daily actions without any intervention by researchers. However, our choice of working from the perspective of the GP also confers some limitations. For example, GPs do not screen or record all CV risk factors in all patients. Therefore, the number of patients eligible for screening and the number of patients with hypertension and/or hypercholesterolaemia will probably have been underestimated. Furthermore, the absence of data on patient smoking habits, the imputation of reference values on the total cholesterol/HDL ratio and assumptions regarding the presence of familial hypercholesterolaemia will have resulted in an underestimation of the number of patients eligible for treatment. Because of this, and the fact that there may be patients with elevated cholesterol and/or BP levels whose condition has not been recognised by their GP or who have not visited their GP, the rate of undertreatment may be considerably higher.

The results of this study should be widely applicable, particularly to other European and industrialised countries that have free-access health care systems.

Conclusion

Our study demonstrates the systematic underperformance that is present in the overall management of hypertension and hypercholesterolaemia in the Netherlands. Considering the high level of CV risk that is commonly observed in patients with both hypertension and hypercholesterolaemia, the latest DCGP guidelines provide a significant opportunity to improve the management of patients with these conditions. Our approach has been to examine the management process using the information available to GPs, which has enabled us to highlight the disparity between guideline recommendations and actual practice. It is clear that a much greater effort is needed in finding ways to help physicians provide optimal screening, pharmacotherapy and monitoring of patients with hypertension, hypercholesterolaemia, and, in particular, both of these conditions.
**Fig. 1.** Prevalence of hypertension, hypercholesterolaemia, and concomitant hypertension and hypercholesterolaemia. Dotted lines indicate the prevalences based on the 2003 hypertension guidelines. Vertical bars represent 95% confidence intervals. Data labels show mean values.

**Fig 2A.** Antihypertensive treatment and blood pressure monitoring rates in patients with newly identified hypertension.

- **8495** newly-identified patients
- **90.9%** were eligible for treatment
- **71.3%** were treated within 1 year
- **64.8%** were monitored during initial treatment
Fig 2B. Lipid-lowering treatment and cholesterol monitoring rates in patients with newly identified hypercholesterolaemia.
Fig 2C. Antihypertensive and lipid-lowering treatment rates, and blood pressure and cholesterol monitoring rates in patients with newly identified concomitant hypertension and hypercholesterolaemia.

*Treatment eligibility is based on the 1999 DCGP guidelines.
†The treatment rate is calculated as the percentage of treatment-eligible patients (with ≥1 year of follow-up data from diagnosis) who had a record of treatment within 1 year of diagnosis.
‡The monitoring rate is calculated as the percentage of treated patients (with ≥1 year of follow-up data from treatment initiation) who had a record of at least one measurement during the first year of treatment.
§Graphs show estimated rates of treatment and monitoring calculated as a proportion of all newly identified patients.
### Table 1. Summary of the DCGP guidelines for hypertension and hypercholesterolaemia

<table>
<thead>
<tr>
<th>Screenings guidelines for condition</th>
<th>Hypertension guidelines 1999 *</th>
<th>Hypertension guidelines 2003 *</th>
<th>Cholesterol guidelines 1999 *</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Once per year for patients at increased risk for CVD due to:</strong></td>
<td></td>
<td></td>
<td>Men 18-70 years and women 18-75 years at increased risk for CVD due to:</td>
</tr>
<tr>
<td>- presence of DM</td>
<td></td>
<td>- CVD (prior MI, angina, CVA, PAI)</td>
<td>- presence of DM; ≥2 CVD risk factors*</td>
</tr>
<tr>
<td>- history of CVA, TIA, or IHD</td>
<td></td>
<td></td>
<td>- hereditary hypercholesterolaemia</td>
</tr>
<tr>
<td>- use of lipid-lowering treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;60 years of age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prior recording of elevated BP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Screening guidelines for condition</strong></td>
<td><strong>Recommended threshold for pharmacological treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No CVD risk factors:*</td>
<td>No CVD or DM: SBP &gt;180; DBP &gt;105 mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1 CVD risk factor:*</td>
<td>Without CVD/DM: SBP &gt;180, DBP 100 mm Hg</td>
<td></td>
<td>Average total cholesterol &gt;5 mmol/L</td>
</tr>
<tr>
<td>SBP &gt;160; DBP &gt;100 mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With DM:</td>
<td>No CVD or DM, 10-year Framingham risk for CVD &gt;20%:</td>
<td></td>
<td>Without CVD: 10-year Framingham risk for CVD stratified by age and DM:</td>
</tr>
<tr>
<td>SBP 140-180 mm Hg (160-180 mm Hg for patients aged ≥60 years)</td>
<td>with DM: CVD, DM, or familial hypercholesterolaemia: SBP ≥140; DBP ≥90 mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment if life expectancy is &lt;5 years; males &gt;70 years; or females &gt;75 years.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitoring guidelines for condition</td>
<td>Initially:</td>
<td>Initially:</td>
<td>Prescribed simvastatin 20 mg:</td>
</tr>
<tr>
<td>Measure BP every 2 weeks</td>
<td>Measure at each GP visit (every 4-6 weeks)</td>
<td></td>
<td>Monitoring TC at 3 months, adjust dose if necessary.</td>
</tr>
<tr>
<td>Following BP control: Every 3 months</td>
<td>Following BP control: Every 3-6 months.</td>
<td></td>
<td>Prescribed pravastatin 40 mg:</td>
</tr>
</tbody>
</table>

*Risk factors for CVD: hypercholesterolaemia; DM; smoking; organ damage to kidney, heart or brain; family history of CVD; age >60 years; male gender. CVD, cardiovascular disease; DM, diabetes mellitus; CVA, cerebrovascular accident; TIA, transient ischaemic attack; IHD, ischaemic heart disease; BP, blood pressure; MI, myocardial infarction; PAI, peripheral arterial disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol.
Table 2. Blood pressure and cholesterol measurements: eligibility for screening and screening rates as of January 1, 2000 and January 1, 2002

<table>
<thead>
<tr>
<th>Category of screening eligibility</th>
<th>Eligible for screening*, n (%)</th>
<th>Screening rates†, n (%)</th>
<th>Blood pressure</th>
<th>Cholesterol</th>
<th>Blood pressure and cholesterol</th>
<th>Not screened for either condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>January 1, 2000 (N = 193,101)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure, all patients‡</td>
<td>41,156 (21.3)</td>
<td>27,949 (67.9)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cholesterol, all patients‡</td>
<td>25,105 (13.0)</td>
<td>–</td>
<td>11,959 (47.6)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Eligible for just one type of screening only:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure only</td>
<td>21,285 (11.0)</td>
<td>10,815 (50.8)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cholesterol only</td>
<td>5234 (2.7)</td>
<td>–</td>
<td>1991 (38.0)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Eligible for both blood pressure and cholesterol screening:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>19,871 (10.3)</td>
<td>17,134 (86.2)</td>
<td>9968 (50.2)</td>
<td>9087 (45.7)</td>
<td>1856 (9.3)</td>
<td></td>
</tr>
<tr>
<td><strong>January 1, 2002 (N = 170,364)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure, all patients‡</td>
<td>35,487 (20.8)</td>
<td>25,304 (71.3)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cholesterol, all patients‡</td>
<td>22,712 (13.3)</td>
<td>–</td>
<td>12,042 (53.0)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Eligible for just one type of screening only:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure only</td>
<td>17,169 (10.1)</td>
<td>9185 (53.5)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cholesterol only</td>
<td>4394 (2.6)</td>
<td>–</td>
<td>1784 (40.6)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td><strong>Eligible for both blood pressure and cholesterol screening:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>18,318 (10.8)</td>
<td>16,119 (88.0)</td>
<td>10,258 (56.0)</td>
<td>9396 (51.3)</td>
<td>1337 (7.3)</td>
<td></td>
</tr>
</tbody>
</table>

*Eligibility for screening based on 1999 guidelines (see Table 1).
†Screening rates are calculated as a percentage of the number of patients eligible for screening.
‡Among patients eligible for blood pressure (or cholesterol) screening either alone or in combination with cholesterol (or blood pressure) screening.
Table 3. Baseline characteristics of patients with newly identified hypertension or newly identified hypercholesterolaemia

<table>
<thead>
<tr>
<th></th>
<th>Newly identified hypertension $\quad (N = 8495)$</th>
<th>Newly identified hypercholesterolaemia $\quad (N = 10,451)$</th>
<th>Newly identified hypertension and hypercholesterolaemia $\quad (N = 964)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>56.4 (15.3)</td>
<td>55.2 (13.9)</td>
<td>55.1 (11.8)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>4494 (52.9)</td>
<td>5141 (49.2)</td>
<td>394 (40.9)</td>
</tr>
<tr>
<td>Sickfund insured, n (%)</td>
<td>5203 (61.2)</td>
<td>6057 (58.0)</td>
<td>539 (55.9)</td>
</tr>
<tr>
<td>Framingham risk score (10-year), mean % (SD)</td>
<td>10.5 (6.9)</td>
<td>14.7 (8.8)</td>
<td>12.9 (7.9)</td>
</tr>
<tr>
<td>Systolic blood pressure*, mm Hg, mean (SD)</td>
<td>161 (23.6)</td>
<td>– –</td>
<td>166 (23.6)</td>
</tr>
<tr>
<td>Diastolic blood pressure*, mm Hg, mean (SD)</td>
<td>93 (12.3)</td>
<td>– –</td>
<td>97 (12.2)</td>
</tr>
<tr>
<td>Grade 1 (140-159/90-99 mm Hg), n (%)</td>
<td>1370 (16.1)</td>
<td>– –</td>
<td>144 (14.9)</td>
</tr>
<tr>
<td>Grade 2 (160-179/100-109 mm Hg, n (%)</td>
<td>2630 (31.0)</td>
<td>– –</td>
<td>334 (34.6)</td>
</tr>
<tr>
<td>Grade 3 (≥180/≥110 mm Hg), n (%)</td>
<td>1600 (18.8)</td>
<td>– –</td>
<td>248 (25.7)</td>
</tr>
<tr>
<td>Missing, n (%)</td>
<td>2895 (34.1)</td>
<td>– –</td>
<td>238 (24.7)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L, mean (SD)</td>
<td>– –</td>
<td>6.2 (1.4)</td>
<td>6.3 (1.0)</td>
</tr>
<tr>
<td>Hypercholesterolaemia, n (%)</td>
<td>2004 (23.6)</td>
<td>– –</td>
<td>– –</td>
</tr>
<tr>
<td>Hypertension†, n (%)</td>
<td>– –</td>
<td>4799 (45.9)</td>
<td>– –</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>2064 (24.3)</td>
<td>2795 (26.7)</td>
<td>289 (30.0)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>701 (8.3)</td>
<td>1158 (11.1)</td>
<td>56 (5.8)</td>
</tr>
<tr>
<td>Any cardiovascular disease, n (%)</td>
<td>1220 (14.4)</td>
<td>1610 (15.4)</td>
<td>231 (24.0)</td>
</tr>
<tr>
<td>Myocardial infarction, n (%)</td>
<td>241 (2.8)</td>
<td>318 (3.0)</td>
<td>76 (7.9)</td>
</tr>
<tr>
<td>Angina, n (%)</td>
<td>627 (7.4)</td>
<td>780 (7.5)</td>
<td>131 (13.6)</td>
</tr>
<tr>
<td>Other ischaemic disease, n (%)</td>
<td>73 (0.9)</td>
<td>127 (1.2)</td>
<td>11 (1.1)</td>
</tr>
<tr>
<td>Peripheral arterial disease, n (%)</td>
<td>183 (2.2)</td>
<td>281 (2.7)</td>
<td>13 (1.3)</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>277 (3.3)</td>
<td>400 (3.8)</td>
<td>34 (3.5)</td>
</tr>
<tr>
<td>Target organ damage, n (%)</td>
<td>111 (1.3)</td>
<td>78 (0.7)</td>
<td>14 (1.5)</td>
</tr>
<tr>
<td>Familial history of cardiovascular disease, n (%)</td>
<td>125 (1.5)</td>
<td>216 (2.1)</td>
<td>14 (1.5)</td>
</tr>
</tbody>
</table>

*Based on measurements taken on or before the index date. †Hypertension defined as blood pressure >160/95 mm Hg, SD, standard deviation.
| Table 4. Treatment and monitoring rates in patients with newly identified (A) hypertension, (B) hypercholesterolaemia, and (C) concomitant hypertension and hypercholesterolaemia |
|---------------------------------------------|-----------------|-----------------|-----------------|
| **A Newly identified hypertension (N = 8,495)** |
| Eligible for antihypertensive treatment*     | Treated with antihypertensive medication† | Blood pressure monitored§ | p  |
| All hypertensive patients                    | 90.9% (7719/8495) | 71.3% (3732/5228) | 64.8% (2361/3646) |
| with existing hypercholesterolaemia          | –                | 75.6% (958/1267) | 63.2% (595/941) |
| without existing hypercholesterolaemia       | –                | 70.0% (2774/3961) | 65.3% (1766/2705) |
| **B Newly identified hypercholesterolaemia (N = 10,451)** |
| Eligible for lipid-lowering treatment*       | Treated with lipid-lowering medication† | Cholesterol monitored§ | p  |
| All hypercholesterolaemic patients           | 15.1% (1580/10,451) | 56.9% (590/1036) | 27.6% (158/572) |
| with existing hypertension                   | –                | 62.7% (421/671) | 25.9% (107/413) |
| without existing hypertension                | –                | 46.3% (169/365) | 32.1% (51/159) |
| **C Newly identified concomitant hypertension and hypercholesterolaemia (N = 964)** |
| Eligible for antihypertensive and lipid-lowering treatment* | Treated with antihypertensive and lipid-lowering medications† | Blood pressure and cholesterol monitored§ | 16.7% (18/108) |
| All patients with concomitant hypertension and hypercholesterolaemia | 24.3% (234/964) | 72.1% (111/154) | 16.7% (18/108) |

*Treatment eligibility is based on the 1999 guidelines. The denominator is the number of patients identified with these conditions based on the definitions used in the 1999 hypertension and cholesterol guidelines. The treatment rate is calculated as the percentage of treatment-eligible patients (with >1 year of follow-up data from diagnosis) who had a record of treatment within 1 year of diagnosis. The monitoring rate is calculated as the percentage of treated patients (with >1 year of follow-up data from treatment initiation) who had a record of at least 1 measurement during the first year of treatment. Hypertension and hypercholesterolaemia were identified within 30 days of each other.
Management of Hypertension & Hypercholesterolaemia

References


Differences between statins on clinical endpoints. A population based cohort study.

Jeanne P Dieleman, Jacobus T van Wyk, Marc AM van Wijk, Gé van Herpen, Sabine MJM Straus, Hans Dunselman, Miriam CJM Sturkenboom

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Current Medical Research Opinion. 2005 Sep;21(9):1461-8.
Abstract

**Background:** Many studies have shown differences between statins based on surrogate endpoints, but few studied differences in reaching clinical endpoints.

**Objective:** We compared the risk of cardiovascular and cerebrovascular events between atorvastatin users and other statin users in daily general practice.

**Research design and methods:** We performed a cohort study in the Integrated Primary Care Information project database, a longitudinal general practice research database with electronic patient records of more than 500,000 individuals in the Netherlands. All new statin users in the period 1 September 1999 to 31 December 2002 were included. Multivariate Cox-regression analysis was used to compare the occurrence of the primary endpoint between atorvastatin users and other statin users.

