ORIGINAL ARTICLE

A methodology pathway to develop a Computer Drug Safety program in Primary health care setting based on clinical audit

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ABSTRACT

Objective: Medications management is an area in Primary health care (PHC) and General Practice (GP) setting where decision making is very important. Computer Decision Support program have been developed to help primary physicians in their decisions and have proved effective in improving the process of care and promising in economic issues.

Methods: In order to create a Computer Drug Safety (CDS) program for managing oral anticoagulant therapy for use in PHC and GP setting with developed Information Technology (IT) System and established electronic Health Records (eHRs), we used clinical audit (a real-life practice analysis) as the methodology framework. We assumed that this method would enable a proposed CDS program to cope with clinical complexity of GP patients taking oral anticoagulants and also suggest this method as the operative framework for Quality of Care (QC) improvement and practice research.

Results: By using clinical audit, we were able to identify the list of elements necessary for building up a feasible CDS program for a long-term oral anticoagulant therapy surveillance, for use in PHC and GP setting. According to this list of elements, we were able to create a paper based concept (a schemata) for this program development. This CDS program would not be a simple drug-dose calculator, but a comprehensive software support system integrated within the existing IT work applications.

Conclusions: The main benefits, expected from this proposed CDS program, include: learning from work experience, oral anticoagulant QC improvement, better patients compliance to long-term treatment with the drug *warfarin*, practice performance follow up and practice research.

Key Words: Primary health care, General Practice, Long-term oral anticoagulant therapy surveillance, *Warfarin*, Computer Drug Safety program, Clinical audit, Electronic health records

1. INTRODUCTION

1.1 Introduction on using Information Technology (IT) for Medication Management in PHC and GP setting

Adverse drug events (ADEs) is an important aspect of the patient safety issue.[1] Since knowledge on this issue rapidly grows, post-approval drug safety surveillance, or pharmacovigilance, has recently been established as an independent branch of science.[2] Data sources for studying ADEs have until recently included only spontaneous reporting systems.[3] Computer programs based on using data mining methods had to be developed to enable information extraction and synthesis from these systems.[4] Except of the need for complex data evaluation methods, other limitations of

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these systems include: voluntary, in contrast to systematic ADEs reporting, incomplete patient information and unjustified population exposure.[5] Along with the trend for global adoption of IT in health care systems in Europe and broader, studies on ADEs shifted focus on use of health care databases, in particular electronic health records (eHRs).[6] Although showed many advantages, including the ability to analyse routinely collected (low cost and readily available) data, this system has also barriers to overcome prior to achieve the goal as the standard ADEs detection method.[7] These barriers include the inconsistency of ADEs definition and the lack of ADEs standard nomenclature.[8] What makes the use of this method difficult is the fact that ADEs are usually context-dependent, that means that they are caused by disease-related and patient-related, rather than drug-related conditions.[9] In order to make detection of ADEs from eHRs much easier, new IT approaches have emerged, putting attention on the precision and strength of ADEs signals generated from medical data.[8] To further strenghten the efforts on ADEs information collection, some supplement data sources have been used to complement the standard ones, including drug labels, biomedical literature and biomedical knowledge.[10] For process of ADEs extraction from these external sources to be more efficient for users, computer applications have been advanced by integrating data mining methods with knowledge discovery systems. Computer approaches have also been developed to address more complex drug safety phenomena, including knowledge retrieval on drug-drug interactions and on clinical context of ADEs generation.[11] Drug-ADEs association rules have been used to assess associations between drugs and symptoms.[9]

Medications are prescribed mostly in PHC, yet information on ADEs from this setting is scarce. In this paper, we want to bridge the gap and to highlight the potential of IT in facing this challenge. Based on the recent literature review, the median prevalence rate of ADEs in PHC setting is 3.45%, but varies across the age groups, from 2.45% in children, 5.27% in adults, to 16.1% in elderly patients, pointing towards the elderly population as a primary target for Computer Drug Safety (CDS) programs development.[12] This statement is in line to the fact that elderly persons usually possess a number of chronic diseases (multimorbidity) and, consequently, use a multitude of drugs (polypharmacy). Related to this, evidence indicates that risks for ADEs are proportional to the number of medications used.[13] Furthermore, for CDS programs to be feasible for use, specifically in PHC, focus should be on medications that are both frequently prescribed in PHC and often reported on ADEs. Here, we present an example of a CDS program for a long-term oral anticoagulant therapy surveillance.

