Warfarin 2.0 - a Computer Program for Warfarin Management. Design and Clinical Use.

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ABSTRACT[1]

Warfarin 2.0 is a computer program that helps physicians optimize treatment of outpatients with warfarin. The main reason for its development was to achieve a good anticoagulation level, avoiding both undertreatment -- which causes thromboembolic complications -- and overtreatment -- which causes hemorrhagic complications. The program was also designed to help educate the anticoagulated patient, standardize warfarin management and audit results of what had been done. The philosophy of continuous quality improvement was applied. Warfarin 2.0 is in clinical operation in the University Hospital, Montevideo, Uruguay, and it has also been used since the end of 1993 in the Favaloro Foundation, Dept. of Hematology, Buenos Aires, Argentina. The results from the first 15 months of use in Montevideo showed an increase in the number of patients being followed (from 91 to 132) and the average number of visits per patient (from one visit every 10.6 weeks to one every 6.5 weeks): The frequency of visits has been in the internationally accepted ranges since the program was implemented. Better anticoagulation levels were achieved after an adjusting period. Unfortunately, the number of undertreated patients is still large, and a thorough analysis of the data is going to be undertaken to continue improving warfarin management.

INTRODUCTION

Uruguay is a small country of 3 million people located between Argentina and Brazil, bordered by the River Plate and the Atlantic Ocean. With a literacy rate of about 96% and life expectancy over 70 years, it also has a disease profile similar to developed countries, with a high prevalence of cardiovascular morbidity and mortality. The University Hospital (Hospital de Clínicas, Montevideo) is a tertiary care center with well-trained physicians and other health care providers, but with very scarce resources. Internists and Cardiologists are in charge of large numbers of anticoagulated patients, and attend to them when a thromboembolic or hemorrhagic complication occurs. Most of the complications are seen in ambulatory patients, and are often due to incorrect use of the drug or infrequent patient visits. Therefore, a computerized solution was proposed. The computer program was designed to emphasize patient education, standardization of treatment and audit of results.

Another important reason for the development of the program is the recent inclusion of non-rheumatic atrial fibrillation as a definite indication for anticoagulation [1]. However, these results were obtained in controlled clinical conditions, in academic institutions, with selected patients. The challenge is to translate these excellent results into routine clinical practice.

Several other computer programs that deal with oral anticoagulation have been developed [2,3,4,5,6,7,8]. However, their approach has been different from ours in several ways: all the British programs relied on empirical formulae to define dosage and date of next visit, and this approach does not allow the physician to understand the rationale for the decision. The same problem is encountered when using pharmacokinetic models or neural networks. In this paper we report on the design of a rule-based system that has been in clinical use for 15 months.

MATERIALS AND METHODS

Program design

One of us (AM) wrote a preliminary version of the program as a thesis project during Internal Medicine training [9]. From that first approach to the problem, the medical concepts and a general modular approach were established. The current version is written in CLIPPER, using DGE V.4 as a graphical library. The program is written for a 386 or higher IBM-PC compatible computer [10]. The system uses a parametric design, i.e., it can be modified by changing the files that the system uses for running. Among the modifiable modules are the main menu and the data entry modules for the first and subsequent visits. It has a normalized system of archiving data -- only positive data are archived, and these data are coded, which saves disk space (all the files with the current data use about 300 kb for all patients). However, the main advantage of using coded data is that information is retrievable for decision support.

The program was designed to be used by physicians, most of whom are not computer-literate,

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in a user-friendly and consistent way. The program also provides both technical and medical help on-line. The following modules are used (presented in the order most frequently used in clinical practice):

1) *Data entry for the first and subsequent visits.* On the first visit, demographic data, dates of use of anticoagulant, reason for anticoagulation, risk for embolic or hemorrhagic events (previous systemic embolism, gastroduodenal ulcer, alcoholism, etc), current medications and prothrombin time (PT) expressed in INR are recorded. The importance of reporting PT in INR (International Normalized Ratio) as a standardized expression of PT has been previously stressed [11]. INR is close to 1 in the normal population, and has a broad therapeutic range from 2 to 4.5, depending on the disease -- the upper limit has been decreased in recent years. In this article, the PT is always expressed as INR. On subsequent visits, a systematic review of complications, new medications and compliance with treatment are reviewed and entered. All these data are stored using a hierarchical coding system.

