Decision support system for Warfarin therapy management using Bayesian networks

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ABSTRACT

Warfarin therapy is known as a complex process because of the variation in the patients' response. Failure to deal with such variation may lead to death as a result of thrombosis or bleeding. The possible sources of variation such as concomitant illnesses and drug interactions have to be investigated by the clinician in order to deal with the variation. This paper describes a decision support system (DSS) using Bayesian networks for assisting clinicians to make better decisions in Warfarin therapy management. The DSS is developed in collaboration with a Swedish hospital group that manages Warfarin therapy for more than 3000 patients. The proposed model can assist the clinician in making dose-adjustment and follow-up interval decisions, investigating variation causes, and evaluating bleeding and thrombosis risks related to therapy. The model is built upon previous findings from medical literature, the knowledge of domain experts, and large dataset of patients.

1. Introduction

Warfarin is an oral anticoagulant that is mainly used for preventing thrombosis and embolism in several clinical disorders including atrial fibrillation and pulmonary embolism. The duration of Warfarin therapy is often between three months and a lifetime [12]. The effects of Warfarin are generally monitored by International Normalized Ratio (INR) which is the ratio of patient's blood coagulation time to a reference sample. Patients' INR values should be kept within a target therapeutic range since mortality risk will increase considerably if the INR value is outside this range [27].

According to a large multicenter randomized study by Poller et al. [28] the quality of the manual Warfarin management is still not adequate as patients can be kept within therapeutic range only 65% of the time. In Sweden, approximately 150,000 patients are treated with Warfarin and this number is increasing steadily [35]. According to Swedish statistics, around 12 patients die each year as a result of bleedings caused by Warfarin therapy and similar anticoagulant therapies [34]. There appears to be a significant room for improvement to keep the patients' INR values within therapeutic range and to minimize Warfarin related risks.

There are a number of 'variation factors' such as drug interactions and concomitant diseases which can increase Warfarin therapy risks by causing unexpected increases or decreases in the INR value [12].

It is difficult to know the presence of these factors in advance since some of the variation factors are commonly consumed products such as leafy vegetables, and their consumption usually varies in time. Clinicians have to investigate the presence of these factors in order to lower the risks of Warfarin therapy.

Decision support systems (DSS) have been used for assisting the decision making in Warfarin therapy since 1976 [40]. The main outputs of the Warfarin DSS are dose adjustments (how much the dose should be adjusted?) and follow-up intervals (when should the patient take the next INR test?) [8]. Various studies have shown that DSS are capable of increasing the quality of Warfarin therapy [10,28]. None of the reviewed DSS assists the investigation of variation factors during Warfarin therapy. Moreover, many existing DSSs such as regression models do not deal with the dynamic nature of the therapy (See Section 2).

This paper proposes a DSS using Bayesian networks (BN) for assisting the management of Warfarin therapy. The objective of this DSS is to support dose and follow-up interval decisions while predicting cerebral bleeding and stroke risks, and to assist the investigation of variation factors. Other advantages of the proposed DSS include its flexibility in terms of inputs and outputs, and training support for clinicians.

The BN model has been built in collaboration with the Skaraborg Hospital Group, SkaS, Sweden. The structure of the model is based on relevant medical findings published in reputable international journals and the knowledge of the physicians and nurses who are actively working on Warfarin therapy. The parameters of the model are identified from a large dataset of patients, elicitations with the domain experts and published statistics in medical literature.

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Genie-SMILE software [11] was used for building and calculating the BN.

The rest of this paper is organized as follows. Previous DSS for Warfarin therapy are reviewed in Section 2. The BN model for Warfarin therapy management is described in Section 3. Validation of the model is presented in Section 4. An example of using the model is provided in Section 5. Discussions and conclusions are presented in Sections 6 and 7 respectively.

2. Decisions support systems for Warfarin therapy

Several modeling approaches have been used to develop DSS for Warfarin therapy (Table 1). The main outputs of these models are similar: dose amounts and follow-up intervals; on the other hand their inputs and working principles differ. In the remainder of this section the advantages and disadvantages of several Warfarin therapy DSS are discussed.

Proportional-derivative [24,36] and Bayes forecasting [33] models calculate the recommended dose adjustments from the patient's previous INR values and dose intakes. These models are suitable for the dynamic nature of the treatment since their outputs are based on historical fluctuations of the INR value. On the other hand, they do not take variation factors into account while calculating their outputs. Proportional-derivative and Bayes forecasting models are relatively simple models with few inputs.