1.2 CDS program for a long-term oral anticoagulant therapy surveillance. Problem description and historical development - a literature overview

Fibrillatio atriorum (FA) is the most prevalent cardiac arrhythmia characterised with a rapid, irregular heart rate which increases the risk for a thromboembolic stroke.[14,15] For stroke prevention, beneficial effect of the anticoagulant drug *warfarin* has been proved for a long time. Unfavourable fact is that *warfarin* dosage has to be repeatedly avoid adjusted, to maintain International Normalized Ratio (INR) values within the therapeutic range of 2.0-3.0, thus minimizing the risk for bleeding (INR > 3.0) and avoiding thromboembolic complications (INR < 2.0).[16–18] Further difficulty, in managing this drug, is associated with its sensitivity on interaction with a range of other medications and with some foods.[19] Recent evidence showed that the net benefit of *warfarin* therapy, in stroke prevention, markedly varies within the magnitude of the risk for stroke. Based on this evidence, the international guidelines on anticoagulant therapy, for patients with FA, have been proposed in the form of the CHADS2 and CHA2DS2VASc scores.[17] In general, patients with higher risk scores are candidates for the therapy with *warfarin* and those with lower risk scores for the therapy with aspirin. Major bleeding, in particular that of intracranial and upper gastrointestinal tract localisations, is the most important complication that largely compromises the efficacy of *warfarin* therapy.[19,20] Many clinical conditions and disease diagnoses have been identified to increase this risk, leading to another group of international guidelines, that based on the risk for bleeding quantification.[20] Current research focus, in patients with FA, is oriented towards information integration on the risk for stroke and the risk for bleeding, in order to provide the net clinical benefit of oral anticoagulant therapy.[21] Efforts are also put on clinical trials results translation into clinical practice, by addressing the clinical context complexity of patients in real life setting taking this therapy.[22]

Managing oral anticoagulant therapy, since so challenging, was the first area where CDS programs, aimed at improving clinicians' decision making, have been developed.[23,24] We have searched papers published in PubMed in the last 30 years, to summarise the evidence on CDS programs historical development. The first of these programs have been established in the Netherlands, in 1972, and soon after that in Italy and the UK.[25–27] The function of these programs was to help clinicians in *warfarin* dose prescription. Based on using the series of INR measurements, follow-up periods, until the next INR testing, have been estimated accordingly. Common characteristics of these early on CDS programs were that they were localy developed, mostly in the academic setting, as

standalone systems, not integrated in the existing health care IT infrastructure. For these reasons, these programs have not been appropriate for wider use, across the entire health care system. In spite of this usage limitation, their effectiveness in *warfarin* dosing has been confirmed, beyond the traditional method based on experience of clinicians working in the hospital anticoagulant clinic.[28,29]

The next phase of these programs development has been associated with the need for the process of decentralisation of oral anticoagulant therapy delivery – from hospital anticoagulant clinics to PHC and General Practice (GP) setting. This process of transition has been guided by the hospital anticoagulant clinics overburden and expanded indications for the long-term oral anticoagulation.[30,31] This new generation of CDS programs had the role to enabling less skilled primary physicians and other PHC professionals maintain the standard level of performance in managing this therapy. In countries with developed PHC, primarily in the UK, these programs found good acceptance.[32] Their evolution have started in Primary Care Antithrombotic Clinics, where they have been used as standalone Windows PCs. After several rounds of subsequent improvements, these programs have achieved a high level of functionality and have been integrated within the health IT systems.

Current options are coping well with GP workflows, including functions such as: 1) maintaining a registar of patients on *warfarin* based on the call/recall system; 2) keeping records on services provided to patients and based on these records; 3) clinical audit at the point of care and at the level of group practices and health care organizations.[32] Recent innovations include the web homepages, which aim is to provide primary physicians with knowledge based materials, in the form of summaries of the evidence base and academic papers, relevant for oral anticoagulant treatment. Recommendations from guidelines, including *e.g.* clinical indications, therapy duration and required therapeutic ranges, have also been installed, but directly within the work application, to enhance patients scoring and selection. The most recent web browser version, reflects efforts to generalise use of this program, by crossing boundaries between PHC and hospital care and by enabling individual patients to loggin in and to self-manage the *warfarin* therapy.

1.3 Critical appraisal on the literature overview and our perspective of the future development of CDS programs for a long-term anticoagulant treatment in PHC and GP setting

As shown above, recent options of CDS programs for a long-term oral anticoagulant therapy surveillance follow the global trend in using IT for medications management in PHC (see Introduction), including: systematic patients registration, quality performance measurement and external knowledge sources, added to CDS work applications,in order to keep primary physicians informed with up-to-date knowledge and to support their decisions. However, even these advanced CDS versions show weak connections with patients eHRs, maintaing configuration as the standalone programs. In these recent options, at least two important requirements, specifically associated with primary physicians working styles, continue to be unfulfilled. The first one deals with a large amount of information which needs to be synthesised by a GP him(her)self, without the possibility for automatic information integration. Another requirement comes from the increased awareness that for selfie medications management, the only information on medication farmacological properties and ADEs are not sufficient, without the knowledge on disease-related and patient-related issues. This latter requirement has been further elaborated here (see below), in order to distinguish patients in PHC and GP setting taking oral anticoagulants, from those registered in anticoagulant clinics and hospitals. Although seems paradoxically, PHC patients are more often, in comparison to the former, endowed with clinical complexity. Additional fact that supports development of CDS programs for a long-term oral anticoagulant therapy surveillance for use in PHC and GP setting, includes scarce evidence on PHC patients taking oral antcoagulants, since they have been usually excluded from randomised clinical trials (RCTs).[22] That the need for designing such programs is not the matter of past, because of the appearance in the market of new oral anticoagulant drugs which do not require regular INR monitoring and don't have high potential for drug-drug and drug-food interactions, it is supported by the evidence showing that, in older patients, well-controlled therapy with *warfarin* continuous to be the gold standard for oral anticoagulant treatment.[20]