2) *An algorithm* uses the above data to suggest a dose and a date for follow up. Also, alerts are triggered in particular cases. The algorithm is the **core** of the program, but would be worthless if not used in the context of the whole system. The knowledge in the algorithm is based on the third Consensus Conference on Antithrombotic Therapy [12]. Nevertheless, since not every detail of antithrombotic therapy was considered by this conference, a detailed analysis of different possible problems was done. The variables considered included: presence of mechanical heart valves, age, last prothrombin time (PT), ratio of the last two PTs, time elapsed since warfarin was started, time elapsed since the current dose was administered, history of new drugs taken, history of bleeding, previous systemic embolism, diseases that can potentially cause bleeding, unstable PT values, alcoholism, extremely high warfarin dosage, ball valve prosthesis, use of an NSAID, distance to the clinic and non-compliance with treatment or scheduled visits. Consider a real case as an example:

- Twenty-five year old male patient.
- mechanical heart valves in the aortic and mitral areas for eight years.
- sinus rhythm.
- past history of duodenal ulcer and upper gastroduodenal bleeding two years ago. No recurrent bleeding thereafter.
- anticoagulated with warfarin for eight years.
- receiving warfarin, 5 mg 3 times a week, 7.5 mg 4 times a week, for the last three months.
- no new drugs , no problems reported.
- previous INR: 3.1 -- it was done 6 weeks ago.
- today's INR: 3.1.
- lives close by Montevideo.
- good compliance with treatment for the last 7 months.

The algorithm suggests:

- an INR goal of 2.5 to 3.5.
- since this goal has been met, no dose adjustment is recommended.
- recommendation of maximum interval until next visit of 6 weeks, because of stable anticoagulation levels, no new drugs added, no recent complications and the fact that the patient lives close to the Capital. If the patient had lived farther away, the recommendation would have been 8 weeks, which is the maximum allowed by the system's logic, according to the third Consensus Conference.

The following alerts are triggered:

- the patient has a condition that predisposes bleeding complications: duodenal ulcer.
- the patient has missed two or more appointments.

3) *A patient data retrieval system,* that helps the physician decide if the algorithm takes into account all the problems encountered with his/her patient. It includes the patient history, a graphical representation of the last 6 INR results and the average daily warfarin dosages, and the alerts and the rules used by the algorithm in this case. Referring to the previous example, some conditions were not considered: gender (the physician may insist on precautions to planning a pregnancy because of the teratogenic effects of warfarin), location and number of mechanical heart valves, and heart rhythm (none of these conditions were considered by the Consensus Conference, but they may affect the incidence of thromboembolic events), long term INR results (stability can also be determined using the graphical display of the last 6 INRs and dosages).

4) *Printouts:* after defining whether the suggestions should be modified or not, an instruction is printed for the patient, and a copy is included in his/her medical history. Also, on the first visit one page of general instructions about the use and potential problems of warfarin is given to the patient. If the patient has to go to the dentist, a printout is provided for the dentist explaining warfarin treatment in that situation.

5) *On-line medical help* is available throughout the program. It includes warfarin interactions with other drugs, what to do if the PT is high or the patient has had bleeding, risk of bleeding with warfarin, laboratory standardization of the PT, etc.

6) *Backup procedures and other tasks:* after seeing all the patients on a given day, a hard copy summary backup of all the visits is done, as well as a compulsory backup to diskette. A printout list of patients who have been rescheduled is given to the receptionist, and letters are sent to the patients who were scheduled but did not come.

7) There are two other important modules: one is *statistical software* for analysis; the other allows us

to *access the hierarchical vocabulary*, with a graphical interface that allows users to add new terms to the data dictionary.

Data analysis

Three periods are compared : 1) Pre-computer phase: nine months of prospectively collected data before the use of the software, from March to November 1992. 2) Computer phase 1 (implementation of the software): the first six months of use of the program, when modules were developed and incorporated, and the main changes to the software and the logic were undertaken. This period began in December 1992 and ended in May 1993. 3) Computer phase 2: the last nine months of use of the software. This last period started in June 1993 and ended in February 1994. Since the PT of the first visit was not impacted by the program, it was not included in the analysis in all three periods.

