Algorithms for monitoring warfarin use: Results from Delphi Method

Eunice Kazue Kano[1], Jessica Bassani Borges[1], Erika Burim Scomparini[1], Ana Paula Curi[2], Eliane Ribeiro[1]*

[1]Department of Pharmacy, Faculty of Pharmaceutical Sciences, Universidade de São Paulo (USP), São Paulo, SP, Brazil
[2]School of Arts, Sciences and Humanities, USP, São Paulo, SP, Brazil

Summary

Warfarin stands as the most prescribed oral anticoagulant. New oral anticoagulants have been approved recently; however, their use is limited and the reversibility techniques of the anticoagulation effect are little known. Thus, our study's purpose was to develop algorithms for therapeutic monitoring of patients taking warfarin based on the opinion of physicians who prescribe this medicine in their clinical practice. The development of the algorithm was performed in two stages, namely: (i) literature review and (ii) algorithm evaluation by physicians using a Delphi Method. Based on the articles analyzed, two algorithms were developed: "Recommendations for the use of warfarin in anticoagulation therapy" and "Recommendations for the use of warfarin in anticoagulation therapy: dose adjustment and bleeding control." Later, these algorithms were analyzed by 19 medical doctors that responded to the invitation and agreed to participate in the study. Of these, 16 responded to the first round, 11 to the second and eight to the third round. A 70% consensus or higher was reached for most issues and at least 50% for six questions. We were able to develop algorithms to monitor the use of warfarin by physicians using a Delphi Method. The proposed method is inexpensive and involves the participation of specialists, and it has proved adequate for the intended purpose. Further studies are needed to validate these algorithms, enabling them to be used in clinical practice.

Keywords: Delphi technique, warfarin, decision-making, medication therapy management.

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***Correspondence:**
Address: Av. Prof. Lineu Prestes, 2.565
São Paulo, SP – Brazil
Postal code: 05508-000
elianer@hu.usp.br

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Introduction

Warfarin was commercially introduced in the market in 1954.[1] Since then, it stands as the most prescribed oral anticoagulant, widely used for prophylaxis and treatment of venous thromboembolism and complications associated with atrial fibrillation and heart valve replacement.[2,3]

New oral anticoagulants, such as direct thrombin inhibitors (DTIs), have been recently approved. However, their use is restricted and reversibility techniques are little known, unlike warfarin, which can be readily reversed by using vitamin K, fresh plasma or recombinant factor VII.[4-6] Thus, despite DTIs show predictable pharmacokinetics, which eliminates the need for serum monitoring, they must be monitored as the causative factors for this risk.[4,6]

Other problems related with DTIs include the need for dose adjustments in renal failure patients, the contraindication of use by liver disease patients and drug interactions.[4-7]

Although some DTIs have shown good risk-benefit ratio,[5,8-10] more information regarding safety, especially in long-term treatment, is still needed,[4-7] as well as confirmation of the findings obtained so far for DTIs in new clinical trials.[11]

Nevertheless, warfarin, which is inexpensive and easily accessible, shows efficacy above 90% in preventing further thrombotic episodes, if correctly used, and constitutes an important therapeutic alternative, especially for low-income populations.[12]

Since the pharmacotherapy involving this drug poses risks to patients due to its narrow therapeutic range, information on the use and monitoring of warfarin are essential to establish algorithms or protocols. These documents must serve as guides to therapeutic management by the health team in patient care in order to ensure efficiency and prevent adverse events.[13,14]

The protocols must include suggestions for clinical management based on the best scientific evidence available, produced in a structured basis, with common sense and honesty. In the absence of evidence or in situations of conflicting evidence, consensus of experienced experts must be achieved. Therefore, relevant information, appropriate for every situation, are obtained in a systematic basis and become the final link between good quality science and good medical practice.[15-17]

The Delphi Method is a widespread technique, used since the early 1960s for the systematic search of expert consensus on a specific issue.[18,19] According to this method, a group of experts is consulted on a particular subject, usually related to low-grade scientific evidence that requires a consensus.[20]

In the health sector, the Delphi Method is being increasingly used due to its ease of application, low cost, the fact that it allows equal participation of all individuals involved, in addition to yielding qualified collective opinion on the subject. Despite these advantages, its use is not free from bias, especially if the choice of panelists is not done carefully. It is also important to emphasize that the results obtained using the Delphi Method represent a specific time and the opinion of some professionals, and it is not an absolute truth.[21]

Thus, while warfarin, despite its limitations, still remains as the drug of choice in anticoagulation therapy, being distributed free of charge by the Brazilian public health system, developing new strategies, such as the development and validation of algorithms/protocols for the drug's use, is fundamental to increase therapy safety and effectiveness.