Patients on usual long-term oral anticoagulant care, in PHC and GP setting, are mostly older people with the diagnosis of FA, or with conditions which predispose them to deep venous thromboembolism.[33,34] Characteristics of patients with FA are that they usually possess one or more risk factors for thromboembolic stroke and at the same time have increased risk for bleeding. In this context, FA typically occurs on the basis of chronic heart failure, the main risk factors for which include: older age, hypertension, diabetes and atherosclerotic artery disease. All these conditions, taking separately, increase the risk for stroke.[14,16,17] On the other hand, these patients are also often burdened with conditions which increase the risk for bleeding, including impaired renal and hepatic functions, as well as some medications use, primarily nonsteroidal anti-inflammatory drugs (NSAIL).[35,36]

Further difficulties arise from the fact that these patients are frequently characterised with multimorbidity and polypharmacy, conditions which substantially increase risks for both, bleeding and ADEs.[37] Because of this described patients' complexity, CDS programs for their surveillance have to be designed in a way to capture this complexity.

2. AIMS AND METHODS

We wanted to create a model of CDS program for managing oral anticoagulant therapy to be appropriate for use specifically in PHC and GP setting, by facing the challenges of PHC patients complexity. Decision making by an expert general practitioner is characterised by problem-solving orientation and mental process automation, a feature that arises from a long-term layers of experience and rule-based knowledge integration.[38] We tried to as much as possible imitate this way of clinical reasoning. As experienced general practitioners and researchers, we were aware that we should have started from the problem-solving workflow, by analysing of what we are doing in our every day practice. In other words, in order to achieve a high level complementarity of our model plan with general practitioner's judgment, we have used a "bottom-up" approach in knowledge management, starting from the point-of-care clinical audit. To the best of our knowledge, this is the first such attempt published in the scientific literature. Justification for this assumption also comes from the novel IT field of Human-Computer-Interaction, arguing that only by a close collaboration between an expert in the field and a computer scientist, high quality user-centred software products can be developed.[39]

Another important advancement of our CDS model plan, not seen in previous solutions, includes using data for practice audit directly from patients' eHRs and this data integration and visualisation by computer programs, making these results visible on the screen of the official Health IT System, at doctor' s work desk. A step further, in our efforts to advancing CDS model for oral anticoagulant therapy surveillance, includes the use of knowledge from external sources, mostly knowledge databases, and knowledge comparison with information drawn from data in eHRs and real-time practice situation, enabling stream integration of alert systems and comments within the Health IT System. These described characteristics of our planned CDS program make it substantially different and much more comprehensive from even the most advanced programs of such types in a current use.

We are coming from the country (Croatia) where the health care IT system is well developed and eHRs, established in PHC and GP setting, have a long-term tradition.[40] IT system and e-applications have been continuously upgraded, in line with the strategic national development directions, aimed at improving system performance, availability and interconnectivity. In order to keep primary physicians being informed with up-to-date clinical guidelines and medical knowledge, the Portal of messaging system has recently been installed. Our assumption, however, is that the health care systems with developed IT and eHRs can provide much more opportunities for Quality of Care (QC) improvement, by integrating within the main IT System of intelligent computer decision support systems. We provide here a suggestion of how to develop and integrate within the IT system of a CDS program for a long-term oral anticoagulant therapy surveillance. We have chosen this topic because it has been already proved that CDS programs of this kind, installed in PHC and GP setting, can add a substantial value to medications management and patient safety issues.