Patients were divided according to the therapeutic goal: 1) PT in INR = 2.0 to 3.0, for patients who do not have a mechanical heart valve. 2) A higher goal in patients with mechanical heart valves. This goal varied throughout the follow up: at the beginning (pre-computer phase and first three months of follow up with the computer) the goal was a INR = 3.0 to 4.5, with the ideal being as close as 3.0 as possible; we based this goal on the second Consensus Conference [13]. After the third Consensus Conference was published, we decided to adapt the goal to the one suggested by the third Conference (2.5 to 3.5). Therefore, we applied a more general goal (INR = 2.0 to 4.5) to compare all three periods for patients with mechanical heart valves, as suggested by Poller et al [4], for auditing purposes .

Statistical analysis: the results were converted to discrete values, dependent on whether the INR result at each visit was within a certain range or not. Chi-square analysis was then performed. Significance was set at the conventional 5% level. The Yates correction was used when comparing 2 by 2 tables.

RESULTS

There were 151 patients registered at the clinic in the two year period. Thirty-one of them (20%) had an INR goal of 2 to 3, and 120 (80%) had a higher therapeutic goal due to the presence of a mechanical heart valve.

Table 1 shows that there was a 45 % increase in the number of patients seen in Computer phase 2 compared to the Pre-computer phase and a 137% increase in the number of visits. This was due not only to the number of patients but also to the number of visits per patient. The percentage of missing values of PTs in INR was 1 % in the two year period, usually because they were not expressed in INR format.

Table 1 : Administrative data from the two-year follow up, beginning in March 1992 and ending in February 1994.

	Pre-comp. 9 months	Comp. 1 6 months	Comp. 2 9 months
# patients	91	107	132
# visits	336	386	796
Patients per visit	9.33	15.44	12.84
Interval between visits	10.6 weeks	7.2 weeks	6.5 weeks

Results for the two therapeutic goals are shown separately, since the populations were different and the knowledge base was not exactly the same for the two goals.

Higher goal (INR = 3.0-4.5 in the first year, 2.5-3.5 thereafter):

The characteristics of the population are as follows: the average age was 55 +/- 14 years. The dose of warfarin was in each phase 5.47 +/- 2.11, 5.15 +/- 1.93, 5.23 +/- 2.03 (range 1 to 13 mg per day).

The rate of INR results within the more general therapeutic goal suggested by Poller (2.0 - 4.5), for auditing purposes, is shown in Table 2. Even if there was a similar percentage within the general goal of 2.0-4.5 in all periods, there was an increase in the number of patients being overtreated (INR>4.5) during Computer phase 1, and a decrease in this number during Computer phase 2 compared to the two previous ones. While more patients were overtreated in Computer phase 1, fewer patients were undertreated compared to the other two periods.

Table 2 : Percentages of visits spent in various INR bands. Higher therapeutic goal.

	Pre-comp.	Comp. 1	Comp. 2
2.0 - 4.5	73.42 %	73.70 %	74.65 %
< 2.0	16.66 %	11.03 %	18.70 %
> 4.5	9.90 %	15.26 %	6.64 %
# of visits	222	308	647

The results of analyzing the different therapeutic ranges for the last 12 months, when a goal of 2.5-3.5 was established, are shown in Table 3. The number of patients in the therapeutic range +/- 0.5 (in this case, 2.0 to 4.0) significantly increased from 65.7% to 75.8% -- comparing March-May to December-February and considering the range 2.0 to

4.0, p=0.03. The number of patients being overtreated decreased to 2.8% for the last three months. This figure is significantly smaller than the pre-computer phase: 9.90%, p=0.0045 . The number of undertreated patients is more important than those overtreated, and has increased in the last period to values slightly greater than the pre-computer phase.

Table 3 : Percentages of visits spent in various INR bands during the period when the higher goal was 2.5 to 3.5. (March 1993- Feb. 1994)

	March-May	June-August	Sept. - Nov.	Dec. - Feb.
2.5-3.5	44.6 %	40.0 %	38.2 %	42.8 %
2.0-4.0	65.7 %	67.7 %	67.0 %	75.8 %
2.0-4.5	73.7 %	72.7 %	72.6 %	78.6 %
< 2.0	9.7 %	19.5 %	17.9 %	18.6 %
> 4.5	16.6 %	7.7 %	9.4 %	2.8 %
# of visits	175	220	212	215

Lower goal (2 - 3):

The characteristics of the population are the following: the age was 62 +/- 13 years. The dose was (in consecutive periods) 4.51 +/- 1.29, 3.90 +/- 1.21 and 4.02 +/- 1.49 (range 1 to 9 mg daily).