**Main outcome measures:** The primary endpoint was the composite outcome of fatal or non-fatal myocardial infarction, admission for unstable angina pectoris, fatal or non-fatal cerebrovascular accidents, or transient ischemic events.

**Results:** 3499 new statin users were identified, including 797 patients with a history of cardiovascular disease. 1341 persons started with simvastatin (38%), 1154 with atorvastatin (33%), 811 with pravastatin (23%) and 193 with other statins (6%). The median follow-up was 1.9 years. Two hundred thirty three patients (6.7%) experienced a primary endpoint. Atorvastatin users had a significantly lower risk of cardiovascular and cerebrovascular events than users of other statins (RR: 0.70, 95%CI: 0.55-0.96). The relative risks of atorvastatin users compared to simvastatin and pravastatin users individually were 0.70 (95%CI: 0.48-1.02) and 0.78 (95%CI: 0.52-1.16), respectively. The protective effect of atorvastatin was more pronounced in persons without a history of cardiovascular or cerebrovascular events.

**Conclusion:** Atorvastatin showed a more favorable effect on fatal and non-fatal cardiovascular and cerebrovascular events in the general population than other statins.
Introduction

Cardiovascular disease (CVD) due to atherosclerosis is a leading cause of death in western countries. Treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) has been widely accepted and implemented in most guidelines for patients with CVD and for primary prevention in patients at increased risk of CVD. Statins exert their action by lowering the concentration of low-density lipoprotein cholesterol (LDL-C), an important modifiable risk factor for CVD. In addition, statins have a beneficial effect on the inflammatory process believed to be involved in atherosclerotic plaque formation. Large scale randomized clinical trials have shown clinical benefit of statins in the treatment and prevention of CVD. Recently, an observational study in the United Kingdom showed that the beneficial effect of statins can be extended to all patients with coronary heart disease.

Although all available statins have demonstrated efficacy, differences between individual statins exist. Rosuvastatin has been reported as being more efficacious than other statins in improving lipid profiles. The anti-inflammatory effects of atorvastatin have been reported as more potent than that of other statins. In addition, the anti-oxidant properties of atorvastatin have been studied, and benefits attributed to the existence of active metabolites. Whereas achieving lipid-lowering goals by different statins has been studied well, the ability of different statins to actually reduce the CVD risk in daily practice has not been addressed to date. In the present study we compared atorvastatin with other statins on clinical endpoints in a primary care setting.

Patients and Methods

Setting

The study was conducted in the Integrated Primary Care Information (IPCI) project database, a longitudinal general practice research database in the Netherlands. All residents in the Netherlands are registered with a general practitioner (GP) independent of their health status. The GP deals with 90% of the health problems and acts as the gatekeeper for access to...
specialized care. The IPCI project was started by the Department of Medical Informatics of the Erasmus MC, University Medical Centre Rotterdam in the Netherlands. The database contains longitudinal data from computer-based patient records of more than 150 GPs throughout the Netherlands. Presently the database comprises data on more than 500,000 subjects (3% of the Dutch population), the age and gender distribution of whom is similar to the Dutch population. Available data include anonymous eligibility and demographic information (age, sex, patient identification, GP registration information), symptoms, diagnoses, specialist findings, hospital admissions, prescriptions, indications for therapy, physical findings and laboratory findings. The International Classification of Primary Care (ICPC) is the coding system used to register patient complaints and diagnoses, although diagnoses and complaints can also be entered as free text. Prescription data include product name, quantity dispensed, dosage regimens, strength and indication. The National Database of drugs, maintained by the Royal Dutch Association for the Advancement of Pharmacy (KNMP), enables the coding of prescriptions according to the Anatomical Therapeutic Chemical (ATC) classification scheme recommended by the World Health Organisation (WHO). The IPCI database system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research.

**Study population**

The source population for this study comprised all subjects of 18 years and older with at least one year of valid database history. A valid database history means that the patient is registered with the GP and that the GP participates in the IPCI project. The study population consisted of all subjects from the source population who started their first statin treatment during the study period (i.e. new users only). The study period for patient inclusion started on 1st September 1999, when the cholesterol guideline from the Dutch GP-society (NHG) was issued, and ended on 31st December 2002. Follow-up lasted from the first statin prescription until the occurrence of a study endpoint, 31st December 2003 or last IPCI data deliverance by the GP, whichever came first.
Statin treatment

Statin use was identified from the prescription files, which contain information on GP prescriptions and repeat prescriptions from specialists. It was classified as secondary prevention if a history of cardiovascular or cerebrovascular disease was present at baseline and as primary prevention if there was no history of cardiovascular or cerebrovascular disease. The analysis included atorvastatin, simvastatin, fluvastatin and pravastatin. Cerivastatin was included, but was withdrawn from the market during the study period. We were unable to include rosuvastatin, since there were insufficient users at the time of analysis.

Duration of treatment was calculated for each prescription as the number of prescribed units divided by the prescribed daily units. We also calculated the starting dosage of statin by multiplying the prescribed daily units by the prescribed unit strength of the first prescription. The starting dose was expressed in defined daily dosage (DDD) equivalents according to the WHO criteria [ATC index with DDDs 2003, WHO Collaborating Centre for Drug Statistics Methodology, Oslo, Norway] in order to allow for comparisons between statins. As equivalence as assumed by the WHO not necessarily indicates equal potency, we additionally categorized the starting dose according to a recently published potency conversion table adapted from Maron and Ilbingworth based on the cholesterol lowering properties of different statins given at a certain dose 30-32. For example, this table considers 10 mg atorvastatin, 20 mg simvastatin, 40 mg pravastatin, 80 mg fluvastatin and 0.4 mg cerivastatin as equipotent at a high potency (27% reduction in total cholesterol).

In order to take account of the potential influence of differences in the course of treatment, we assessed treatment discontinuation and switching behavior. Discontinuation of statin treatment was defined as the absence of a new prescription for at least 6 months after the end of the last prescription. Switching was defined as the prescription of another type of statin within 6 months of the end of the last prescription. We estimated adherence to statin treatment per individual statin as the number of days in a year that statins were prescribed for, divided by the number of days of follow-up in that year, censored for treatment discontinuation and switching.
**Study endpoints**

As primary outcome of our study we considered a composite of cardiovascular and cerebrovascular outcomes comprising fatal and non-fatal myocardial infarction, acute hospital admission for angina pectoris, fatal and non-fatal cerebrovascular accidents and transient ischemic attack. As a secondary outcome measure we looked at cardiovascular events only, thereby ignoring cerebrovascular accidents. All diagnoses occurring in the database, either as free text or as ICPC code were considered and reviewed in the patient records by two medically qualified investigators who were blinded for relevant exposure. In addition, we described the cholesterol lowering effect of statins as the maximal reduction in cholesterol/HDL ratio within 6 months after starting statin treatment for patients with an elevated ratio at baseline (ie. cholesterol/HDL >5).

**Co-variates**

Apart from statin use we considered other potential risk factors for cardiovascular and cerebrovascular events, such as age, gender, health care insurance, history of cardiovascular and cerebrovascular disease, presence of diabetes mellitus, hypertension or antihypertensive treatment, cholesterol/HDL ratio, smoking and Framingham risk score. Where missing in subjects treated for primary prevention we imputed average population values of the cholesterol/HDL ratio for calculation of the Framingham risk score.

**Analysis**

Baseline differences between statin users were tested by using a Pearson’s Chi-square for categorical variables, T-test for continuous normally distributed variables and Mann-Whitney U for continuous skewed variables. The difference in risk of cardiovascular and cerebrovascular events between statins was analyzed by using univariate and multi-variate Cox-regression analysis. Since the median follow-up time was 1.9 years, we censored the analysis at 2 years. In the analysis we compared atorvastatin, being the statin with the highest LDL-C reducing potency, to other statins individually and as one reference group. Multivariate or adjusted analysis included all co-variates that were associated with the primary endpoint at a p-value
of 0.1 and all other known risk factors for the study outcome. Since total cholesterol and HDL measurements are rarely performed in daily practice, we used missing indicators for missing cholesterol/HDL ratios in the analyses. In the Cox-model, exposure to statin treatment was principally considered as intention-to-treat, thereby ignoring treatment discontinuations and switches. To evaluate the influence of treatment discontinuation and switching we also performed an as-treated-analysis in which follow-up was additionally censored upon discontinuation or switching. In an exploratory analysis we also compared the effect of statins between persons treated for primary prevention and persons treated for secondary prevention and performed a sensitivity analysis with cardiovascular events as the only study endpoint.

Statistical significance was accepted at a two-sided p-value of <0.05. All statistical analyses were performed in SPSS version 10.0.

Results

Patient population

Between September 1999 and December 2002, 3499 persons started treatment with a statin, 1341 on simvastatin (38%), 1154 on atorvastatin (33%), 811 on pravastatin (23%) and 193 on other statins (6%). Patient characteristics are summarized in table 1. In brief, 43% were female, the mean age was 60.6 (SD 11.6) years, and 22.8% had a prior history of cardiovascular or cerebrovascular events. Cholesterol/HDL ratios were available for 569 (16%) patients. The median ratio was 5.0 (inter quartile range [IQR]: 3.9-6.3) and accordingly 280 (49%) patients had a ratio above 5.0. With respect to relevant patient characteristics the following differences were found between users of various statins. There were more females among fluvastatin users and more males among cerivastatin users than among atorvastatin users. Pravastatin users were slightly older, more often had a history of cardiovascular or cerebrovascular disease and more often had cholesterol/HDL levels above 5. There were more smokers among simvastatin users. Fluvastatin and cerivastatin were given at relatively lower dosages. Overall, the potency of the prescribed atorvastatin regimens was higher than that of other statins (Table 1).

Patients contributed a total of 6862 years of follow-up with a median duration of 1.9 years
Differences between Statins

(IQR: 1.2-2.7).

**Statin treatment**

The total number of treatment days on statins during the first year of follow-up accumulated to 1469 years with a median of 160 days per patient (IQR: 90-215). Forty-six percent of patients did not persist with the initial treatment during the study period, mainly due to discontinuation (82.5%). The rate of non-persistence with atorvastatin was lower than with fluvastatin (p=0.001) and cerivastatin (p<0.001) but similar to simvastatin and pravastatin. It should however be noted that cerivastatin was withdrawn from the market during the study period.

Overall adherence with statin use was low but was similar for all statins. The median adherence was 55.7% (IQR: 35.3-72.9), which means that patients had statins available for 55.7% of the follow-up time based on prescription refills issued until treatment discontinuation, switch or the end of follow-up. The median daily dosage used at treatment initiation was 10 mg for atorvastatin, 20 mg for simvastatin, and 40 mg for pravastatin, corresponding to more than 1 DDD of simvastatin and pravastatin (Table 1).

**Study endpoints**

During follow-up 233 patients experienced a cardiovascular or cerebrovascular event, 102 (43.8%) of whom following a history of cardiovascular or cerebrovascular disease. Events comprised non-fatal myocardial infarction (n=75), fatal myocardial infarction (n=20), hospital admission for instable angina pectoris (n=56), non-fatal cerebrovascular accident (n=35), fatal cerebrovascular accident (n=3) and transient ischemic attack (n=44). Atorvastatin users had the lowest one-year risk of cardiovascular and cerebrovascular events (hazard rate 3.10 per 100 persons, 95%CI: 2.08-4.12) and fluvastatin users had the highest risk (Figure 1). The two-year risks were 5.24 (95%CI: 3.82-6.65) for atorvastatin, 6.69 (95%CI: 5.22-8.16) for simvastatin, 7.59 (95%CI: 4.26-10.92) for pravastatin, 10.35 (95%CI: 4.25-16.45) for fluvastatin and 10.54 (95%CI: 3.54-17.54) for cerivastatin.

Risk factors for cardiovascular and cerebrovascular events in our study population included age, gender, history of cardiovascular disease and cholesterol/HDL ratio above 5 (Table 2).
Including these in the multivariate analysis together with other known risk factors (smoking, diabetes, hypertension and number of defined daily doses) resulted in an adjusted RR of 0.70 (95%CI: 0.55-0.96) for atorvastatin compared to other statins together (Table 3). Comparing atorvastatin to each individual statin separately showed a statistically non-significant lower risk of cardiovascular and cerebrovascular events than pravastatin (RR: 0.78, 95%CI: 0.52-1.16) and simvastatin (RR: 0.70, 95%CI: 0.48-1.02) and a statistically significant lower risk than fluvastatin (RR: 0.38, 95%CI: 0.19-0.76) and cerivastatin (RR: 0.41, 95%CI: 0.20-0.88).

In the as-treated analysis, in which we additionally censored upon treatment switch or discontinuation, the protective effect of atorvastatin relative to other statins remained the same (RR: 0.70, 95%CI: 0.50-0.97). Stratification for primary or secondary prevention showed a more favorable effect of atorvastatin in the group treated for primary prevention (RR: 0.61, 95%CI: 0.39-0.97 n=2702) than in those treated for secondary prevention (RR: 0.82, 95%CI: 0.51-1.30; n=797) but the effect-modification was not statistically significant. Restricting the outcome to cardiovascular events lowered the RR estimate slightly (atorvastatin versus other statins adjusted RR: 0.65, 95%CI: 0.43-0.97).

Out of 280 patients with a baseline cholesterol/HDL ratio above 5, only 78 (28%) had a repeat measurement within 6 months. Cholesterol/HDL ratio reduction to below 5 was achieved in 54% of atorvastatin users, 55% of simvastatin users, 46% of pravastatin users, 40% of fluvastatin users and 33% of cerivastatin users (p=0.904).

**Discussion**

The results of this observational population based cohort study suggest that atorvastatin is associated with a lower risk of cardiovascular and cerebrovascular events than other statins under uncontrolled everyday circumstances of a primary care setting. This finding was not influenced by known risk factors for cardiovascular and cerebrovascular disease such as age, gender, diabetes, smoking and a prior history of cardiovascular or cerebrovascular disease and remained in an as-treated analysis. The difference seemed most pronounced in subjects who were treated for primary prevention and was greatest compared to fluvastatin. A 30% statisti-
Differences between Statins

cally non-significant risk lower risk was observed with atorvastatin compared to simvastatin and pravastatin. Restriction of the outcome to cardiovascular events increased the observed differences.

In contrast to the controlled conditions and well defined populations in the clinical trial setting, which repeatedly demonstrated the beneficial effects of statins, our data were derived from a primary care setting under every day circumstances. Only one earlier study reported the effect of statins in such a setting. They concluded that the beneficial effect observed in clinical trials is also observed in the primary care setting. Our data further suggest a difference between individual statins.

The short-term preventive effect of atorvastatin appears to be substantial as shown in our study and is in keeping with other studies. It is unknown whether the reported anti-oxidant and anti-inflammatory properties of atorvastatin can explain the observed early reduction in cardiovascular events. It would support the dynamic model of atheroma plaque formation and ruptures, which suggests that anti-inflammatory treatment can produce immediate vascular wall protection. On the other hand, differences in cholesterol lowering properties between statins may account for the observed differences in clinical effect. Our data showed acceptable cholesterol/HDL ratio reductions in approximately half the population with elevated ratios at baseline. There were no significant differences between statins. However, we cannot draw any firm conclusions from this observation since cholesterol measurements were very infrequent and our study was not powered to examine small differences.