We used, as the point of care, a single GP practice located in the town of Osijek, North-Eastern Croatia. For the purpose of clinical audit, we used oral anticoagulant therapy-related data from eHRs, for patients with the diagnosis of FA, including one-year period of observation (2013). In data analysis, we followed the logic of the local GPs' workflow in managing oral anticoagulant treatment. In this GP practice, there were 36 patients with the diagnosis of FA, out of a total of 1,332 patients (40% $\geq$ 65 y) registered on the list. Of this 36 patients, 19 have been receiving *warfarin* and 17 aspirin, or neither of the drugs. We defined the main objectives of this point of care audit, by taking into account: the availability of data from eHRs, known steps of the established oral anticoagulant management protocol and knowledge from the current guidelines. These objectives were as follows:

(1) Age distribution of FA;
(2) Assessment of the level of complementarity between patients receiving a particular oral anticoagulant treatment and what is recommended according to CHADS2 and CHA2DS2-VaSc Scores;
(3) Assessment of the quality of *warfarin* therapy control (expressed by the number of INR measurements maintaing within the optimal therapeutic range);
(4) Analysis of the testing frequency of some routine laboratory tests, of interest for bleeding complications on *warfarin*, including: hepatic transaminases, serum creatinine (a measure of renal function) and the urine sediment red blood cells;
(5) Determination of the number and types of diagnoses and of the number of drugs prescribed per patient, in particular those important for bleeding complications.

Results under each of these statements were additionally checked on evidence, by searching papers published in MEDLINE/PubMed in last 30 years. We wanted to identify the

points where evidence does exist and can be used for comparison with the clinical audit results, or reversely, the points where evidence is scarce and where more intense clinical practice research is needed.

Based on the results of the practice audit, we were able to form: 1) a list of important elements of oral anticoagulant therapy care which have to be automated and included into the proposed CDS program; 2) points where connections with knowledge are needed; and 3) points where data integration of any kind are planned, including computer visualisation techniques, data storage, or data integration by using data mining and knowledge discovery methods. Finally, this elaborated list of elements was then graphically transformed into a schemata, to serve as the background document for building up a CDS program.

3. RESULTS

Results showed a dominant prevalence of FA in elderly age groups (median 75.5), which is in line with the knowledge.[14] All of 36 patients with this diagnosis had justified indications for oral anticoagulant therapy, either *warfarin* or aspirin, according to CHADS2 and CHA2DS2-VaSc Scores.[17] We reestimated patients using aspirin or neither of the drugs, according to the CHADS2 Score, and showed that these patients, more often than those on *warfarin*, had boarderline scoring results, but performed well by using the modified CHA2DS2-VaSc Score. Conclusion was that both scoring systems should be integrated within the proposed CDS program, with the CHA2DS2-VaSc Score being more appropriate for patients with lower ranked risk for stroke.

The quality of *warfarin* therapy control was expressed as the proportion of INR measurements maintaining within the optimal INR range of 2.0-3.0. This quality measure was easier to estimate from native laboratory data, than the standard one, in the form of "*time spent in therapeutic INR range*", which needs a validated algorithm for its estimation.[41] There was a half of all INR measurements, performed in a yearly period in our cohort, with suboptimal values (INR < 2.0), and a third of INR measurements with values above the range considered optimal (INR > 3.0), corresponding with increased risk for bleeding. This result was in line with the evidence, showing poor control of *warfarin* therapy in general population and provided us a confirmation of the assumption that there is a need for CDS program integration within the IT system, in PHC and GP setting, to support primary physicians in *warfarin* dosing and safety management.[42] We also performed a more detailed analysis, by using data from eHRs, to reveal the clinical contexts of episodes of care showing increased risk for bleeding complications. Associations were found with: 1) changes in *warfarin* dosing; 2) intercurrent infections; 3) time when new drugs are added to the exisiting therapeutic scheme; and 4) a combination of reasons, indicating that there is a need for an Emergency Alert System to be introduced within the proposed CDS program, along with these clinical situations. The same analysis also showed that in a part of patients, optimal INR values (2.0-3.0) have never been achieved. These patients deserve special attention, or are candidates for pharmacogenetics.[43]