The ranges of anticoagulation for the three periods are shown in Table 4. The number of patients undertreated is important and has increased, but the range of patients under "broad range" (goal +/- 0.5, in this case 1.5 to 3.5) has also increased. The number of patients that were overtreated during Computer phase 1 is high, and there was also a greater dispersion of values during that time.

Table 4 : Percentages of visits spent in various INR bands. Lower therapeutic goal.

	Pre-comp.	Comp. 1	Comp. 2
2.0 - 3.0	48.4 %	43.6 %	44.8 %
1.5 - 3.5	77.4 %	72.7 %	81.6 %
< 1.5	3.2 %	9.0 %	13.6 %
> 4.5	0 %	5.5 %	2.4 %
# of visits	31	55	125

CONCLUSIONS

When Warfarin 2.0 was put into use in this population of patients, we knew it was going to be difficult to improve on the status quo, since many patients were on stable anticoagulation levels, and the whole population was within internationally accepted rates of success [4]. However, there was room for improvement with the computer program due to long periods between visits, the possibility of standardizing care, and the chance for better patient education and control. The group most likely to benefit were those patients who were newly started on warfarin and those who were non-compliant. The compulsory use of the INR, a standard measurement of PT, was another element that could improve anticoagulation with warfarin [14].

Warfarin 2.0 had the following impacts on the *processes* involved in patient care: 1) The frequency of visits increased, with an average visit per patient every 10.6 weeks in the first nine months and every 6.5 weeks in the last nine months. The frequency of visits is now within the recommended ranges [12]. 2) Seven to eleven minutes dedicated exclusively to anticoagulation, with a standard questionnaire, selective data retrieval, a standard management guideline and a printed instruction to the patient each visit.

The overall *results* regarding anticoagulation are promising in patients with a goal of 2.5 to 3.5 (80% of the patients). A large majority of them were in the therapeutic ranges most of the time, and showed steady improvement over the months. Still, there were a large number of visits with patients' INR results under 2, these results are being audited individually to clarify the reason. The results in the group of patients with a lower goal are acceptable, but there is room for improvement, particularly in the undertreated group. Case by case auditing will be done. The philosophy of continuous quality improvement was applied [15,16]. A goal was established, and a reduction in variability both in processes and outcomes was pursued. The cycle was then restarted as a part of a continuous improvement effort.

There were problem areas in the study as well: a number of patients were overtreated during the implementation phase -- Computer phase 1 --. The number was not as large as that reported in other series with the same goal [4]. Particular attention has to be paid to the first phase of implementation of a clinical information system, because the sum of the impact on the environment and problems with the system logic could be detrimental rather than beneficial.

We did not separate the overall change to the environment from the program logic while we were analyzing the impact of Warfarin 2.0 on the levels of anticoagulation. We were interested in dealing with warfarin management from a global perspective. Otherwise, it would have been a basic clinical experiment, not a practical development.

We are also aware that intermediate outcomes (in our case, amount of care provided and PT results) were not necessarily a reflection of end results (major bleeding, thromboembolism, death) [17]. There is a module in the program to trace patients who stopped attending the clinic. These patients may then have had a severe complication that would have gone undocumented otherwise. After this

step, a thorough report and analysis will be done. Since the goal of anticoagulation ultimately depends on an equilibrium between risk of major bleeding and thromboembolic complications [18], this analysis would be helpful if the sample size is large enough. At this time, the size of the population would allow us to demonstrate substantial differences only, and preliminary data does not show this kind of result.

Warfarin 2.0 uses rules to represent knowledge. This strategy allows the clinician to understand the reasoning of the program. There are other strategies, some of them validated within clinical practice [2-5], and others still experimental to a greater or lesser degree [6-8]. It would be useful to identify the cases where each approach yields the best results, and combine them.

It will be important for our perception of transferability issues to observe the success and modifications that have to be made in the Favaloro Foundation in Buenos Aires. This site follows about 100 patients a week.

The development of a computerized decision support system is a complex task. Furthermore, its implementation is even more challenging. However, computers are excellent tools for providing real-time feedback to physicians. The complexity of the task should not undermine our efforts.

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