This observational cohort study using data from a primary care setting may have important limitations. Although there is no reason to believe from current data that statins are prescribed differentially between persons with different cardiovascular risk profiles, we cannot completely exclude the presence of confounding by indication. However, the distribution of baseline characteristics and known risk factors did not point at a consistently different patient type among the statins. Nevertheless, since atorvastatin is supposed to have unique cardiovascular benefits in addition to its LDL lowering potency it could theoretically be prescribed to persons with a higher risk. Hence confounding by indication, if any, would work in the opposite
direction of our findings. Misclassification of exposure and of exposure duration is of no major concern in the intention-to-treat analysis. Misclassification of outcome may have occurred in terms of omitting events in the GP record. Such misclassification is unlikely to be differential between different statins, since review of potential cases was blinded for the exposure under study and the research question, and data in the IPCI database are collected for health care purposes independently of any research question studied in the database.

Finally, it may seem odd that some known risk factors for cardiovascular and cerebrovascular events, such as diabetes and hypertension, did not appear as a risk factor in our analysis. It should however be noted that we investigated a sample from the general population already treated with statins by the GP. The risk profile of such a population is not comparable with the risk profile of an untreated population. All our patients have risk factors for cardiovascular disease for which reason they received statin treatment.

**Conclusions**

In conclusion, this study suggested a favorable effect of atorvastatin compared to other statins in the prevention of fatal and non-fatal cardiovascular and cerebrovascular events in the general population. The risk reduction was observed across all statins, but only reached statistical significance if compared to all statins together and to fluvastatin and cerivastatin individually. The observed effect was most pronounced in primary prevention and mostly driven by the prevention of cardiovascular events.
Table 1 Baseline characteristics of patients starting statin treatment according to type of statin

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin (n=1154)</th>
<th>Simvastatin (n=1341)</th>
<th>Pravastatin (n=811)</th>
<th>Fluvastatin (n=102)</th>
<th>Cerivastatin (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>41.9</td>
<td>44.7</td>
<td>41.4</td>
<td>54.9*</td>
<td>30.8*</td>
</tr>
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<td>58.1</td>
<td>55.3</td>
<td>58.6</td>
<td>45.1*</td>
<td>69.2*</td>
</tr>
<tr>
<td><strong>Age (years, %)</strong></td>
<td></td>
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<tr>
<td>&lt;=53</td>
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<td>29.2</td>
<td>23.2*</td>
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<td>27.5</td>
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<tr>
<td>54-61</td>
<td>24.8</td>
<td>23.9</td>
<td>24.2*</td>
<td>26.5</td>
<td>25.3</td>
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<td>62-69</td>
<td>24.2</td>
<td>22.7</td>
<td>23.8*</td>
<td>28.4</td>
<td>22.0</td>
</tr>
<tr>
<td>&gt;=70</td>
<td>22.5</td>
<td>24.2</td>
<td>28.9*</td>
<td>27.5</td>
<td>25.3</td>
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<td><strong>Known risk factors (%)</strong></td>
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<tr>
<td>Diabetes</td>
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<td>25.9</td>
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<td>18.7</td>
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<td>32.4</td>
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<td>30.5*</td>
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<td>16.5</td>
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<td>Cholesterol/HDL &gt;5 (real values only, n=569)</td>
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<tr>
<td>Median values [IQR]</td>
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<td>5.9 [4.2-7.0]*</td>
<td>5.8 [4.4-7.0]</td>
<td>4.3 [3.3-5.2]*</td>
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<td>Median dose [IQR] (n=3475)</td>
<td></td>
<td></td>
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<td>Ddd</td>
<td>1.0 [1.0-2.0]</td>
<td>1.3 [1.3-1.3]</td>
<td>2.0 [1.0-2.0]*</td>
<td>1.0 [0.5-1.0]*</td>
<td>1.0 [1.0-1.8]*</td>
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<tr>
<td>Mg</td>
<td>10 [10-20]</td>
<td>20 [20-40]</td>
<td>40 [20-40]</td>
<td>40 [20-40]</td>
<td>0.2 [0.2-0.4]</td>
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<tr>
<td><strong>Potency* (n=3455)</strong></td>
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<tr>
<td>2: Low</td>
<td>0.0</td>
<td>0.0*</td>
<td>6.7*</td>
<td>27.7*</td>
<td>10.5*</td>
</tr>
<tr>
<td>3: Medium</td>
<td>0.0</td>
<td>16.9*</td>
<td>25.3*</td>
<td>54.5*</td>
<td>63.2*</td>
</tr>
<tr>
<td>4: High</td>
<td>53.3</td>
<td>72.1*</td>
<td>66.6*</td>
<td>17.8*</td>
<td>26.3*</td>
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<td>5</td>
<td>37.4</td>
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<td>1.4*</td>
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<td>6</td>
<td>8.7</td>
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<tr>
<td>7</td>
<td>0.6</td>
<td>0.0*</td>
<td>0.0*</td>
<td>0.0*</td>
<td>0.0*</td>
</tr>
</tbody>
</table>

Bold print represents statistically significant difference with atorvastatin: \*p=0.01 to 0.05; \*p=0.005; \*p=0.001; IQR = Inter Quartile Range; CVD = cardiovascular or cerebrovascular disease; DDD = defined daily dose; \*according to Goettsch et al.³⁰
### Table 2  Risk factors for cardiovascular and cerebrovascular events

<table>
<thead>
<tr>
<th></th>
<th>RR*</th>
<th>95%CI</th>
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</thead>
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<td><strong>Sex</strong></td>
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<td>Female</td>
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<td>Reference</td>
</tr>
<tr>
<td>Male</td>
<td>1.29</td>
<td>[0.96-1.72]</td>
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<tr>
<td><strong>Age (years)</strong></td>
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<td></td>
</tr>
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<td>&lt;=53</td>
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<td>Reference</td>
</tr>
<tr>
<td>54-61</td>
<td>1.02</td>
<td>[0.65-1.59]</td>
</tr>
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<td>62-69</td>
<td>1.40</td>
<td>[0.92-2.11]</td>
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<tr>
<td>&gt;=70</td>
<td>1.87</td>
<td>[1.26-2.74]</td>
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<tr>
<td><strong>Known risk factors</strong></td>
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</tr>
<tr>
<td>Diabetes</td>
<td>0.93</td>
<td>[0.66-1.30]</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.26</td>
<td>[0.94-1.68]</td>
</tr>
<tr>
<td>Hypertensive treatment</td>
<td>0.91</td>
<td>[0.43-1.93]</td>
</tr>
<tr>
<td>history of CVD</td>
<td>3.04</td>
<td>[2.29-4.01]</td>
</tr>
<tr>
<td>Cholesterol/HDL &gt;5#</td>
<td>1.8</td>
<td>[0.68-4.52]</td>
</tr>
<tr>
<td>Smoker</td>
<td>1.02</td>
<td>[0.75-1.37]</td>
</tr>
<tr>
<td>Framingham risk score (per unit increase)</td>
<td>1.03</td>
<td>[1.01-1.05]</td>
</tr>
</tbody>
</table>

* Univariate Cox regression analysis; # based on real values (n=569)

CVD = cardiovascular or cerebrovascular disease
### Table 3. Association between statin use and the risk of cardiovascular and cerebrovascular events

<table>
<thead>
<tr>
<th>Type of statin</th>
<th># Events within 2 years</th>
<th>Crude analysis</th>
<th>Adjusted analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95%CI</td>
<td>RR</td>
</tr>
<tr>
<td><strong>Atorvastatin versus other statins</strong> (n=3475)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 DDD</td>
<td>17</td>
<td>0.81 [0.47-1.36]</td>
<td>0.70</td>
</tr>
<tr>
<td>1-1.99 DDD</td>
<td>99</td>
<td>0.82 [0.61-1.10]</td>
<td>0.70</td>
</tr>
<tr>
<td>&gt;=2 DDD</td>
<td>79</td>
<td>1 reference</td>
<td>0.70</td>
</tr>
<tr>
<td>Potency (n=3455)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>6</td>
<td>1.11 [0.47-2.62]</td>
<td>0.61</td>
</tr>
<tr>
<td>Medium</td>
<td>35</td>
<td>1.13 [0.72-1.78]</td>
<td>0.61</td>
</tr>
<tr>
<td>High</td>
<td>113</td>
<td>0.91 [0.63-1.30]</td>
<td>0.61</td>
</tr>
<tr>
<td>Highest groups</td>
<td>39</td>
<td>1 reference</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>Primary prevention (n=2702)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin versus other statins</td>
<td>27</td>
<td>0.62 [0.40-0.96]</td>
<td>0.61</td>
</tr>
<tr>
<td><strong>Secondary prevention (n=797)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin versus other statins</td>
<td>25</td>
<td>0.92 [0.58-1.47]</td>
<td>0.82</td>
</tr>
<tr>
<td><strong>Atorvastatin versus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>76</td>
<td>0.78 [0.55-1.11]</td>
<td>0.70</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>51</td>
<td>0.65 [0.44-0.96]</td>
<td>0.78</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>10</td>
<td>0.45 [0.23-0.88]</td>
<td>0.38</td>
</tr>
<tr>
<td>Cerivastatin**</td>
<td>8</td>
<td>0.51 [0.24-1.08]</td>
<td>0.41</td>
</tr>
</tbody>
</table>

* Cox regression analysis adjusted for type of statin, gender, smoking, diabetes, hypertension, history of cardiovascular or cerebrovascular disease, daily dose and cholesterol/HDL ratio above 5 (real values and missing indicator used)

DDD = defined daily dose

** Cerivastatin was withdrawn from the market during the study period
Figure 1. Kaplan Meier diagram of survival until fatal or non-fatal cardiovascular or cerebrovascular events within two years after starting statin treatment (A = atorvastatin; S = simvastatin; P = pravastatin; C = cerivastatin; F = fluvastatin)
Differences between Statins

References


3. Castelli WP. Cholesterol and lipids in the risk of coronary artery disease—the Framingham Heart Study. Can J Cardiol 1986;4 Suppl A:5A-10A.


17. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a


Differences between Statins


CholGate – An integrated clinical decision support system for primary and secondary prevention in cardiovascular disease

Jacobus T. van Wyk; Marc A. M. van Wijk; Mees Mosseveld; Peter W. Moorman; Johan van der Lei
Abstract

Cardiovascular disease (CVD) is the leading cause of mortality in industrialized countries. Researchers report low primary and secondary prevention performance of physicians: they only seem to monitor and treat conditions in isolation (like hypertension or diabetes mellitus) without translating the measurements of single conditions to overall cardiovascular risk management. To improve both primary and secondary prevention of CVD, we developed the decision support system CholGate, based on the guidelines of the Dutch College of General Practitioners. Taking advantage of the use of electronic health records (EHR) by Dutch general practitioners, CholGate is integrated within the EHR to provide decision support in the clinician’s workflow. We discuss the underlying knowledge base of the system. Secondly, we highlight issues in gathering relevant patient data to identify patients at risk. Thirdly, we discuss the system’s user interface and workflow impact, and, finally, we focus on special considerations in implementing the system.
Introduction

Cardiovascular disease (CVD) is the leading cause of mortality in industrialized countries \(^1\). Modifiable risk factors for developing CVD include smoking, diabetes mellitus, hypertension, and abnormal blood lipids. Evidence exists that managing these modifiable risk factors in primary care plays an important role in decreasing the morbidity and mortality due to CVD \(^2,3\). Identifying and managing the modifiable risk factors for CVD before the onset of CVD, so-called *primary prevention*, is becoming more important in primary care \(^4\). However, getting this evidence into practice is a major challenge. To deal with the rapidly expanding amount of medical knowledge, guidelines are increasingly viewed as a mechanism for distributing knowledge to practitioners \(^5,6\).

A number of studies have shown that the availability of guidelines does not necessarily lead to the use of these guidelines by physicians. Even when authoritative guidelines are available, changing the behaviour of physicians has proved to be difficult \(^7,8\). In daily practice, for example, Dutch general practitioners (GPs) seem to start performing preventative activities after being confronted with a trigger event, so-called *secondary prevention*, although well defined guidelines for primary prevention are available \(^9\). Physicians only seem to monitor and treat conditions in isolation (like hypertension or diabetes mellitus) without translating the measurements of that individual condition to an overall cardiovascular risk profile management \(^10\).

An effective strategy for guideline implementation is integrating guideline based clinical decision support systems (CDSS) into the electronic health record (EHR) \(^11,12\). The objective of these systems is to help the physicians in making guideline-based decisions at the point of care.

To improve both primary and secondary prevention of CVD, we developed the CDSS CholGate, based on the guidelines of the Dutch College of General Practitioners (DCGP). We firstly discuss the underlying knowledge base of the system. Secondly, we highlight issues in gathering relevant patient data to identify patients at risk. Thirdly, we discuss the system’s user interface and impact on workflow, and finally, we focus on special considerations in implementing the system.
Designing and implementing the system

The knowledge base

In the Netherlands, the DCGP develop evidence-based guidelines for the primary care domain; these guidelines generally have a high acceptance rate among GPs\(^\text{13}\). We used the six DCGP practice guidelines that deal with CVD risk factor management to construct the system’s knowledge base\(^\text{14}\). These guidelines centre on two main decision points for CVD risk factor management in primary care: Identifying patients who need to be screened and identifying screened patients who need to be treated.

Identifying patients who need to be screened

The Dutch guidelines emphasize the need to screen specific, well-defined populations. As a result, the guidelines contain detailed, sometimes complex descriptions of the various conditions that should lead to screening a patient\(^\text{9}\). For example, a 45 year old male who smokes, has diabetes mellitus, and hypertension should be screened. If that same patient does not smoke, however, the guideline recommends abstaining from screening.

When a patient is identified as eligible for screening, the guidelines recommend specific actions. These actions, however, depend on the patient’s current risks. For example, a patient with diabetes mellitus needs measurement of blood pressure, cholesterol/HDL ratio, and smoking habits. However, a patient younger than 50 who smokes and has no other risk factors for CVD needs no additional measurements. Once a patient is screened, the guidelines suggest various treatment options.

Identifying patients to be treated

The guidelines distinguish between primary and secondary treatment decisions. The DCGP guidelines require calculation of a risk score for every patient who needs primary prevention. This risk score is based on the Framingham risk function for CVD\(^\text{15}\). In the current paper-based guidelines, the score is deduced from a series of tables stratified by age, gender, diabetes mellitus, systolic blood pressure, smoking, and cholesterol/HDL cholesterol ratio. For every age
group a threshold Framingham score exists where treatment is recommended. Different colours in the tables are used to aid the physician: green meaning no treatment, orange meaning treatment is needed if there is a family history of coronary heart disease before the age of 60, and red indicating treatment.

In secondary prevention, the treatment decision is more straightforward. Any patient with CVD attributed to atherosclerosis and with a serum cholesterol level greater than 5mmol/l (193 mg/dL) should be treated with statins.

Finally, any patient with an abnormally high serum lipid value (Cholesterol > 9 mmol/l or Cholesterol/HDL ratio > 8mmol/l or Triglyceride >4mmol/l) should be referred to a specialist.

**Information retrieval**

CholGate retrieves and interprets data (e.g. diagnoses, risk factors, or laboratory measurements) from the electronic health record (EHR). This task of retrieving and interpreting data, however, is non-trivial: The CDSS is dependent on the way the physician has entered the data in the EHR. Information retrieval is facilitated when the physician enters data according to national or international classification systems. Physicians, however, enter data not only according to international standards but also in self-defined codes or free text. We distinguish, therefore, three categories of data the CDSS has to deal with. Firstly, **coded data** relies on widely used coding schemes to record data. In our system, this consists of the International Classification for Primary Care (ICPC) for coding diagnoses and the Anatomical Therapeutical Classification (ATC) for coding medication. Secondly, **structured data** relies on locally defined coding schemes (that is, each individual practice has their own coding scheme). In our system, this involved identifying on the level of an individual practise the codes used for specific conditions or measurements (e.g. constructing a local conversion table for laboratory measurements). Thirdly, **free text data** consists of data recorded in free text. In our system, we rely on the behaviour of physicians who, in busy daily practice, often use repetitive free text in their medical narrative. Using this principle of recurring free text, we construct for individual users specific profiles containing the free text entries specific to that user. For example, a user might use “smoking +” in the record, indicating smoking where another user might use “smoker”.
Coded data are similar across different practices. The use of structured data, however, requires the system to be tuned to each individual practice. Furthermore, the use of free text data requires the system to be tuned to an individual practitioner in that practice.