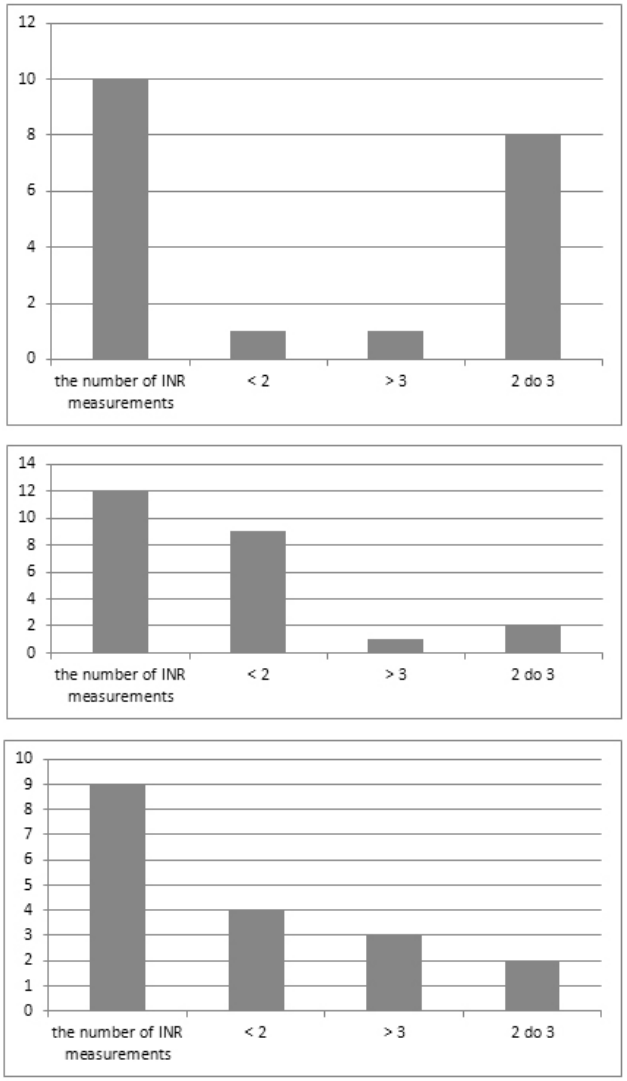

Figure 1. Graphical presentation of different patterns of variation in INR values

The measure used is "the number of optimal INR values (2.0-3,0) achieved per patient in one year period".

We also performed simple graphics to show how data used from eHRs can be easily integrated and made visible. For example, graphical presentation of the simple estimate "*the number of optimal INR values (2.0-3.0) achieved per patient in one year period*", can provide to primary physicians a

brief insight into the quality of *warfarin* therapy control, by using only native laboratory data from patients eHRs (see Figure 1). Different types of graphs, classified according to the patterns of variation in INR values, can easily guide primary physicians in patients risk stratification.

Analysis of INR testing frequency showed that only a half of patients receiving *warfarin* have been checked regularly, every one or two months, while another half have been checked much rarely, once in 4 or more months, indicating that INR testing frequency should be under the automated control of the Alert System. Similarly, the performance frequency of routine laboratory tests, of interest for complications on *warfarin*, including hepatic transaminases, serum creatinine and urine sediment red blood cells, showed very variable patterns, indicating that this point of *warfarin* care would be also a candidate for standardisation and integration within the proposed CDS program. That means that patients with increased values of these tests have to be considered for more intensive INR follow up.

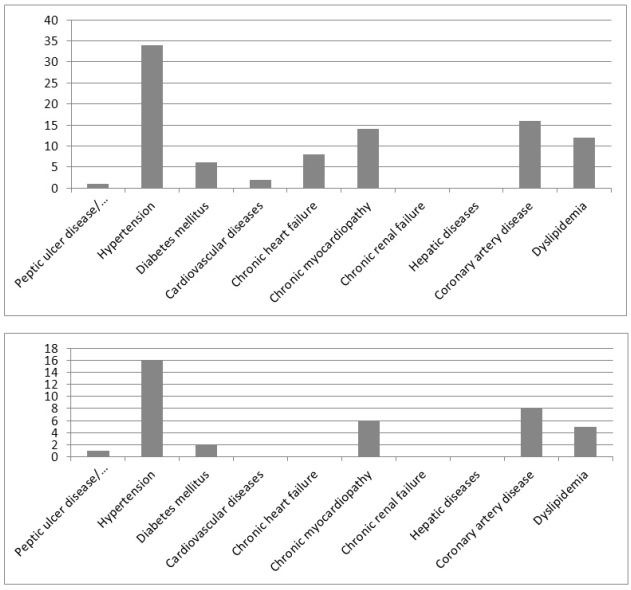

Figure 2. Distribution of diagnoses known to increase the risk for hemorrhagic complications on *warfarin* in patients with the diagnosis of FA. Differences between patients receiving and those not receiving *warfarin*

Graphical presentations of the distribution of the number of diagnoses per patient and the number of drugs prescribed per patient (not included in the paper), have gained an insight into the complexity of clinical context of PHC patients taking oral anticoagulant therapy. According to these graphs, almost $\frac{3}{4}$ of patients in our cohort had 7 and more, to the maximum of 18 different diagnoses, indicating a high level of multimorbidity. Similar conclusion we could get for the number of drugs prescribed per patient, that was varying between 7-20, with a third of patients having more than 10 different drugs, indicating a high level of polypharmacy.

We then separately analysed only diagnoses and medications of the particular interest for interactions with *warfarin*. The results that showed a high increase in these numbers in the elderly patient group ($\geq$ 65), compared to younger age groups (statistically significant difference), were in line with the general knowledge. The most common diagnoses, known to increase the risk for hemorrhagic complications on *warfarin*, included hypertension and heart diseases (both coronary artery disease and chronic myocardiopathy/heart failure) (see Figure 2). Of drugs known to interact with *warfarin*, the most frequently prescribed were hypolipidemic drugs statins, NSAIL, antibiotics and amiodarone (see Figure 3). Both results were in line with evidence.[19] However, we could observe some differences in the distribution of these diagnoses and drugs between patients receiving and those not receiving *warfarin* (see Figure 2, Figure 3).