Regression models for Warfarin therapy [31,39] output a single dose recommendation based on several variables about the patient's background and variation factors. The previous dose intakes and INR values are not inputs for the reviewed regression models; therefore, these models do not provide decision support on adjusting the dose amount in the long term-therapy. Moreover, regression models are not flexible in terms of required inputs. For example, if a patient's height is an input for a regression model that predicts a Warfarin dose, then the user of the model must know or estimate the height of a particular patient to get the output of the model. This may not be practical if there are numerous inputs and the model is frequently used.

Rule-based models for Warfarin therapy [25,41] are based on clinical guidelines and expert knowledge. These models can have many inputs including variation factors and patient background. On the other hand, they assume that presence of the variation factors and patient background is already known by the user. In other words, these models output a dose-recommendation and a follow-up interval if the user has information about the presence of the variation factors; however they do not assist the user to find the cause of an unexpected INR increase. Moreover, rule-based models are inflexible in their required inputs like the regression models.

3. Bayesian network model for the Warfarin therapy DSS

Bayesian networks have been widely used in medical reasoning for diagnosis, treatment selection, risk analysis, and knowledge discovery [21–23,38]. However, their applications to the management of long-term medical therapies have been rare. The DSS presented in this paper is for managing Warfarin therapy, the duration of which is usually between three months and a lifetime [12]. Section 3.1 presents general information about BN and their benefits

for Warfarin therapy. Sections 3.2 and 3.3 explain respectively how the BN's graphical structure is developed and its parameters are learnt.

3.1. Why Bayesian networks?

Bayesian networks are graphical models that represent probabilistic relations and conditional independence among a set of random variables. This section provides a brief overview about BNs; the readers are referred to Koller and Friedman [17] for a more thorough explanation.

A BN consists of a graphical structure and numerical parameters. The structure of the BN is an acyclic graph that consists of nodes that represent the variables and directed arcs that represent the conditional independence assumptions between these variables [17]. If there is an arc from one node to another, the latter is called a child node and the former is called a parent node. The probability of each node is conditioned only on their parent nodes; therefore each node is conditionally independent of their non-descendants given their parents. The joint probability distribution of the model can be represented compactly in a factorized way due to these independence assumptions. The graphical structure and conditional independency assumptions of the BNs are suitable for eliciting causal and associational knowledge from experts and published research results [17].

The parameters of a BN determine the strength of the probabilistic relations between its nodes. Each node in the BN has a set of mutually exclusive and collectively exhaustive states with a probability distribution conditional on the states of its parent nodes, or an unconditional distribution if the node does not have any parents. The conditional and unconditional probabilities can be learned from available data, elicited from domain experts, or gathered from published statistics in medical literature [17]. A BN can have discrete or continuous variables. A discrete variable's probability distribution is shown by a conditional probability table (CPT). All the variables in our BN are discrete; readers are referred to [20,26] for a detailed discussion about using continuous nodes in BNs.

A BN can calculate the posterior probability distributions of its unobserved nodes given the states of the nodes that have been observed (instantiated). It is possible to instantiate any number of nodes in any part of the model and to calculate the posterior probability distributions for the remaining nodes accordingly. Therefore, BNs gives the user a great deal of freedom since the inputs and outputs of the model are not distinguished.

Bayesian networks can be used to make either predictive or diagnostic inferences depending on the available observations. Diagnostic inference is done from symptoms to causes, in the opposite direction of a BN's arcs. For example, if a clinician observes an unusually low INR value, this will increase the belief about a higher Vitamin K intake since a low INR value could be a symptom of high Vitamin K level. Predictive inference is done from causes to effects, in the direction of a BN's arcs. For example, if the clinician has not yet measured the INR value but knows that a patient increased the intake of Vitamin K, this will increase the belief about a lower INR value.

3.2. Structure of the model

The model was developed for the patients that have been receiving Warfarin therapy for more than 14 days, described as the maintenance phase of the therapy [8]. There were two main reasons for limiting the model to these patients. Firstly, at the start of therapy, patients are closely monitored by a physician since the drug's effect for these patients may not yet be known [1]. However, patients in the maintenance phase are reviewed at greater intervals. Interventions and follow-up intervals have to be carefully arranged for these patients since there will be a delay before undesired effects are observed and precautions are taken. Secondly, the number of patients

Table 1
Methods used in DSSs for Making Dose Adjustment and Follow-up interval Decisions.

Type of DSS	Dose amount	Follow-up interval
Proportional-derivative controllers [24,36]	X	
Bayesian forecasting [33]	X	
Regression models [31,39]	X	
Rule-based approaches [25,41]	X	X