The system will use the available data to assess the patient’s condition. In this process, the system may infer certain conditions to be present in the light of the guidelines, while the physician has not (yet) recoded that entity. For example, when an average of consecutive blood pressure measurements in six months is higher than 140/90 mmHg, the system assigns the label hypertension the patient, while the physician has not (yet) recorded that diagnosis. Similarly, diabetes mellitus is inferred if insulin prescriptions are issued. As shown in Figure 1 for hypertension, the distinction between the data directly retrieved from the EHR and the data inferred based on the available data in the EHR is always explicitly displayed in the user interface.

**CholGate user interface and system integration**

The CholGate system is integrated within two widely used EHRs in the Netherlands: Elias (Isoft BV) and HetHis (Microbias BV). The general practitioners use these systems during consultation. Data are entered in the record by the physicians themselves during the patient contact. Because CholGate is tightly integrated with these EHRs, the system is easily accessible by the physician. The user interface of the CDSS is identical to the user interface of the host system – as a result, navigation and use of the system are already familiar to the user (e.g., entering data, selecting functions, finding help text etc.)

The essence of the system is to continually update the patient specific CVD risk profiles and recommend appropriate actions. To achieve this, the system continually retrieves key variables and displays them. The physician can change existing variables or add new data; these changes are subsequently included in the EHR. If the recommendation is an order (e.g. laboratory test) the system initiates that order (e.g by creating appropriate patient specific lab form to print). Any the change in the available results in an updated risk profile.

CholGate supports two methods of interfacing with the user. First, the user decides when decision support is needed and then activates CholGate we call this order entry method.
Alternatively, the user is alerted when advice is available on a patient, so called alerting method. In alerting method, the system does not require the physician’s decision to activate the system but alerts the physician when screening or treatment is needed based on the data in the medical record. The method of interaction with the user is independent of the content of the knowledge base; that is, in both methods, the system relies on exactly the same knowledge base.

**Implementation issues**

The fact that the system is tightly integrated with the EHR in a given site has consequences for the implementation of CholGate in a specific site. Whereas coded data is similar across different sites, structured data reflect local practices of that specific site, and free text data reflect the practices of individual users of the system. As a result, the system needs to be tuned to both a local practice and the recording behaviour of the individual practitioner. For coded data, we identified all relevant entries in the ICPC and ATC classification systems. Structured data is identified in each individual practise by creating a mapping of all structured data to the CholGate system (figure 2.) Free text data is identified for every specific user by querying the user what free text they use. All mapped coded data and free text data can be reviewed and changed at any time by users. The setup process takes on average 30 minutes per practice.

Slow responses of systems may have a negative impact on the effectiveness and usability of systems. After the author configures the initial conversion table, the system performs an optimization routine. This routine calculates the CVD risk profile for every patient and attaches it to the patient’s record prior to the patient encounter. In this way, we increase performance of the system by preventing delays in searching and processing information during patient contact. Additionally, CholGate pre-fetches all relevant data connected to a patient that is not directly entered by a physician. For example, blood results are automatically downloaded from the pathology laboratories and used to update the CVD risk profile for that patient.

**Discussion**

We developed the CholGate decision support system to improve primary and secondary
prevention of CVD in the setting of primary care.

For primary and secondary prevention of CVD, the DCGP developed several guidelines in the Netherlands. These guidelines aim to assist the GP in providing evidence-based care. The DCGP guidelines are viewed as authoritative and have a high acceptance rate\(^3\). However, having authoritative and well accepted guidelines available does not directly translate into compliance to guidelines. Although the guidelines stress the importance of primary prevention, Dutch GPs tend to focus on secondary prevention of CVD in spite of the availability of sufficient relevant information\(^\text{10}\). Adherence to the DCGP cholesterol guideline in primary practice is low, mainly due to the complexity of the guideline and interruption of the workflow process of the general practitioner\(^\text{19}\). The essence for developers of a CDSS, therefore, is not building or constructing a new guideline, but rather using well accepted guidelines and integrating the recommendations and goals of these guidelines into the workflow of care providers.

The first step when integrating a guideline within the workflow of a physician is to integrate the recommendations of the guideline with the data in the EHR. Implementing guidelines across different platforms (that is, different GP information systems) and across different institutions (that is, multiple practices) requires tailoring the system to these different environments. Other researchers have discussed this issue; the developers of the Arden syntax, for example, use the term "curly brackets"\(^\text{20}\) to denote the need for defining local mappings from variables in the electronic patient record to variables known to the CDSS. In the development of CholGate, we distinguish three different types of data that need to be extracted from the EHR: coded data, structured data and free text. Coded data are similar across different platforms, structured data are similar for all practitioners in one setting, and free text are specific for each individual user. The consequence of such an integrating of the CDSS with the local environment results in tailoring the system to each environment, including each individual user. The fact that time and effort are required for that integration, therefore, is a direct consequence of the need to integrate the system to the local workflow.

In addition to mapping the input data of the CDSS to the local setting, we also constructed the system taking into account several determinants that appear to be critical to the successful
introduction of CDSS in daily practice 18: providing automatic support as part of the clinician’s workflow, providing decisions at the point of care, providing recommendations rather than just assessments, and providing computerized decision support. Firstly, CholGate provides automatic decision support as part of the clinician’s workflow. When constructing the system, we had to be aware not only of the various decisions we had to support, but also on the impact our system would have on the workflow of the physician. We feel it is not appropriate to suggest an action to a physician without providing an extra incentive to follow that suggestion. For example, if the system identifies a patient who needs screening, the physician has the option to print a patient specific laboratory order form including the recommended test(s); this prevents any double actions by the physician. Secondly, CholGate provides the decisions at the time and location of decision making. In a busy daily practice, a physician generally does not stop and or change the direction of the consult to interact with a CDSS 21. Because CholGate is tightly integrated with an EHR, constantly retrieving information for specific patients and evaluating CVD risk, the system is optimized to give decision support at the time when the physician interacts with the computer regarding a specific patient. As a result, the system provides decision support when it is at its most relevant: during patient encounter. Thirdly, CholGate provides recommendations rather than just assessments. CholGate does not only provide assessments of the patient’s condition, but provides, if needed for that specific patient, the relevant action(s) that should be taken. To avoid overloading the user with recommendations (leading to the users ignoring or not using the system; a phenomenon called alert fatigue) the system only provides alerts when an action needs to be taken during this patient encounter. Additionally, once a user has seen an alert, the alert disappears for that session. The user can always ignore the alert and continue the consultation.

Kawamoto et al could not comment on system speed as a factor in influencing physician due to the paucity of studies that specifically addressed this issue. Taking into account reported failures of CDSS by slowing the physician, we optimized the system for speed as much as possible.21,22.
Limitations of the system

Tightly integrating a CDSS with many various EHR’s in the Netherlands is difficult. Therefore, the system is currently only running on two of the six available EHR platforms in Dutch primary care. At the time of writing, 60 Dutch general practices including 120 general practitioners use the system.

The fact that we chose to incorporate coded, structured, and free text data into our system, makes system deployment more complicated. A typical installation of CholGate takes 30 minutes per practice. Users have the option to change their preferences at any time or map new users to the system.

Additionally, although the principles of managing patients for prevention of CVD is the same for both primary and secondary care setting, our system is geared to the workflow of primary care. Further research will have to show whether our system is suitable for environments outside of the primary care domain.
**Figure 1.** The ChoLGate user interface in the Elias Electronic health record shows inferred data to the user, in this case hypertension (hypertensie) and the identification of a primary prevention patient who needs statin therapy (patient detail is fictional).

![CholGate user interface](image)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>14/11/2005</td>
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</tr>
<tr>
<td>RRZ</td>
<td>14/11/2005</td>
<td>170/85</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15/10/2005</td>
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</tr>
<tr>
<td>Glucose</td>
<td>14/11/2005</td>
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<td>Length</td>
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</tr>
<tr>
<td>Weight</td>
<td>15/10/2005</td>
<td>102</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>14/11/2005</td>
<td>4.1</td>
</tr>
<tr>
<td>Risk</td>
<td>Ja</td>
<td></td>
</tr>
<tr>
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<tr>
<td>Risk HVZ 10 yr</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>Risk cholesterol</td>
<td>Rood</td>
<td></td>
</tr>
</tbody>
</table>

Risico (33% CHD) --> STATINE.
Figure 2. Example of mapping practice specific coded data to the CholGate system in the HetHis electronic health record (patient detail is fictional).
References


CholGate, the effect of alerting versus on-demand computer based decision support on treatment of dyslipidaemia by general practitioners
- A randomized trial

Jacobus T van Wyk, Marc AM van Wijk, Miriam CJM Sturkenboom, Mees Mosseveld, Peter W Moorman, Johan van der Lei

Submitted
Abstract

**Background:** Indirect evidence show alerting users with clinical decision support systems (CDSS) seem to change behaviour more than requiring users to actively initiate the system. However, randomized trials comparing these methods in a clinical setting are lacking.

**Objective:** Using the CholGate CDSS we study the effect of alerting and on-demand decision support with respect to screening and treatment of dyslipidaemia.

**Intervention:** Alerting physicians with a CDSS or actively requiring initiation of CDSS.

**Design, participants, settings and analysis:** Cluster Randomized Controlled trial that included 38 general practices in the region of Delft, the Netherlands with a total of 87851 patients. Practices were randomly assigned to three groups: 13 practices to use the CDSS method that alerted practitioners (alerting arm), 14 practices to the method requiring users to actively initiate the system (on-demand arm) and 11 practices to a control arm. Patients were followed in the practice electronic health record for at least a year from June 2004 and identified as needing screening or treatment for dyslipidaemia. Multilevel regression methods were applied to account for the clustered design.

**Main outcome measures:** The percentage of correctly screened and correctly treated patients using anonymous patient record data.

**Results:** In the alerting group 65% of patients were screened (OR\textsubscript{adj} 5.17 95% CI[3.15-8.50]) compared to 35% of patients (OR\textsubscript{adj} 1.68 95%CI[1.03-2.75]) in the on-demand group, and 25% of patients in the control group. In the alerting group 65% of patients were treated (OR\textsubscript{adj} of 3.75 95% CI[2.40-5.87]) compared to 39% of patients (OR\textsubscript{adj} 1.53 95% CI[0.97-2.41]) in the on-demand group, and 36% of patients in the control group.

**Conclusion:** Both the On-demand and Alerting version of CholGate improved screening performance for dyslipidaemia. Only CholGate Alerting significantly improved treatment performance for dyslipidaemia by general practitioners.
Introduction

Computerized clinical decision support systems (CDSS) are information systems that aim to optimize physicians' clinical decision making. Investigators report beneficial effect of introducing CDSS in daily practice on physicians' performance. Several determinants appear to be critical to the successful introduction of CDSS in daily practice: providing automatic support as part of the clinician's workflow, providing decisions at the point of care, and providing recommendations rather than just assessments. In a recent systematic review, Garg et al studied the effect of CDSS on practitioner performance and patient outcomes. They concluded that studies in which users were automatically prompted (alerted) to use the system seemed to indicate better performance than studies in which users were required to actively (on-demand) initiate the system. However, this conclusion was based on comparing the results of studies conducted in different settings, using different methods, and involved heterogeneous populations. A randomized controlled trial comparing the automatic alerting method with the on-demand method on physicians' performance is lacking.

Cardiovascular disease (CVD) is the leading cause of mortality in industrialized countries. Researchers report low primary and secondary prevention performance of physicians. To improve both primary and secondary prevention of CVD, we developed the decision support system CholGate, based on recommendations for lipid management from the guidelines of the Dutch College of General Practitioners. Taking advantage of the use of electronic health records (EHR) by Dutch general practitioners, CholGate is integrated within the EHR to provide decision support as part of the clinician's workflow. We conducted a randomized trial to compare the effect of two versions of CholGate with no CDSS, on screening and treatment of dyslipidaemia among general practitioners.

We hypothesize that a CDSS will improve physicians' performance with respect to having no CDSS. In addition we hypothesize that the alerting method will have a better effect in increasing physician performance compared to a CDSS that requires manual activation.
Methods

CDSS Intervention

The CholGate system is a CDSS which aids a general practitioner in the primary and secondary prevention of CVD with regards to lipid management. The system uses three layers of data available in the EHR to provide decision support: Coded data, structured data, and free text data. Coded data relies on widely used coding schemes to record data. In the Netherlands all practices use the International Classification for Primary Care (ICPC) for coding diagnoses and the Anatomical Therapeutical Classification (ATC) for coding medication. Structured data relies on locally defined coding schemes (that is, each individual practice has their own coding scheme). For each practice we identified codes on the level of an individual practice used for specific conditions or measurements (e.g. constructing a local conversion table for laboratory measurements). Free text data consists of data recorded in free text. For each practitioner we relied on the physician’s recording habits, who, in busy daily practice, often use repetitive free text in their medical narrative. After gathering relevant data the system identifies two types of patients: those who need screening for lipid abnormalities, and secondly, those who need treatment for lipid abnormalities. The Dutch guidelines emphasize the need to screen specific, well-defined populations. As a result, the guidelines contain detailed, sometimes complex descriptions of the various conditions that should lead to screening a patient. When a patient is identified as eligible for screening, the guidelines recommend specific actions. The guidelines distinguish between primary and secondary treatment decisions. The DCGP guidelines require calculation of a risk score for every patient who needs primary prevention. This risk score is based on the Framingham risk function for CVD. In the 1999 paper-based guidelines, the physician had to deduce the score from a series of tables stratified by age, gender, diabetes mellitus, systolic blood pressure, smoking, and cholesterol/HDL cholesterol ratio. For every age group a threshold Framingham score exists where treatment is recommended. Researchers have argued that the relevant tables are complex and might be difficult to use in daily practice. In secondary prevention, the treatment decision is more straight-forward.
with CVD attributed to atherosclerosis and with a serum cholesterol level greater than 5mmol/l (193 mg/dL) should be treated with statins.

To test our hypothesis we developed two versions of the CholGate DSS; CholGate On-demand and CholGate Alerting. Both versions analyse and interpret the patient data generating patient specific recommendations for preventative activities. An overview screen presents a patient's current risk profile to the user, as well as suggesting an action on lipid management. This overview is interactive: the user can enter new diagnosis, or change measurement values and is immediately updated. All changes are registered into the patient’s record, preventing duplication of tasks. This is an example of the system supporting workflow of the practitioner as far as possible, resulting in completing various workflow tasks as well as getting decision support, also. In both versions the user has access to the overview screen to see a patient’s risk profile and recommendations. The only difference between the two versions is the alerting functionality.

In CholGate Alerting, the recommendations are automatically shown to the user during record interaction. The alert is presented in the EHR’s patient record screen. In CholGate On-demand a user has to actively access the recommendations of the system.