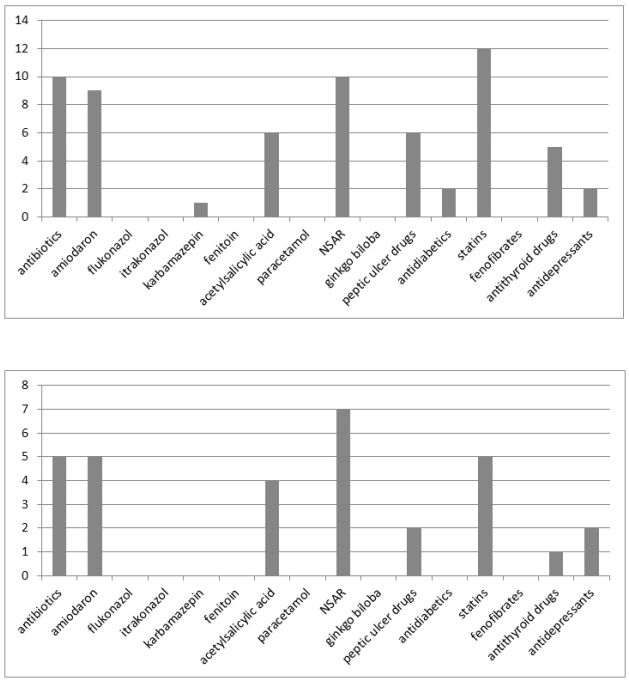

Figure 3. Distribution of drugs known to interact with *warfarin* in patients with the diagnosis of FA. Differences between patients receiving and those not receiving *warfarin*

Building up schemata as the background document to developing a CDS program for a long-term oral anticoagulant therapy surveillance for use in PHC and GP setting

Results of the audit (a real-life practice analysis) have allowed us to identify the list of elements need to be automated

when building up the proposed CDS program for a long-term oral anticoagulant therapy surveillance, for use in PHC and GP setting (see Table 1). This "bottom-up" and systematic procedure have also enabled us identification of the points where knowledge from external sources have to be included and compared with the results of the audit. Based on this list of necessary elements, we could also easily make a decision on which elements are appropriate for graphical presentation. In order to make the list of elements to be more appropriate for human cognition, we have taken a structure into this list, by forming a schemata that shows the future organization of the units and functions of the proposed CDS program (see Figure 4).

Table 1. Summary of the characteristics and findings of included studies

• Listing patients with the diagnosis of FA, separately according to the type of treatment	• To ensure treatment options justification
• Automated CHADS2 and CHA2DS2-VaSc Score estimation, comments provided	• To ensure treatment options justification
• Graphical presentation of INR values taken out from the Laboratory tests panel of eHR	• To ensure a physician a rapid look over anticoagulant treatment outcomes
• Linking the search engine, to find out information from EBM on how clinical and genetic factors may affect the stability of INR values	• To increase understanding of a physician The point of enhancing clinical practice research
• Linking monograms or recommendations on the initial and maintenance *warfarin* dosage	• To support decision making and improve dosage adjustment when necessary (especially important in the situations when clinical conditions are changed)
• Automated analysis of the number and frequency of INR values measured - link to evidence on dosage adjustment	• To help justifying INR measurements and reducing the number of INR measurements
• Evidence are scarce on optimal frequency of INR testing over time	• The point of enhancing clinical practice research
• Requirement for the systematic data collection of routine laboratory tests, hepatic transaminases, serum creatinine and urin sediment red blood cells	• To ensure the protocol of a long-term anticoagulant therapy surveilance standardisation
• Alert system for those patients with abnormal values of the above mentioned laboratory tests	• The point of enhancing clinical practice research: frequency of testing optimization, association between abnormal values of laboratory tests and INR values maintenance
• Graphical presentation of the number of diagnoses per patient and the number of drugs prescribed, separately for patients with FA receiving and for those not receiving *warfarin*	• To get insight into the distribution of risk for ADEs within the patient sample (at a single practice level)
• Graphical presentation of the distribution of the number of diagnoses and the number of medications known to interact with *warfarin*, according to the age groups	• To get insight into the distribution of risk for ADEs within the patient sample (at a single practice level)
• Link to the list of diagnoses known to synergise bleeding complications Link to the list of medications known to interact with *warfarin*	• To provide understanding and enhance learning
• Link to the literature reviews on *warfarin*-drug interactions Link to published case-reports on ADEs on *warfarin*	• To provide understanding and enhance learning
• Storage box, as a part of eHRs, for case-reports on ADEs on *warfarin* Link to the on-line ADEs reporting system	• Forming the local ADEs database on ADEs
• Graphical presentation of the distribution of diagnoses known to increase the risk of bleeding, within the patient sample - link to patients' ID codes Graphical presentation of the distribution of drugs known to interact with *warfarin*, within the patient sample - link to patients` ID codes Data on ADEs on *warfarin* integration - ranking high risk patients for ADEs - link to the knowledge base	• To allow comparison with EBM knowledge To provide understanding and enhance learning Detection of patients at higher risk for bleeding complications
• Integrated patient-related data, including age, sex, the list of diagnoses and the total number of diagnoses, the type and the number of medications, results of laboratory testing on hepatic and renal function	• To use data-mining for INR values or ADEs clinical context modeling