The objective of our study was to develop algorithms for therapeutic monitoring of patients taking warfarin based on the opinion of medical experts.

Method

The development of the algorithm was performed in two stages: (i) a literature review for developing the algorithm; and (ii) the algorithm's evaluation by medical experts.

In the first stage, a search was performed in the following electronic databases for the years 2008 to present: "PubMed" and "Medline" (International Medical Literature), Lilacs (Latin American and Caribbean Literature on Health Sciences), and Embase (International Biomedical Literature). The UptoDate (Wolters Kluwer Health) evidence-based clinical decisions database was also used. The combination of the following terms was applied: warfarin, algorithm, therapeutic, dose adjustment, DRR, INR, drug monitoring, dose and response.

Full-text publications available in Portuguese, English or Spanish on human studies presenting primary data, or review articles on the subject were included. In addition to this strategy, some articles were selected from references of articles found in the databases searched. From the analysis of the articles, we elaborated the first algorithm and questions to be responded by medical experts in anticoagulation according to the Delphi Method.

The questions were sent to a group of experts, anonymously and systematically. Three rounds of questionnaires containing questions that did not reach consensus in the previous stage were applied.

Anonymity, the lack of personal contact among respondents, the statistical representation of the distribution of results, and the feedback to the group for reassessment of responses in subsequent rounds were the main features used from said method.[20]

Our project was approved by the Research Ethics Committee of the University Hospital of University of São Paulo, number 764/07 and SISNEP 0048.0.198.018-07; all respondents signed an Informed Consent (IC) form.

Nineteen (19) medical doctors experts in warfarin anticoagulation, from different specialties and different institutions, all linked to teaching hospitals in São Paulo, were invited to participate in the research. The medical experts were selected after curriculum review, contacts in university hospitals and search on university websites.

The inclusion criteria were:

- being a general practitioner, cardiologist, hematologist and/or vascular surgeon;
- working in universities and/or hospitals in the city of São Paulo that conduct scientific research;
- being experienced in the clinical use of warfarin.

The first contact with medical experts was performed over the phone, and then an invitation letter containing the study objectives and responsibilities of the respondents was electronically sent. In cases where the physician agreed to participate in the study, a date was scheduled so that the researcher could provide more details on the project and collect a signed IC form.

Elaboration and application of questionnaires

For the first questionnaire (Q1), 25 questions were elaborated about conflicting theoretical data to be answered in a maximum of 30 minutes. Q1 was developed in electronic and printed forms, with open fields for answers only, and was divided into four parts:

a. Introduction and general guidelines.

b. Personal data such as age, gender, specialty, and type of service in which he/she worked at the time were requested.
c. Questions about conflicting data, and about the evaluation algorithm itself.
d. Generic questions, in order to evaluate the usefulness of the algorithm in medical practice.

From the analysis of Q1 responses, a second questionnaire (Q2) was elaborated and sent to those same experts, this time divided into two parts: a) letter to the expert; b) multiple-choice questions which did not reach consensus in Q1, with a graph showing the percentage results obtained in Q1, so that respondents could know the answer trend for each question. Then, the third questionnaire (Q3) was elaborated, containing questions that did not reach consensus in Q2, divided into two parts, with an explanatory letter and multiple-choice questions. After reviewing the responses in Q3, a letter expressing our gratitude and containing feedback from the study results was elaborated and sent to each respondent.

Quantitative analysis of the responses obtained in Q1, Q2 and Q3 was performed by using basic descriptive statistics, including means, medians, and standard deviation. For qualitative data, the responses were expressed in percentage (response distribution frequencies). Consensus was achieved whenever a minimum of 70% of respondents chose the same alternative.

Results

Development of algorithm for therapeutic drug monitoring in patients taking warfarin

Based on the analyzed articles, two algorithms were developed: "Recommendations for the use of warfarin in anticoagulation therapy" (Figure 1A) and "Recommendations for the use of warfarin in anticoagulation therapy: dose adjustment and bleeding control" (Figure 1B).

Algorithm evaluation by medical experts by Delphi Method

Figure 2 shows the flowchart of the Delphi Method used for applying the questionnaires to medical experts.