**Study population and setting**

To avoid bias by different vendor systems we chose to integrate CholGate into the Elias EHR (ISoft B.V.). In May and June 2004 all 56 practices in the region Delft and Westland, in the Netherlands, using the Elias (ISoft BV) EHR were invited to participate in the study. Only practices that fully replaced paper-based records with electronic records during patient encounters and who have been working in this manner for a year or more were eligible for the study. A total of 38 practices (80 GPs) agreed to participate in the study.

The general practice, with one or more practitioners, was chosen as unit of randomization because it was a definable entity and a logical foundation for implementing a primary care based intervention. In addition this prevented knowledge gained from decision support in one patient influencing the action on a possible control patient thereby underestimating the effect of the intervention. Practices were randomly assigned into one of three arms; a control arm,
Comparing Alerting versus On-demand

and two intervention arms, an on-demand arm and an alerting arm.

The CholGate CDSS was implemented by the authors at the practices that participated in the study. The authors configured the system to the local practice setting and users were given a tutorial on the use of the system. We installed CholGate On-demand in the on-demand arm and CholGate Alerting in the alerting arm. In the control arm CholGate was installed but all functionality was disabled for daily use. At all practices an initialization procedure was performed directly after installation. This procedure gathered data on the practices screening and treatment performance of the 360 days preceding the intervention as well as gathering the baseline characteristics of the patient population. As the DCGP guidelines restrict lipid management recommendations to males between 18 and 70 years and females between 18 and 75 years we only included these patients in our study.14-19.

After initialization all data of patient record interactions, patient characteristics, and follow-up data were obtained from the EHR by the system. Eligibility of patients for screening and treatment actions were determined from the computerized patient data (diagnoses, problems, prescriptions) that were available in the EHR. Eligible patients entered the study at the moment the patient record was opened in the GP practice during the study period. At that moment CholGate classified the patient as needing screening or needing treatment. If a patient needed screening the interval in days were counted from entry until a screening action was performed or follow-up ended. If a patient needed treatment the interval in days were from entry counted until a treatment action was performed or follow-up ended. Patients who were screened after classified as needing screening and subsequently classified as needing treatment were included in both the screening analysis and treatment analysis. This procedure was followed in all arms; however, in the control arm users did not have access to the system, and did not have any indication that the system was active.

All patients were followed for at least one year, or until the general practice changed EHR vendors, that is stopped using the ELIAS system, or until the patient died.

All patient data was anonymous. Ethical approval was waived for the study as the intervention was on the practice level, and physicians were not forced to follow any suggestions.
Outcome measures

The primary study outcomes were the percentage of correctly screened and correctly treated\textsuperscript{1} patients according to the DCGP guidelines' recommendations on lipid management in relation to the primary and secondary prevention of CVD\textsuperscript{14-19}.

Covariates

The cluster randomized design does not necessarily eliminate confounding due to differences in, for example, the patient mix. As covariates we considered the various patient characteristics (age, gender, cardiovascular disease, hypertension, diabetes mellitus, and smoking status). Since the follow-up time was not fixed and influenced the possibility the required actions we considered this as a covariate as well as the number of interactions with the EHR. In addition we assessed the screening and treatment percentage in the year preceding the intervention to adjust for possible confounding.

Statistical analysis

Logistic regression was used for comparing screening and treatment rates between intervention arms; in these analyses the odds were compared between the alerting arm and the control arm and between the on-demand arm and the control arm while adjusting for the covariates that confounded the univariate association between treatment arm and outcome. Assessment of the confounders was based on the 10 percent change in estimate method\textsuperscript{28}. For analysis of the screening odds the numbers of interactions with the EHR and time between being first eligible for screening or treatment until the end of follow-up were confounders. For assessment of the treatment odds the number of interactions with the EHR, the time between being first eligible for screening or treatment until the end of follow-up, existing CVD, and diabetes mellitus were included as confounders. To estimate the effect of the interventions while taking into account the clustered randomization we used logistic regression with the general practice as a random effect, using PROC NLMIXED in SAS. All analyses were performed with SPSS version

\textsuperscript{1} The percentage of just screening is the number of patients eligible for screening and then screened, divided by the total number of patients eligible for screening. The percentage of just treatment is the number of patients eligible for treatment and then treated, divided by the total number of patients eligible for treatment.
Comparing Alerting versus On-demand

Results

Thirty eight general practices with a total of 87851 eligible patients participated in the study, 11 practices were randomised to the control arm, 13 to the CholGate Alerting version and 14 to the CholGate On-demand version (figure 2). Two practices in the on-demand group were lost to follow up: Both practices upgraded to a better hardware solution with the vendor inadvertently deleting our study data.

Practice characteristics differed slightly between the treatment arms, for example screening and treatment performance in the year preceding the start of the CholGate program were lower in the on-demand arm (Table 1). Patient characteristics were quite similar between the treatment arms, except for the percentage of smokers, family history of CVD, systolic blood pressure and the percentage of patients (table 1). For 3210 of the 87851 patients, the CholGate module determined that according to the DCGP guidelines screening was needed (table 2), the percentage was highest in the on-demand arm (39.8%) versus 34.6% in the automatic alerting arm and 37.8% in the control arm. The majority of patients who were identified as eligible for screening was male, around 60 years of age, approximately 40% had CVD (mostly angina or a prior myocardial infarction) and 26% had diabetes (table 2).

Table 3 shows for 2953 of the 87591 patients, CholGate determined that treatment was needed either at becoming eligible for the study or after being screened during the study period (376 patients in total). A high percentage of treatment eligible persons had CVD, diabetes or had a Framingham risk score above 20%, which is the treatment eligibility criterium for primary prevention patients, between 40-50% of patients were eligible because of secondary prevention and the rest because of primary prevention (table 2).

Sixty five percent of screening eligible patients in the automatic alerting arm were screened versus 35% in the on-demand arm and 25% in the control arm (table 3). The automatic alerting arm had a 5 fold increased odds to be screened than patients in the control arm (OR_adj=5.17, 95%CI: 3.15-8.50), whereas patients in the on-demand arm had a 1.68 fold
increased odds of being screened ($OR_{adj} = 1.68, 95\% CI 1.03-2.75$). Of the treatment eligible persons 65% was treated in the automatic alerting arm, 39.7% in the on-demand arm and 35.9% in the control arm. After adjustment for differences between arms the odds of treatment was 3.75 fold higher in the automatic alerting arm ($OR_{adj} = 3.75, 95\% CI 2.40-5.87$) and 1.53 fold higher in the on-demand arm in comparison to the control arm ($OR_{adj} = 1.53, 0.97-2.41$). The automatic alerting arm had significantly higher odds of being screened and treated than the on-demand arm (table 3).

**Discussion**

This study showed that CholGate improves screening and treatment performance of dyslipidaemia in general practice. The CholGate Alerting version improved screening and treatment rates significantly more than CholGate On-demand. The on-demand version improved screening of dyslipidaemia compared to no intervention but did not significantly improve treatment rates.

**Explanation of findings**

The observation that the system increased physician performance in relation to dyslipidaemia recommendations from the guidelines can be understood when taking the workflow of GPs into account. In a busy general practice there is frequently insufficient time to calculate the risk scores which is necessary for decisions on primary prevention according to the guidelines. The time needed to read and interpret paper-based guidelines might hamper physician adherence. As our results show, displaying recommendations from guidelines to complex decisions in a way that fits into the workflow of the physician, increases performance by obviating the break in the clinical workflow.

The observation that a system that alerts a user to screening and treatment actions is associated with better performance than a system that requires a user to actively access recommendations can be understood when taking the awareness of physician of trigger events into account. Primary prevention requires GPs to take various factors into account when identifying patients at risk. In that case a clear event that triggers the primary prevention actions is lacking29. However, physicians' awareness of the need for secondary prevention activities is
frequently triggered by a CVD event. The results of our study demonstrate that increasing awareness with alerts leads to better performance in both primary and secondary prevention.

**Findings in relation to other studies**

In a recent major review of 100 CDSS studies on practitioner performance and patient outcomes, the authors found that improved practitioner performance was associated with CDSS that automatically prompted (alerted) users compared with requiring users to activate the system. However, none of the 100 studies under review directly studied this observation. Our work is the first study that confirms this association in a randomized controlled trial setting. Recently authors have identified the critical determinants for CDSS to be successful. However, we did not evaluate the effect of these factors in our study, but rather kept them similar across the intervention groups. This means that we could measure the difference between the intended interventions (alerting and on-demand activation), without taking the various system effects listed by others into account.

The clinical implications of our findings could be profound. It is known that both primary and secondary prevention of CVD is sub-optimally performed. The effects of our study show that interventions such as CDSS can improve the primary and secondary prevention of CVD, and then especially if GPs are alerted to the need for action. It can be argued that an increase in adherence to the guidelines, as effected by our system, will lead to a decrease in mortality and morbidity due to CVD. However, further research will have to show that this is indeed the case.

**Limitations**

Recently authors have argued that evaluation of CDSS should focus on the effect on patient outcomes as the gold standard for evaluating CDSS. Our study is limited by the fact that it only assesses the effect of CDSS on changing physician behaviour rather than on patient outcomes. However, if the CDSS is grounded on well accepted evidence based guidelines, one can argue that improvement in physician adherence to guidelines will result in eventual better patient outcomes. Further research will have to clarify whether this supposition is correct.

The performance of the CDSS depends on the way physicians capture data in their EHR.
Inappropriate coding of data will translate into lack of alerting or inappropriate alerting. Therefore, we were unable to control for patients that needed screening or treatment, but no data was in the record. However, we believe as benefit from a CDSS, coding practices will improve. Further research will have to show what the best strategies are for helping appropriate coding of data.

Randomization was conducted on a practice level, and this does not deal with potential differences in patient characteristics between treatment arms. Through the multilevel logistic regression analysis we adjusted for baseline differences that confounded the effect estimate while taking the clustered design into account. Because of logistical reasons, the follow-up time differed between practices. Since time is an important determinant for screening and treatment, we adjusted for this difference.

Apart from screening for all CVD risk factors, we focused on treating only one risk factor: lipid abnormalities. We did not perform CDSS treatment interventions on other CVD risk factors. Performing these extra interventions will induce exponential complexity to the system. Although we have been able to introduce a CDSS that effectively supports the longitudinal lipid management aspects of primary and secondary prevention of CVD, further research will have to show whether introducing more workflow patterns in the CDSS will have additional effects on physicians’ performance.

In conclusion, this study shows that both the On-demand and Alerting version of CholGate greatly improve screening performance for dyslipidaemia. In addition, although CholGate On-demand seemed to improve treatment performance, only CholGate Alerting significantly improve treatment performance for dyslipidaemia by general practitioners.
Figure 1 Practice randomization and study flow
### Table 1. Characteristics of practices participating in the study

<table>
<thead>
<tr>
<th>Study arms</th>
<th>Alerting</th>
<th>On-demand</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Practice characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enrolled practices</td>
<td>13</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Number of GPs median</td>
<td>2</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Practice size mean (SD)</td>
<td>2400.5 (977.1)</td>
<td>2607.9 (1269.4)</td>
<td>2304.5 (1186.2)</td>
</tr>
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<td>Single practices mean (SD)</td>
<td>1695 (190)</td>
<td>1550 (346)</td>
<td>1461 (364)</td>
</tr>
<tr>
<td>Group practices mean (SD)</td>
<td>2841 (1019)</td>
<td>3137 (1233)</td>
<td>2787 (1257)</td>
</tr>
<tr>
<td>Record interactions mean (SD)</td>
<td>9 (9.1)</td>
<td>9 (9.3)</td>
<td>9 (10.1)</td>
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<tr>
<td><strong>Screening performance % in year preceding intervention mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26.1 (10.6)</td>
<td>22.8 (6.0)</td>
<td>23.7 (7.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment performance % in year preceding intervention mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>33.0 (12.5)</td>
<td>27.1 (13.5)</td>
<td>34.0 (11.3)</td>
<td></td>
</tr>
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<td><strong>Patient characteristics</strong></td>
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<tr>
<td>n=25350</td>
<td></td>
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<td>n=31325</td>
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<tr>
<td>Male sex, n (%)</td>
<td>14065 (45.1)</td>
<td>14082 (45.0)</td>
<td>11286 (44.5)</td>
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<td>Age Mean (SD)</td>
<td>43.4 (14.80)</td>
<td>43.2 (14.99)</td>
<td>43.7 (14.50)</td>
</tr>
<tr>
<td>CVD, n (%)</td>
<td>1182 (3.8)</td>
<td>1414 (4.5)</td>
<td>1058 (4.2)</td>
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<tr>
<td>MI, n (%)</td>
<td>299 (1.0)</td>
<td>369 (1.2)</td>
<td>289 (1.1)</td>
</tr>
<tr>
<td>Angina, n (%)</td>
<td>563 (1.8)</td>
<td>567 (1.8)</td>
<td>442 (1.7)</td>
</tr>
<tr>
<td>Tia/CVA, n (%)</td>
<td>269 (0.9)</td>
<td>328 (1.0)</td>
<td>257 (1.0)</td>
</tr>
<tr>
<td>PVD, n (%)</td>
<td>107 (0.3)</td>
<td>107 (0.3)</td>
<td>102 (0.4)</td>
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<tr>
<td>Smoking, n (%)</td>
<td>1188 (3.8)</td>
<td>1357 (4.3)</td>
<td>1426 (5.6)</td>
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<tr>
<td>Hypertension, n (%)</td>
<td>3036 (9.7)</td>
<td>2962 (9.5)</td>
<td>2312 (9.1)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>1115 (3.6)</td>
<td>1379 (4.4)</td>
<td>990 (3.9)</td>
</tr>
<tr>
<td>Hypertension &amp; DM, n (%)</td>
<td>455 (1.5)</td>
<td>503 (1.6)</td>
<td>358 (1.4)</td>
</tr>
<tr>
<td>Family history of CVD, n (%)</td>
<td>285 (0.9)</td>
<td>278 (0.9)</td>
<td>445 (1.8)</td>
</tr>
<tr>
<td>Cholesterol/HDL ratio Mean (SD)</td>
<td>4.6 (1.38)</td>
<td>4.7 (1.68)</td>
<td>4.5 (1.40)</td>
</tr>
<tr>
<td>Cholesterol Mean (SD)</td>
<td>5.5 (1.04)</td>
<td>5.5 (1.90)</td>
<td>5.4 (1.52)</td>
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<tr>
<td>Glucose Mean (SD)</td>
<td>5.4 (1.84)</td>
<td>5.6 (1.84)</td>
<td>5.5 (1.62)</td>
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<td>Weight Mean (SD)</td>
<td>81.0 (19.00)</td>
<td>80.6 (19.25)</td>
<td>78.8 (17.45)</td>
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<tr>
<td>HDL Mean (SD)</td>
<td>1.3 (0.40)</td>
<td>1.3 (0.39)</td>
<td>1.3 (0.39)</td>
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<tr>
<td>Height Mean (SD)</td>
<td>171.3 (12.38)</td>
<td>170.8 (34.03)</td>
<td>170.0 (11.06)</td>
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<td>BMI Mean (SD)</td>
<td>28.8 (4.82)</td>
<td>28.9 (5.38)</td>
<td>28.4 (4.91)</td>
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<tr>
<td>Diastolic BP Mean (SD)</td>
<td>80.2 (9.93)</td>
<td>80.9 (9.90)</td>
<td>79.2 (10.32)</td>
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<tr>
<td>Systolic BP Mean (SD)</td>
<td>134.1 (19.09)</td>
<td>134.5 (19.57)</td>
<td>131.1 (19.34)</td>
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<tr>
<td>Triglycerides Mean (SD)</td>
<td>1.6 (1.37)</td>
<td>1.8 (1.44)</td>
<td>1.6 (1.12)</td>
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<tr>
<td>Patients on Statins, n (%)</td>
<td>1460 (4.7)</td>
<td>1420 (4.5)</td>
<td>1275 (5.0)</td>
</tr>
</tbody>
</table>