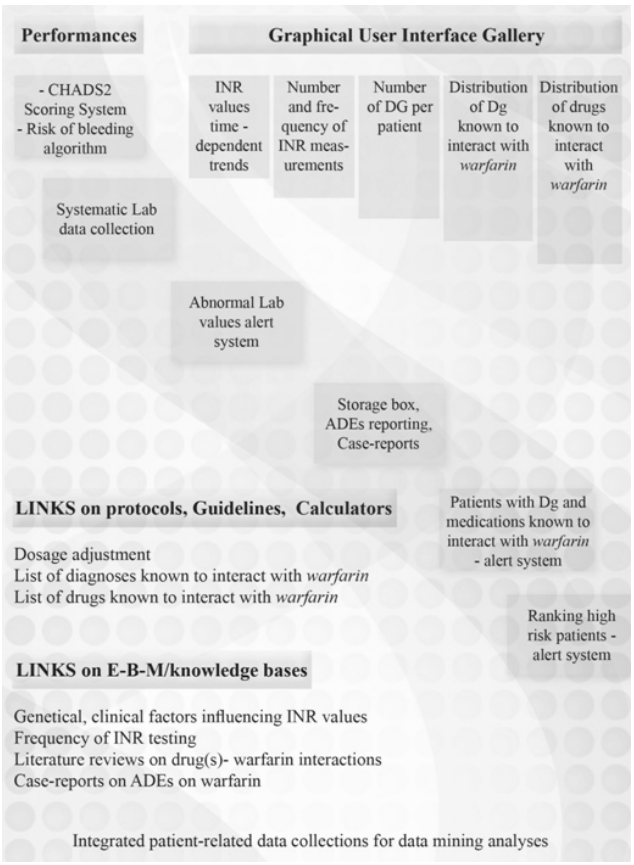

Figure 4. A CDS program schemata

4. DISCUSSION

In this paper, we provide a paper based program (schemata), as the background document for building up a computer program for a long-term oral anticoagulant therapy surveillance, appropriate for use in PHC and GP setting with developed IT system and established eHRs. This would not be a simple, standalone drug-dose calculator, known from before, but a comprehensive software managing system, integrated within the main IT work application. The capacity of this proposed program to draw patients personal and medical information directly from the IT system and eHRs, will enable primary physicians (users) to gain knowledge on a broader spectrum of patients taking oral anticoagulant therapy, out of limited conditions defined in RCTs and international guidelines.[22]

To better illustrate our idea, we provide here a detail description of this proposed CDS program, which units and functions are presented in the background program's schemata (see Figure 4).

By integration of the call/recall system within the work IT application, together with the appropriate guidelines, we would be able to ensure the systematic uptake of patients with indications for oral anticoagulant therapy, directly from the patient list, allowing at the same time their ranking on both, on the risk for stroke and the risk for bleeding complications. Further risk stratification refinement would be possible by using data from the Laboratory tests panel, of the main IT system, including information on the results of INR measurements (see Figure 1) and renal and hepatic functions testing, as well as data from eHRs, including the list of diagnoses (see Figure 2) and data on medications use (see Figure 3). By having all this data at glance, it is not difficult to achieve their integration by graphical presentation (see Figure 1, Figure 2, Figure 3), allowing primary physicians to briefly and quickly get insights into the issue.

In general, user-friendly interfaces, that we argue here, would provide primary physicians with brief data overview and information visualisation, strongly supporting their decision-making. For example, classification of patients based on graphical presentation of variations in patterns by which they attain INR control (see Figure 1), might make decisions on intervals until the next INR testing easier, without the need for estimation by using complex mathematical algorithms. We also suggest integration of knowledge from external sources within the proposed CDS program, including Alerts and Reminders and Care Scheme Schedules, which can be provided by links and websites contaning Protocols and Excerpt Lists of Diagnoses and Drugs known to interact with *warfarin* (see Figure 4). In order to further optimise efforts of primary physicians in managing oral anticoagulant therapy, by means of avoiding ADEs and of selection of patients who need extra attention, we propose the integration, directly within the Alerts, or Patient Care Plan Templates, of the Knowledge Management Systems (KMSs). These systems contain both, information retrieval tools and knowledge resources that consist of elaborated primary literature on evidence-based practices. As such, they have a potential to selectively provide information relevant to a particular patient or clinical situation (see Figure 4).[44]

Some additional advances of this proposed CDS program are based on the possibility of data integration and follow-up over time, specifically for INR values and other related issues, either by statistics, or graphical presentations, which would allow clinical audit at the level of the single practice, as well as among practices comparison.

The proposed CDS program would be continuously upgraded, by new parameters and units added to the program, enabling the process of parameters standardisation.

Finally, the availability of different types of data, including that provided in a native form, that used from the laboratory tests panels and eHRs, as well as that already selected and used from the storage boxes and ADEs reporting systems (see Figure 4), would allow advanced data analysis, by

using data mining and knowledge discovery methods. Hidden patterns, found in data in this way, would add to the general knowledge and strongly strengthen clinical practice research.[11]

After all, the main advantages of this proposed CDS program include: 1) learning from clinical practice, that means, from the natural and local-environment context; 2) possibility of adaptation on changeable patient conditions; and 3) capacity for creation of local ADEs and case-report databases - all these components important to strengthening clinical practice research.

From patients' perspective, the main benefits include: 1) the possibility of getting insights into the process of care which, in turn, would improve patients' compliance to treatment and laboratory checkups; 2) getting knowledge on harmful influences; and 3) shared decisions on therapeutic options, taking care on patients values and preferences.[45]

We are aware, however, that a full realisation of this paper-based concept, to produce a commercially validated product, would be on the long run. Presented CDS program schemata is between 2 and 3 stages of R&D process (Development ideas) and there is a lot of work to do before the licensed product enters the maket. Yet, since this CDS program schemata is well elaborated and planned to be naturally integrated within the existing IT system and work applications, as their parts, we assume that its engineering will not be faced with any serious barriers. The most demanding requirements will be associated with the knowledge management search engines, where excerptions from evidence-based medicine and other professional materials have to be compared with the results of practice audit, in order to produce alerts, commentaries and recommendations. The second demanding function will be associated with the analysis of broader clinical contexts, based on using plain text data from patients' eHRs. Signals recognition and strenghtening methods will be necessary to meet these requirements.

The next step of the R&D process, according to the established standards, would be assessment of the potential market readiness to accept a new product/invention. In our case, that means dealing with primary physicians (proposed users) attitudes and motivation to use our CDS program routinely, in every day practice. As experience teaches us, it is difficult to change doctors' behaviour beyond the traditional routine; it happens usually when it is commanded by the law.[46,47] Specifically, evidence on implementation in GP and PH setting of the clinical guidelines, as the key barriers shows: insufficient familiarity of primary physicians, inability to adjust guidelines with patient preferences and inconsistency between algorithms and currently available recommendations.[48] However, important to point out here is the fact that exactly these statements would be more properly addressed by estalishing our CDS program within the routine workflow. One of the most important areas, opened here to address these issues, includes personalisation of patient centred approaches, based on clinical context dependent analysis and its connection with knowledge excerptions, made upon a wider scope of evidence than it is by strictly using international guidelines and recommendations. In any case, this approach, by considering patients' complexity, will lead to the refinement of their risk status and enrichment of knowledge on both sides, including the pool of general knowledge, especially in areas where evidence is still insufficient, as well as knowledge of primary physicians and their sensitivity for patients fine distinction. For these reasons, we believe in a near future realisation of this project, in health systems where it is wellcoming and easy-to-install, such as those with developed IT infrastructure and established patient eHRs. Finally, well pointed topic for a CDS program development, which deals with areas difficult to decision making, such as a long-term oral anticoagualnt therapy surveillance, has a great chance to be well acquired by primary physicians, as recent experiences from the UK PHC system show us.[32] User friendly graphical presentations of the results of the practice audit, will significantly contribute to this program acceptance.

5. Conclusions

Decision making in PHC and GP setting is difficult and associated with a high level of uncertainty, as dealing with patients clinical complexity and the need for a large amount of information integration.[49,50] Consequently, evidence that arises from practice research is scarce.[51–53] In their decision making, primary physicians in a great part rely on experience and intuition, because the external knowledge, in the form of EBM, is known to arise from RCTs and is deficient in the context complexity.[50] One of the most important area of decision making, in PHC and GP setting, is medications management. It has been already shown that computer programs, when integrated in clinical practice workflows to support medications management, can be effective in improving the process of care and promising in economics terms.[54] From this perspective, a CDS program which would be used to managing important medication problem solving task in GP setting, such as a long-term oral anticoagulant therapy surveillance, could be in particular useful. The concept presented here is based on clinical audit, that means, it is a real-life-context dependent and suitable to cope with users (primary physicians) requirements. For this reason, although started from a local practice analysis, this proposed CDS program could be appropriate for more general use, specifically in health care systems and PHC and GP setting with well developed IT infrastructure and established eHRs.

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