CVD: Cardiovascular disease, MI: Myocardial infarct, TIA: Transient ischaemic attack, CVA: Cerebrovascular accident, DM: Diabetes Mellitus, HDL: High density lipoprotein, BMI: Body mass index, BP: Blood Pressure
### Table 2: Characteristics of patients identified for screening and treatment by study arm

<table>
<thead>
<tr>
<th>Eligible for screening (percentage from total population)</th>
<th>Alerting</th>
<th>On-demand</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=1079 (3.5)</td>
<td>n=1249 (4.0)</td>
<td>n=882 (3.5)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age mean (SD)</th>
<th>59 (8.8)</th>
<th>59 (8.7)</th>
<th>58 (8.9)</th>
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</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>682 (63.2)</td>
<td>839 (67.2)</td>
<td>598 (67.8)</td>
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<tr>
<td>All CVD, n (%)</td>
<td>402 (37.3)</td>
<td>501 (40.1)</td>
<td>370 (42.0)</td>
</tr>
<tr>
<td>MI, n (%)</td>
<td>129 (12.0)</td>
<td>164 (13.1)</td>
<td>129 (14.6)</td>
</tr>
<tr>
<td>Angina, n (%)</td>
<td>161 (14.9)</td>
<td>162 (13.0)</td>
<td>163 (18.5)</td>
</tr>
<tr>
<td>TIA/CVA, n (%)</td>
<td>109 (10.1)</td>
<td>152 (12.2)</td>
<td>101 (11.5)</td>
</tr>
<tr>
<td>PVD, n (%)</td>
<td>40 (3.7)</td>
<td>43 (3.4)</td>
<td>41 (4.6)</td>
</tr>
<tr>
<td>HT, n (%)</td>
<td>431 (39.9)</td>
<td>451 (36.1)</td>
<td>305 (34.6)</td>
</tr>
<tr>
<td>DM, n (%)</td>
<td>279 (25.9)</td>
<td>326 (26.1)</td>
<td>235 (26.6)</td>
</tr>
<tr>
<td>Family history, n (%)</td>
<td>12 (1.1)</td>
<td>23 (1.8)</td>
<td>21 (2.4)</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>186 (17.2)</td>
<td>254 (20.3)</td>
<td>229 (26.0)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Eligible for treatment (% from total population)</th>
<th>n=1218 (3.9)</th>
<th>n=969 (3.1)</th>
<th>n=766 (3.0)</th>
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</thead>
<tbody>
<tr>
<td>Patients needing treatment and screened during study period n (%)</td>
<td>201 (16.6)</td>
<td>94 (9.8)</td>
<td>72 (9.4)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>58 (9)</td>
<td>59 (9)</td>
<td>58 (10)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>746 (61.2)</td>
<td>554 (57.2)</td>
<td>438 (57.2)</td>
</tr>
<tr>
<td>CVD, n (%)</td>
<td>481 (39.5)</td>
<td>488 (50.4)</td>
<td>360 (47.0)</td>
</tr>
<tr>
<td>MI, n (%)</td>
<td>73 (6.0)</td>
<td>88 (9.1)</td>
<td>71 (9.3)</td>
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<tr>
<td>Angina, n (%)</td>
<td>238 (19.5)</td>
<td>222 (22.9)</td>
<td>155 (20.2)</td>
</tr>
<tr>
<td>TIA/CVA, n (%)</td>
<td>122 (10.0)</td>
<td>111 (11.5)</td>
<td>90 (11.7)</td>
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<tr>
<td>PAD, n (%)</td>
<td>43 (3.5)</td>
<td>31 (3.2)</td>
<td>36 (4.7)</td>
</tr>
<tr>
<td>HT, n (%)</td>
<td>524 (43.0)</td>
<td>410 (42.3)</td>
<td>351 (45.8)</td>
</tr>
<tr>
<td>DM, n (%)</td>
<td>358 (29.4)</td>
<td>345 (35.6)</td>
<td>246 (32.1)</td>
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<tr>
<td>Family history, n (%)</td>
<td>237 (19.5)</td>
<td>116 (12.0)</td>
<td>91 (11.9)</td>
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<tr>
<td>Smokers, n (%)</td>
<td>228 (18.7)</td>
<td>185 (19.1)</td>
<td>173 (22.6)</td>
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<tr>
<td>CHD risk, mean (SD)</td>
<td>21.3 (7.4)</td>
<td>23.2 (7.1)</td>
<td>22.6 (7.9)</td>
</tr>
</tbody>
</table>

Bold print signifies statistically significant difference with control group p < 0.05
CVD: Cardiovascular disease, MI: Myocardial infarct, TIA: Transient ischaemic attack, CVA: Cerebrovascular accident, DM: Diabetes Mellitus, HDL: High density lipoprotein, BMI: Body mass index, BP: Blood Pressure
Table 3 Observed screening and treatment performance by study arms and effect of intervention

<table>
<thead>
<tr>
<th></th>
<th>Alerting</th>
<th>On-demand</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening</strong></td>
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<td></td>
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</tr>
<tr>
<td>Total patients needing screening</td>
<td>1079</td>
<td>1249</td>
<td>882</td>
</tr>
<tr>
<td>Patients screened n (%)</td>
<td>701 (65.0)</td>
<td>438 (35.1)</td>
<td>225 (25.5)</td>
</tr>
<tr>
<td>Follow up time mean (SD)</td>
<td>316.8 (83.6)</td>
<td>267.9 (99.9)</td>
<td>284.4 (69.9)</td>
</tr>
<tr>
<td>Adjusted Odds ratio (vs. control arm), 95%CI</td>
<td>5.17 3.15-8.50</td>
<td>1.68 1.03-2.75</td>
<td>reference</td>
</tr>
<tr>
<td>Adjusted Odds ratio (vs. on-demand arm), 95%CI</td>
<td>3.06 1.73-5.39</td>
<td>reference</td>
<td></td>
</tr>
</tbody>
</table>

| **Treatment**    |          |           |         |
| Total patients needing treatment | 1218     | 969       | 766     |
| Patients treated n (%) | 801 (65.7) | 385 (39.7) | 275 (35.9) |
| Follow up time mean (SD) | 316.0 (78.6) | 286.0 (92.6) | 298.9 (57.1) |
| Adjusted Odds ratio (vs. control arm), 95%CI | 3.75 2.40-5.87 | 1.53 0.97-2.41 | reference |
| Adjusted Odds ratio (vs. on-demand arm), 95%CI | 2.51 1.57-4.01 | reference |

* adjusted for time between eligibility and end of follow up, interactions with record
& adjusted for time between eligibility and end of follow up, interactions with record, CVD, Diabetes mellitus
Comparing Alerting versus On-demand

References


General Discussion
The aim of this research was to study the effect of two methods used in providing clinical decision support in primary care, on-demand/order entry and alerting/critiquing. Within the overall objective we investigated the impact of a computer-based intervention that supports the general practitioner in performing primary and secondary prevention of CVD. To achieve this objective we analyzed the practice guidelines of the Dutch College of General Practitioners with respect to recommendations for primary and secondary prevention of CVD, analysed current practises of Dutch general practitioners with regards to primary and secondary prevention of CVD, designed the decision support system CholGate, and conducted a randomized trial to assess which method of decision support yields most effect on GP compliance to the recommendations of the DCGP guidelines. Separate conclusions can be drawn from different parts of our study, but at the same time new questions arise. We will now discuss those conclusions and give suggestions for future research that might give an answer on the newly raised questions.

**Cross sectional analysis of guidelines**

Clinical guidelines are widely used in medicine to standardize medical treatment. Most clinical guidelines are published as free-text files, which can not be directly used for further computer processing. Therefore, clinical guidelines have to be translated first into a machine-readable formal representation. To assist knowledge engineers in developing a computable version of narrative guidelines several tools have been developed. Formalization of guidelines, however, requires consistency of guideline statements. To assess the possibility to formalize the DCGP guidelines on lipid management we analysed all recommendations for management of CVD risk factors from these guidelines on (in)consistencies.

Our analysis showed that with respect to the management of CVD risk factors, most statements in the selected guidelines were consistent between the guidelines. However, we identified eight statement inconsistencies (Chapter 2). Although the clinical relevance of the contradictions remains open for debate it is important to consider them from different perspectives. From the patient outcome perspective, the difference might not be large. From designing a CDSS’s perspective, however, the inconsistencies constitute different recommendations; if these statements between guidelines are inconsistent, appropriate assistance through a CDSS
will not be possible. Clinical relevance aside, guideline adherence inadvertently suffer from inconsistencies; a user can be adherent to one guideline but at the same time non compliant to another guideline. All these factors underscore the care that guideline developing organizations must take when developing guidelines with recommendations spread across different guidelines.

In January 2006 the DCGP published a new guideline dealing with the management of risk factors for CVD, both in primary and secondary prevention setting\(^3\). This guideline consolidates the recommendations previously distributed across various guidelines into a single guideline. In the new guideline the DCGP acknowledges the previous distribution of recommendations across different guidelines and attempts to provide a better, more consolidated set of recommendations. The cross consistency in statements between guidelines and the cross consistency in referencing to related guidelines should in our opinion be added to the checklist for guideline development. We believe that if our suggestions are applied to all future DCGP guidelines, both new and updated, developing CDSS for Dutch primary care will be easier.

**Risk factor identification and management**

The correct identification of patients to which recommendations pertain is the starting point of any guideline. For the DCGP guidelines on lipid management the starting point is the identification of patients with the four so called "conventional" risk factors (diabetes mellitus, hypertension, smoking, and hypercholesterolemia).

To estimate the potential of a decision support system on lipid management we had to ascertain whether the identification and registration of the various risk factors as suggested by the guidelines, is part of the daily work flow of general practitioners. In addition, intending to tightly integrate the system into the EHR - one of the success factors of a CDSS - we had to assess whether sufficient data is available for the system to process decision rules and calculations. Our study (presented in Chapter 4) shows that with respect to the risk factors for CVD, data regarding risk factors is identified, registered and sufficiently available. The availability of the data, however, was frequently too "late". Relating the registration of data to a CVD event, our research showed that the occurrence of a CVD event was the trigger for Dutch general
practitioners to identify and register the four conventional risk factors. This indicates that Dutch GPs seem to focus on the secondary prevention of CVD. In addition, relating the data to performance of practitioners according to the DCGP guidelines (Chapter 3), we demonstrated the systematic underperformance in the management of hypercholesterolemia and hypertension across the entire management process (screening, treatment, and treatment monitoring). A number of studies have shown that the availability of guidelines does not necessarily lead to the use of these guidelines by physicians. Even when authoritative guidelines are available, changing the behaviour of physicians has proved to be difficult³,⁴.

For effectively changing preventing behaviour of GP, the focus has to be on the awareness of performing preventive actions in the time frame preceding the CVD event. We realized that giving GP’s the tools to identify patients eligible for primary prevention, might urge them to perform associated measurements for CVD risk factors in the correct time frame. Therefore, unlike previous efforts in decision support systems we argue that the focus should not be on the rules and algorithms that guide these systems - this is contained in evidence based medicine itself - but rather on increasing the awareness of physicians in obtaining the relevant data. Giving effective feedback on the interpretation of data in relation to cardiovascular risk might lead to better case finding of patients.

**Designing an integrated clinical decision support system**

When implementing evidence based recommendations from guidelines into a CDSS, developers have to take into account the difference between the static recommendations of the guidelines and the continuous flux of the evidence on which the recommendations are based. Evidence-based medicine requires that guidelines be revised in the light of the available randomized clinical trials⁵. New trials that first appear in medical journals are read by physicians, and may subsequently result in revision of guidelines. Adoption of recent knowledge into daily practice could therefore precede dissemination of revised guidelines.

The 1999 Dutch cholesterol guideline, for example, recommended only two drugs of the statin class at publication: simvastatin and pravastatin. The DCGP acknowledged that other drugs of the statin class could have been included in their guidelines, but refrained from
including these drugs because of paucity on large trials on efficiency, effect and safety. After 1999 various articles appeared showing that other statins such as atorvastatin and cerivastatin have similar effect, efficiency and safety profiles.

In Chapter 5 we showed that other statins prescribing includes 39% of new statin prescriptions. This might be an indication of GPs adopting new knowledge into daily practice. For successful introduction into daily practice a designer of a CDSS has to take this into account. Restricting prescription recommendations to the two recommended statins by the DCGP guideline could have hampered the successful introduction of CholGate into daily practice. Because our goal was to improve primary and secondary prevention of CVD by GPs, we focused on the treatment actions necessary to accomplish this, rather than the restrictive prescription recommendations of the guidelines. Prescribing a statin accomplishes this treatment action. We believe that this pragmatic approach enhances the successful introduction of CDSS into daily practice.

The first step when integrating a guideline within the workflow of a physician is to integrate the recommendations of the guideline with the data in the EHR. Implementing guidelines across different platforms (that is, different GP information systems) and across different institutions (that is, multiple practices) requires tailoring the system to these different environments. Other researchers have discussed this issue; the developers of the Arden syntax, for example, use the term “curly brackets” to denote the need for defining local mappings from variables in the electronic patient record to variables known to the CDSS. In the development of CholGate, we distinguish three different types of data that need to be extracted from the EHR and mapped to the CDSS: coded data, structured data and free text. Coded data are similar across different platforms, structured data are similar for all practitioners in one setting, and free text is specific for each individual user. The consequence of such an integrating of the CDSS with the local environment results in tailoring the system to each environment, including each individual user (Chapter 6). The fact that time and effort are required for that integration, therefore, is a direct consequence of the need to integrate the system to the local work flow. This raises the question of optimum balance between time and effort, and system functionality in CDSS.
modern CDSS not only needs to provide clinical decision support, but simultaneously support practitioner workflow as well. Historically, researchers have focused on the decision making aspect of CDSS. However, the more various determinants for the successful implementation of CDSS had been identified, the more it became clear that workflow integration and support is likely to be the most important determinant for successful CDSS implementations. This entails that future development of CDSS have to pay attention to the workflow aspects of CDSS: as CDSS becomes more complex, so will the various workflow aspects. Future research will have to identify and analyze methodologies to support this increased complexity.

**Comparing alert driven decision support with activating the system**

In Chapter 7 our results show that compared to current practice, physicians using a CDSS integrated into the daily workflow have a significantly better primary and secondary prevention performance with respect to screening patients. In addition our results show that a CDSS alerting practitioners results in better treatment performance performance than a CDSS requiring a user to actively access the recommendations of the system. That both methods of CDSS – alerting and on-demand – resulted in better physician performance than current practice raises the question which method of CDSS is most appropriate for a specific care setting. In a busy general practice, making physicians aware of advisable preventive actions has clear influence on their preventive behaviour. On the other hand, CDSS only having an on-demand functionality demonstrated effect on physician behaviour as well. For example, the BloodLink system, which provided on-demand decision support on blood test ordering, showed clear impact on test ordering behaviour of Dutch GPs without using any alerting. The BloodLink success was probably a result both of effective workflow support, and delivering decision support. Integrated in daily practice, BloodLink relieved the physician of routines by printing a patient-specific blood order form that included the necessary patient data (such as name, age, address, etc.), the tests ordered and the specific instructions for the laboratory. BloodLink’s use of already entered administrative data eliminated the need for the general practitioner to re-enter these data. The on-demand method of BloodLink was successful as part of the diagnostic process where physicians identify patients that need test ordering to prove or disprove a working hypothesis. Thus
the physician has already made a decision on the action (blood tests) but needs support for the most appropriate tests. The decision to order blood tests always precedes the need for decision support. Similarly to BloodLink, CholGate On-demand also required physicians to have made a decision on needing support prior to activating the system. BloodLink’s use of EHR data was not used for clinical reasoning, but only for performing administrative workflow support. Both the on-demand and alerting version of CholGate, however, while incorporating the same principles for workflow support as BloodLink, uses available EHR data for both administrative support and to identify the patient’s eligibility for primary or secondary prevention of CVD.

CholGate Alerting, functioning in the background, is not part of the diagnostic process. That is a patient visiting the GP for pulmonary complaints may at the same time have comorbidity like hypertension or diabetes. Based on the available EHR data, CholGate Alerting will identify this patient as eligible for primary prevention of CVD and alerts the physician. Independant from the reason for encounter, CholGate initiates decision support on preventive activities, thus creating opportunities to perform appropriate actions during the same visit. In this case decision support precedes the decision of the physician on the recommended action.

When designing a decision support system developers have to be aware of the characteristic features of a specific diagnostic process in order to meet the requirements for successful implementation of decision support in a specific care process.

BloodLink provides decision support for a single occurrence (blood test ordering) in a care process across multiple domains (all guidelines of the DCGP) whereas CholGate provides decision support for multiple occurrences (e.g. blood test ordering and statin prescriptions) in a care process across a single domain (CVD guidelines of the DCGP).

On-demand therefore might be the appropriate method of decision support in the case where physicians have already decided on an action in a care process, requiring single actions in multiple domains. Alerting might be the most appropriate method of decision support in the case where physicians are not yet aware of the need to initiate actions in a care process, requiring multiple actions in a single domain.
Future directions

We have conducted a study to assess the effect of two methods of CDSS in the domain of CVD on physician behaviour. Various authors have argued that large cluster randomized trials evaluating clinically relevant patient outcomes is the most appropriate way to assess the real effects of any CDSS. However, it can be argued that if physician’s behaviour is changed according to well accepted evidence based guidelines, patient outcomes will improve. Physician compliance to guidelines is not the only factor that determines patient outcomes. The patient’s own compliance with lifestyle recommendations and medication prescriptions is the ultimate determinant. Therefore, even if a CDSS achieves a 100% physician compliance to guidelines, patient compliance will still influence outcomes. Finding ways in which to increase both physician compliance, and maybe more importantly, increase patient compliance becomes more important. As both physicians and patients are partners in the care process, involving both in future work on CDSS should be a focus in future research.
References


Cardiovascular disease (CVD) is the leading cause of mortality in industrialized countries. Coronary heart disease and stroke are the principle components of CVD. Risk factors for developing CVD include smoking, male gender, diabetes mellitus, hypertension, haemostatic factors, family history of CVD, age, and abnormal blood lipids. Evidence exists that managing CVD risk factors in primary care plays an important role in decreasing the morbidity and mortality due to cardiovascular disease. Drug treatment for elevated cholesterol in patients with an increased risk for cardiovascular disease leads to a decreased morbidity and mortality. The management of CVD risk factors is generally referred to as primary and secondary prevention of CVD. Primary prevention aims to lower the incidence of the event, in other words, prevent the occurrence of CVD. Secondary prevention aims at reducing more and severe occurrences of CVD after the onset of initial CVD. The general practitioner is in a large part responsible for effective primary and secondary prevention of CVD.

Clinical decision support systems (CDSSs) are information systems that aim to optimize physicians’ clinical decision making. Two methods of introducing CDSS in daily practice have been studied: on demand mode and alerting mode. In the on demand mode, the user decides when decision support is needed and then activates the CDSS. In the alerting mode, the user is alerted when advice is available on a patient. Although it is known that both systems are effective in providing decision support in various settings, no direct comparison of the two methods has been made.

The aim of this research was to study the effect of two methods used in providing clinical decision support in primary care: on demand/order entry and alerting/critiquing. Within the overall objective, we investigated the impact of a computer-based intervention that supports the general practitioner in performing primary and secondary prevention of CVD. To achieve this objective we analyzed the practice guidelines of the Dutch College of General Practitioners (DCGP) with respect to recommendations for primary and secondary prevention of CVD, analysed current practices of Dutch general practitioners with regards to primary and secondary prevention of CVD, designed the CholGate CDSS, and conducted a randomized trial to assess which method of decision support yields most effect on GP compliance to the
recommendations of the DCGP guidelines.

Consistency of the guidelines

In order to implement a guideline in a DSS, developers need to formalize the statements of the guideline. However, with respect to the management of chronic diseases, more than one guideline can be applicable. In addition patients may have more than one disease. If a statement in one guideline is inconsistent with a statement in another guideline the developer is confronted with ambiguous recommendations. In Chapter 2 we analyzed statements in the practice guidelines of the DCGP with respect to the management of risk factors for CVD. This was done to identify the possible inconsistency of statements among these guidelines which would be relevant when constructing a CDSS. We performed a cross sectional analysis of all electronically available DCGP practice guidelines dealing with CVD risk factor management for statement inconsistencies and reference inconsistencies. We found that six out of 74 electronically available DCGP guidelines had either CVD or CVD risk factors as subject of the guideline. Eight statement inconsistencies were found and for each statement inconsistency a reference inconsistency was present. Given that inconsistencies were found, we recommend that organizations that maintain a set of guidelines update the guidelines using a cross sectional analysis of guidelines. Inconsistencies between guidelines might lead to physicians being unintentionally non-compliant with guideline recommendations. However, the inconsistencies were of such a nature that we could use the guidelines as a viable knowledge base to construct a CDSS

Identification of “conventional” risk factors for CVD

Detecting and managing the four major “conventional” risk factors – smoking, hypertension, diabetes mellitus, and hypercholesterolemia – is pivotal in the primary and secondary prevention of CVD. To assess the preventive activities of general practitioners regarding the four conventional risk factors, and the associated measurements for cardiovascular risk factors by general practitioners in relation to the time of first clinical presence of CVD, we analysed data in the IPCI database. IPCI is a large longitudinal general practice research database in
the Netherlands. In Chapter 3 we analysed anonymous data from all patients older than 18 with newly diagnosed CVD with at least one year of history before and after first clinical diagnosis of CVD. Details on conventional risk factors and associated measurements for the four cardiovascular risk factors were assessed in relation to the first clinical diagnosis of CVD between September 1999 and August 2003. In total 157,716 patients met the inclusion criteria. Of the 2594 patients with newly diagnosed CVD, at least one of the four investigated risk factors was observed in 76% of females and 73% of males. In 40% of cases no risk factor was recorded before the date of first CVD. In 16% of cases no associated measurements were present before the first CVD diagnosis. We found that in daily practice general practitioners seem to focus on secondary prevention of CVD. Intervention strategies that aim to influence general practitioners’ case finding behaviour, such as the CholGate project, should focus on increasing the awareness of physicians in performing risk factor associated measurements in patients eligible for primary prevention of CVD.

**Management of hypertension and hypercholesterolaemia**

The DCGP developed screening, treatment and monitoring guidelines for hypertension and hypercholesterolaemia to assist physicians in providing evidence based healthcare. In Chapter 4 we report on a retrospective study to assess the management of patients with these single or combined conditions in Dutch general practice. This study once again used data from the IPCI project. Management of hypertension and hypercholesterolaemia was assessed from 2000–2003 by measuring the numbers of patients screened for these conditions, treated pharmacologically, and monitored for treatment success. Approximately 11%, 3% and 10% of participants were eligible for screening for hypertension alone, hypercholesterolaemia alone and both conditions, respectively. Blood pressure screening was high in patients eligible for both blood pressure and cholesterol screening (>85%), whereas cholesterol screening was low (<56%). Among patients newly identified with hypertension or hypercholesterolaemia who were eligible for pharmacotherapy, 29% and 43%, respectively, were not treated within one year of diagnosis. Undertreatment was significantly lower in patients with both conditions (24% and 37% for antihypertensive and lipid-lowering treatment, respectively and 28% were
Summary

not treated for both). Among newly treated patients, in the first year of treatment there was no record of a blood pressure or cholesterol assessment, for 35% and 72%, respectively. Management was sub-optimal in patients with hypertension or hypercholesterolaemia as well as in those with both of these conditions. The results are likely to be widely applicable, particularly to other European and industrialised countries that have similar free-access health care systems as the Netherlands. The results show that there was the possibility to improve physician behaviour with a CDSS such as CholGate.
Statins and clinical endpoints

Evidence-based medicine requires that guidelines be revised in the light of the available randomized clinical trials. New trials that first appear in medical journals are read by physicians, and may subsequently result in revision of guidelines. Adoption of recent knowledge into daily practice could therefore precede dissemination of revised guidelines. In Chapter 5, we analyzed statin prescription by Dutch GP’s and compared the risk of cardiovascular and cerebrovascular events between atorvastatin users and other statin users in daily general practice. We performed a cohort study in the IPCI database. All new statin users in the period 1 September 1999 to 31 December 2002 were included. Multivariate Cox-regression analysis was used to compare the occurrence of the primary endpoint between atorvastatin users and other statin users. The primary endpoint was the composite outcome of fatal or non-fatal myocardial infarction, admission for unstable angina pectoris, fatal or non-fatal cerebrovascular accidents, or transient ischemic events. We identified 3499 new statin users, including 797 patients with a history of cardiovascular disease. 1341 persons started with simvastatin (38%), 1154 with atorvastatin (33%), 811 with pravastatin (23%) and 193 with other statins (6%). The median follow-up was 1.9 years. Two hundred thirty three patients (6.7%) experienced a primary endpoint. Atorvastatin users had a significantly lower risk of cardiovascular and cerebrovascular events than users of other statins (RR: 0.70, 95%CI: 0.55-0.96). The relative risks of atorvastatin users compared to simvastatin and pravastatin users individually were 0.70 (95%CI: 0.48-1.02) and 0.78 (95%CI: 0.52-1.16), respectively. The protective effect of atorvastatin was more pronounced in persons without a history of CVD. Atorvastatin showed a more favourable effect on fatal and non-fatal cardiovascular and cerebrovascular events in the general population than other statins. Therefore, although the guidelines did not explicitly state that ‘other’ statins should be used in dealing with high cholesterol, we chose to incorporate other statins in the design of our system.

Designing the system

After we analyzed the guidelines, analyzed current care practices, and concluded that we should include all statins in our system because of prevalent use, we proceeded to construct
CholGate (Chapter 6). Taking advantage of the use of electronic health record (EHR) by Dutch general practitioners, CholGate was integrated within the EHR to provide decision support in the clinician’s workflow. As researchers reported low primary and secondary prevention performance of physicians - they only seem to monitor and treat conditions in isolation (like hypertension or diabetes mellitus) without translating the measurements of single conditions to overall cardiovascular risk management – CholGate needed to be able to assimilate all data from an EHR and integrate it into the workflow of the GP. We constructed the underlying knowledge base of the system from the guidelines of the DCGP. We used various methods to gather relevant patient data to identify patients at risk. These methods include using structured, coded, and free text data. CholGate’s user interface had to fit the EHR environment and the aim was to have a positive impact on physician workflow by, for example, automating repetitive task. Finally, we developed CholGate to function in both an on demand and alerting mode, giving us the opportunity to test both methods in a randomized trial.

**The effect of Alerting or On-demand decision support**

Alerting users of clinical decision support systems (CDSS) seem to change physician behaviour more than requiring users to actively initiate the system (on demand activation). However, randomized trials comparing these methods were lacking. Using CholGate we compared the effect of alerting and on demand decision support with a control group with respect to screening and treatment of dyslipidaemia among Dutch general practitioners. We conducted a Cluster Randomized Controlled trial (Chapter 7) that included 38 general practices in the region of Delft, the Netherlands with a total of 87851 patients. Practices were randomly assigned to three groups; two interventions and one control. Patients were followed in the practice electronic health record for at least a year from June 2004 and identified as needing screening or treatment for dyslipidaemia. Multilevel regression methods were applied to account for the clustered design. Thirteen practices were assigned to use the module that alerted practitioners (alerting arm), 14 practices were assigned to the module requiring users to actively initiate the system (on demand arm) and 11 practices served as controls. The percentage of correctly screened and correctly treated patients using anonymous patient record data was taken as
main outcome measure. In the alerting group 65% of patients were screened (OR_{adj} 5.17 95% CI[3.15-8.50]) compared to 35% of patients (OR_{adj} 1.68 95%CI[1.03-2.75]) in the on demand group, and 25% of patients in the control group. In the alerting group 65% of patients were treated (OR_{adj} of 3.75 95% CI[2.40-5.87]) compared to 39% of patients (OR_{adj} 1.53 95% CI[0.97-2.41]) in the on demand group, and 36% of patients in the control group. Both the On-demand and Alerting version of CholGate improved screening performance for dyslipidaemia. Only CholGate Alerting significantly improved treatment performance for dyslipidaemia by general practitioners. Further research will have to show whether the findings can be translated to other settings; that is settings other than primary care, or settings including different disease domains.
Samevatting
In de geïndustrialiseerde landen zijn hartvaatziekten (HVZ) de belangrijkste doodsoorzaak. Hartinfarct en CVA dragen binnen de groep HVZ het meest bij aan de mortaliteit. De risicofactoren voor HVZ zijn: roken, mannelijk geslacht, diabetes mellitus, hypertensie, stollingsstoornissen, voor HVZ belaste familie anamnese en afwijkend lipidenspectrum. Het in de eerste lijn opsporen en (medicamenteus) behandelen van deze risicofactoren is bewezen effectief voor het terugdringen van de morbiditeit en mortaliteit ten gevolge van HVZ. Deze preventieve maatregelen kunnen onderverdeeld worden in primaire preventie en secundaire preventie.

Het doel van primaire preventie is het optreden van HVZ te voorkomen. Met secundaire preventie wordt getracht om, nadat een eerste HVZ is opgetreden een tweede mogelijke ernstiger verlopend HVZ te voorkomen. Primaire en secundaire preventie is een belangrijke taak voor de huisarts.

Beslissingsondersteunde systemen zijn informatie systemen die gericht zijn op het ondersteunen en optimaliseren van het besluitvormingsproces van een arts.

Twee methoden van invoeren van beslissingsondersteunde systemen in de dagelijkse praktijk zijn uitgebreid bestudeerd: de methode die gebaseerd is op de behoefte van de gebruiker aan beslissingsondersteuning en de methode waarbij het systeem de gebruiker er op aanspreekt dat voor een specifieke patiënt beslissingsondersteuning beschikbaar is. Daar waar de effectiviteit van beide methoden afzonderlijk wetenschappelijk werd vastgesteld, ontbreekt tot nu toe een vergelijking van beide methoden met elkaar. In onze studie vergelijken wij het effect van beide methoden van beslissingsondersteuning op de primaire en secundaire preventie in de huisartsenpraktijk.

Daartoe onderzochten wij eerst the standaarden van het Nederlands Huisartsen Genootschap (NHG) op aanbevelingen voor primaire en secundaire preventie van HVZ. Vervolgens bestudeerden wij hoe op dit moment in de huisartsenpraktijk primaire en secundaire preventie wordt toegepast. Daarna ontwerpen wij de beslissingsondersteunende module CholGate en voerden ten slotte een gerandomiseerde klinische studie uit om vast te stellen welke methode van beslissingsondersteuning het meeste effect heeft op het zich houden aan de NHG-standaarden door de huisartsen.
Consistentie van de NHG-standaarden

Voor de implementatie van standaarden in een beslissingsondersteunende module dienen de aanbevelingen uit de standaard eerst geformaliseerd te worden. In het geval van chronische ziekten kan het zijn dat meer dan één standaard van toepassing is. Bovendien kunnen patiënten meer dan één ziekte hebben. Als een aanbeveling uit de ene standaard niet overeenstemt met een vergelijkbare aanbeveling uit een andere standaard, dan wordt de ontwikkelaar van beslissingsondersteunende module geconfronteerd met ambiguité in de aanbevelingen. In Hoofdstuk 2 vergeleken wij alle NHG-standaarden op aanbevelingen voor risicomanagement van HVZ met als doel eventueel bestaande inconsistenties tussen de standaarden op het spoor te komen. Door middel van een cross sectionele analyse onderzochten wij alle elektronisch beschikbare NHG-standaarden, die HVZ risicomanagement als onderwerp hadden, op inconsistentie in aanbevelingen en literatuur referenties. Van de 74 elektronisch beschikbare NHG-standaarden bleken zes standaarden HVZ of risicofactoren voor HVZ als onderwerp te hebben. In deze standaarden stelden wij 8 inconsistentete aanbevelingen vast. Tussen elk van die inconsistentete aanbevelingen was ook sprake van inconsistentie in de literatuur referenties. Voor organisaties die richtlijnen uitgeven en onderhouden is het aanbevelenswaardig om voorafgaand aan de uitgave van een nieuwe richtlijn danwel de update van een al bestaande richtlijn een, als door ons beschreven, cross sectionele analyse van de in beheer zijnde richtlijnen uit te voeren. Immers inconsistentie tussen richtlijnen kan aanleiding geven tot ongewild afwijken van de aanbevelingen uit die richtlijnen door artsen. Gezien de beperkte hoeveelheid gevonden inconsistenties konden wij de richtlijnen gebruiken als kennisbank bij de ontwikkeling van CholGate.

Identificatie van de “conventionele” risicofactoren voor hartvaatziekten

Het opsporen van de vier belangrijkste “conventionele” risicofactoren – roken, hypertensie, diabetes mellitus en hypercholesterolemie - staat centraal bij primaire en secundaire preventie. Om een indruk te krijgen van de mate waarin huisartsen het risicoprofiel van hun patiënten in de dagelijkse praktijk vaststellen in relatie tot een eerste episode van HVZ, analyseerden wij gegevens uit de IPCI database, een grote onderzoeksdatabase gevolgd met door huisartsen
geleverde patiëntgegevens. In **Hoofdstuk 3** beschrijven wij onze analyse van geanonimiseerde gegevens van patiënten 18 jaar en ouder met een eerste episode van HVZ, van wie minimaal een jaar voorafgaand en een jaar na het begin van deze episode gegevens beschikbaar waren. Voor de periode september 1999 tot augustus 2003 stelden wij voor deze patiënten vast of en in welke mate het risicoprofiel vóór en na het begin van de episode van HVZ aanwezig was in het patiënten dossier. In totaal voldeden 157.716 patiënten aan de inclusiecriteria. Van de 2495 patiënten bij wie een eerste episode van HVZ werd vastgesteld was bij 76% van de vrouwen en bij 73% van de mannen minstens een van de risicofactoren aanwezig in het dossier. In 40% van de gevallen was geen enkele risicofactor vastgelegd voorafgaand aan de eerste HVZ episode. In 16% van de gevallen was geen risicoprofiel bekend voorafgaand aan de eerste HVZ episode. Wij stelden vast dat in de huisartsenpraktijk het accent vooral ligt op secundaire preventie van HVZ. Dit betekent dat projecten, zoals het CholGate project die bedoeld zijn om gedragsverandering van huisartsen te bewerkstelligen zich vooral zullen moeten richten op het zich bewust worden van huisartsen van de noodzaak van het vaststellen van het risicoprofiel bij patiënten die in aanmerking komen voor primaire preventie.

**Management van hypertensie and hypercholesterolemie**

De door het NHG ontwikkelde hypertensie en hypercholesterolemie standaarden geven huisarts houvast bij het screenen, vervolgen en behandelen van specifieke doelgroepen en het leveren van evidence based gezondheidszorg.

In **Hoofdstuk 4** laten wij de resultaten zien van een retrospectieve studie in de huisartsenpraktijk naar de manier waarop Nederlandse huisartsen in de dagelijkse praktijk omgaan met de begeleiding en behandeling van patiënten met hypertensie en/of hypercholesterolemie. Ook deze studie maakte gebruik van data uit het IPCI project. Wij gingen voor de periode 2000-2003 de mate van opsporen, behandelen en begeleiden van patiënten met hypertensie en hypercholesterolemie na door telling van het aantal patiënten dat gescreend was op hypertensie en hypercholesterolemie, door telling van het aantal medicamenteus behandelde patiënten en door telling van het aantal patiënten bij wie het resultaat van de behandeling door de huisarts was vastgesteld. Voor alleen hypertensie screening kwam 11% van de onderzochte populatie in
aanmerking. Voor hypercholesterolemie kwam 3% en voor zowel hypertensie als hypercholesterolemie kwam 11% van de onderzochte populatie in aanmerking voor screening. In de groep die in aanmerking kwam voor zowel hypertensie als hypercholesterolemie screening bleek in meer dan 85% de bloeddruk gemeten en in minder dan 56% het cholesterol bepaald. Van de nieuw geïdentificeerde patiënten met hypertensie en hypercholesterolemie die in aanmerking kwamen voor medicamenteuze behandeling werd respectievelijk 29% en 43% tot één jaar na de diagnose nog niet behandeld.

Onderbehandeling kwam significant minder voor bij patiënten die zowel hypertensie als hypercholesterolemie hadden (24% geen behandeling voor hypertensie, 37% geen behandeling tegen te hoog cholesterol en 28% geen behandeling voor zowel hoge bloeddruk als hoog cholesterol). Van de nieuw behandelde patiënten was in 35% van de gevallen geen uitslag van een bloeddrukmeting en in 72% van de gevallen geen uitslag van een cholesterol bepaling in het dossier aanwezig gedurende het eerste jaar van de behandeling. De resultaten van ons onderzoek laten zien dat in Nederland sprake is van een suboptimale begeleiding van patiënten met hypertensie en hypercholesterolemie. Het lijkt aannemelijk dat voor andere Europese en geïndustrialiseerde landen met vergelijkbare vrije toegang tot de gezondheidszorg de resultaten niet veel beter zullen zijn. Met behulp van beslissingsondersteunende systemen als CholGate zou mogelijk een meer optimale begeleiding van deze patiëntencategorie bereikt kunnen worden.

Statines en klinische eindpunten

Evidence based geneeskunde vereist een continue herziening van richtlijnen in relatie tot de resultaten van gepubliceerde gerandomiseerde onderzoeken. Echter voordat herziene richtlijnen uitgebracht worden kunnen artsen de onderzoeken, waarop de herzieningen van de richtlijn gebaseerd zijn, al gelezen hebben in de wetenschappelijke medische tijdschriften. Dit kan tot gevolg hebben dat recente inzichten al toegepast worden in de dagelijkse praktijk nog voordat de herziene richtlijn is gepubliceerd. In Hoofdstuk 5, onderzoeken wij het voorschriftgedrag van Nederlandse huisartsen voor wat betreft statines en vergelijken de kans op hartvaatziekten tussen gebruikers van atorvastatine en andere statines in de dagelijkse praktijk. Wij voerden
daartoe een cohort studie uit in de IPCI database. Wij includeerden alle nieuwe gebruikers van statines in de periode 1 september 1999 tot 31 december 2002. Om het optreden van klinische eindpunten te vergelijken tussen gebruikers van atorvastatine en gebruikers van andere statines pasten wij de multivariabel Cox-regressie analyse toe. Het primaire eindpunt was het opgetelde resultaat van het aantal fatale of niet fatale hartinfarcten, ziekenhuisopnames vanwege instabiele angina pectoris, aantal fatale of niet fatale CVA of aantal TIA's. Wij identificeerden 3499 nieuwe statine gebruikers, van wie 797 met HVZ in de voorgeschiedenis. Van de 3499 nieuwe gebruikers kregen 1341 patiënten simvastatine (38%) voorgeschreven, 1154 atorvastatine (33%), 811 pravastatine (23%) en 193 een van de andere statines. De mediane follow up was 1,9 jaar. Twee honderd drieëndertig (6,7%) patiënten kregen te maken met een primair eindpunt

Patiënten die atorvastatine slikten hadden een significant lager risico op HVZ dan patiënten die een van de andere statines slikten (RR: 0.70, 95%CI: 0.55-0.96). Het relatieve risico van atorvastatine slikkers was 0.70 (95%CI: 0.48-1.02) vergeleken met simvastatine en 0.78 (95%CI: 0.52-1.16) vergeleken met pravastatine. Het beschermende effect van atorvastatine kwam het duidelijkst tot uiting bij patiënten zonder HVZ in de voorgeschiedenis. Atorvastatine had een beter beschermend effect op fatale en niet fatale hartvaatziekten in de algemene populatie dan de andere statines.

Hoewel in de NHG-standaarden atorvastatine niet genoemd wordt als voorkeurmedicatie bij de behandeling van hypercholesterolemie hebben wij, op grond van deze bevindingen, ervoor gekozen om behalve simvastatine – het voorkeurmedicijn in de NHG-standaard - ook de mogelijkheid van het voorschrijven van andere statines op te nemen in CholGate.

Het ontwerpen van CholGate

Uitgaande van onze bevindingen uit onze analyse van de NHG-standaarden en onze bevindingen uit onze retrospectieve studie in de huisartsenpraktijk ontwikkelden wij de module CholGate (Hoofdstuk 6). Het feit dat Nederlandse huisartsen algemeen gebruik maken van een huisartsen informatie systeem (HIS) stelde ons in staat CholGate in het HIS te integreren en op die manier beslissingsondersteuning aan te bieden ingebed in de dagelijkse praktijkvoering.
Omdat uit onderzoek was gebleken dat artsen beperkt uitvoer geven aan primaire en secundaire preventie van HVZ - risicofactoren als hypertensie en diabetes mellitus worden afzonderlijk vastgelegd en behandeld zonder dat de vertaalslag plaatsvindt naar het vastleggen en aanpakken van het complete cardiovasculaire risicoprofiel moest CholGate in staat zijn om alle in het HIS aanwezige gegevens beschikbaar te maken voor HVZ risico-inventarisatie tijdens de dagelijkse praktijkvoering. Voor de onderliggende kennisbank van CholGate gebruikten wij de relevante NHG-standaarden. Voor het verkrijgen van relevante patiëntgegevens uit het HIS pasten wij verschillende methoden toe om gebruik te kunnen maken van gestructureerde, gecodeerde en vrije tekst gegevens. Het gebruikers interface van CholGate moest aansluiten bij de interface van het gebruikte HIS. Het doel van CholGate was een positieve bijdrage leveren aan de dagelijkse praktijkvoering van huisartsen, bijvoorbeeld door het automatiseren van herhaald voorkomende taken. Om de methode die gebaseerd is op de behoefte van de gebruiker aan beslissingsondersteuning en de methode waarbij het systeem de gebruiker er op attent deert dat er voor een specifieke patiënt beslissingsondersteuning beschikbaar is in een gerandomiseerd onderzoek met elkaar te kunnen vergelijken, zorgden wij ervoor dat beide methoden door CholGate toegepast konden worden.

Het effect van beslissingsondersteuning volgens de methode “behoeftgebruiker” en de methode “attenderen gebruiker”

Systemen die gebruikers attenderen op beschikbaarheid van beslissingsondersteuning lijken meer invloed te hebben op gedragsverandering van artsen dan systemen die gebaseerd zijn op de behoefte van de gebruikers aan beslissingsondersteuning. Gerandomiseerd onderzoek dat beide methoden vergelijkt ontbreekt tot nu toe. Door middel van een cluster gerandomiseerd onderzoek (Hoofdstuk 7) vergeleken wij het effect van beide methoden op het screenen en behandelen van hypercholesterolemie door huisartsen die gebruik maakten van CholGate met een controle groep. Dit onderzoek omvatte 38 huisartsenpraktijken in de regio Delft, met in totaal 87851 patiënten. De praktijken werden gerandomiseerd in 3 groepen: twee interventie groepen en 1 controle groep. Vanaf juni 2004 werden patiënten gedurende tenminste 1 jaar gevolgd en in die periode werd vastgesteld of bij hen sprake was van een indicatie voor scree-
Samevatting

Ning en behandeling van hypercholesterolemie. Vanwege het clusteren in de opzet van ons onderzoek pasten wij multilevel regressie analyse. Dertien praktijken werden gerandomiseerd in de “attenderen gebruiker” arm, 14 praktijken in de “behoefte gebruiker” arm van het onderzoek en 11 praktijken in de controle groep. Als primaire uitkomstmaat kozen wij het percentage correct gescreende en correct behandelde patiënten op basis van geanonimiseerde patiënten data. In de “attenderen gebruiker” groep werd 65% van de patiënten gescreend (ORadj 5.17 95% CI[3.15-8.50]) vergeleken met 35% van de patiënten in de “behoefte gebruiker” groep (ORadj 1.68 95%CI[1.03-2.75]) and 25% van de patiënten in de controle groep. In de “attenderen gebruiker” groep werd 65% van de patiënten behandeld (OR_adj 3.75 95% CI[2.40-5.87]) vergeleken met 39% van de patiënten (OR_adj 1.53 95% CI[0.97-2.41]) in de “behoefte gebruiker” groep (OR_adj 1.68 95%CI[1.03-2.75]) and 36% van de patiënten in de controle groep. Zowel in de “attenderen gebruiker” als in de “behoefte gebruiker” groep gaf CholGate aanleiding tot een statistisch significant betere screening op hypercholesterolemie. Een statistisch significant betere behandeling trad alleen op in de “attenderen gebruiker” groep. Verder onderzoek moet uitwijzen of onze bevindingen ook van toepassing zijn in een andere setting dan de eerste lijnssetting en voor andere ziekte domeinen dan HVZ.
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“Give thanks to the LORD, for he is good; his love endures forever.”
1 Chronicles 16:34

Ever since I have been in the Netherlands I am accused of thanking people too often! However, I believe that it is important to say thank you. But taking this observation to heart, I will say this: Those who know and needed to be thanked have been thanked many, many times! However, if you read this thank you again!

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To Charlotte. You support, you give, and you ask nothing in return. All my love is for you.
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After working at the department of Clinical Epidemiology at the University of Pretoria as project manager he moved to the Netherlands where, in 2001, he obtained a Masters in Medical Informatics at the Netherlands School of Health Sciences (NIHES) on a Nuffic Scholarship. After his MSc he continued working at the department of Medical Informatics, obtaining a Doctor of Science in Medical informatics (DSc) in 2003 while working in the field of decision support systems in primary care. In 2003 he also received a Bachelors degree in Commerce with specialization in Informatics from the University of South Africa. His work at the department of Medical Informatics resulted in several publications.

Since 2004 he has partaken in various consultancy projects on hospital information systems, with a focus on clinical informatics and order management systems.

Cobus enjoys keeping up to date with advances in both medicine and information technology, and plans to continue working in the important junction between these disciplines.

Cobus is married to Charlotte since June 2004.