Medical experts participating in the study

Most medical experts (63%) were male, aged 41.5±10.13 (mean±SD) years, with a length of education of 14.46 years after medical internship. Nineteen percent (19%) worked in public institutions, 6.25% in private institutions, and 75% in both.

These experts represented the following medical areas: 68% cardiology, 16% hematology, 11% general practice and 5% vascular surgery.

Algorithms evaluation

In the first round, out of 19 questions sent, 16 were answered and sent back to us, representing a loss of 15.79%.

Regarding miscellaneous data, all the doctors reported that the algorithms are useful tools for warfarin dose adjustment in clinical practice. Sixty-three percent (63%) considered it important to apply the algorithm in public and private hospitals, and medical offices.

Based on the results observed in this first round, it became clear that the optimum dosage of warfarin is controversial. The doubts raised and the lack of standardization are so great that 100% of the doctors who answered the questionnaire considered the use of the algorithm as an important decision tree for the prescription of warfarin dose.

The conflicting questions in Q1 were classified according to the percentage found: with consensus and without consensus. Those questions without consensus in the first round were repeated in the second round (Q2), and those for which no consensus was obtained in the second round were repeated once again in the third round (Q3). Table 1 shows the questions contained in all questionnaires as well as their responses.

In Table 1, it is noted that, for 18 conflicting questions in the first round, subdivided into 27 questions, consensus was reached with 70% or higher agreement for 17 (62.96%=17/27).

Q2 comprised ten multiple-choice questions sent to 16 experts who participated in the first round. Of these, 11 responded to the questions. Therefore, there was a loss of 31.25% compared to the previous round, and 42.10% of the total.

In three (3/12=25%) out of 12 questions, consensus was reached with ≥ 70% agreement; Q3 was sent to the 11 respondents from the previous round, including eight questions that achieved no consensus in the second round, as well as frequency graphs for the responses in the previous questionnaire.

Eight experts responded to this round (72.72%=8/11). Based on the previous round, there was a loss of 27.27% of respondents. For all the rounds, the registered loss was 57.89% (8/19).

Consensus of ≥ 70% was reached for two questions, and at least 50% for the other six.

Based on the three rounds, only the algorithm "Recommendation for using warfarin in anticoagulation therapy: bleeding control" was changed; pending questions and those which did not reach consensus with agreement of 70% or higher were underlined; and those showing agreement > 50% are described in italics (Figure 3).

TABLE 1 Questions contained in Q1, Q2 and Q3 and responses obtained from medical experts after their application in first, second and third rounds. The responses were classified according to their percentage of agreement.

Questions	First Round		
	Response	Amount (%) (responses/ doctors)	Consensus (> 70%)
1. What is the initial dose of warfarin for an adult outpatient who has never taken warfarin and whose desirable INR range for therapy is between 2 and 3?	5 mg/day	94% (15/16)	Yes
	2.5 mg/day	06% (16/01)	
2. And for those patients in poor nutritional status, the elderly, patients with liver disease or those at high risk of bleeding?	2.5 mg/day	75% (12/16)	Yes
	2.0 mg/day	13% (02/16)	
	5 mg/day	06% (16/01)	
	I would not use	06% (16/01)	
3. Is there any difference in the initial dose of warfarin between inpatients and outpatients?	No	75% (12/16)	Yes
	Yes	25% (04/16)	
*4. After how many days from taking the initial dose should the first INR testing be done to assess the patient?	5 days	50% (08/16)	No
	3 days	25% (04/16)	
	7 days	25% (04/16)	
*5. What should be the frequency of INR monitoring until the desired range is reached?	weekly	63% (10/16)	No
	every 2-3 days	31% (05/16)	
	Daily	06% (16/01)	
*6. Is there a preferable period in a day to collect blood for INR testing?	Yes, morning.	56% (09/16)	No
	No	44% (07/16)	
7. What should be the frequency for monitoring of INR after reaching the therapeutic range?	monthly	81% (13/16)	Yes
	every 6 weeks	13% (02/16)	
	weekly	06% (16/01)	
8. When should dose adjustment be done?	If INR is out of the therapeutic range, after 4-6 days from the beginning of therapy.	75% (12/16)	Yes
	If INR is out of the therapeutic range, in two consecutive measurements;	44% (07/16)	
	If after 3 days using warfarin, the patient has not yet reached the expected INR range	06% (16/01)	
**9. Which INR ranges would determine an action for changing the dose?	INR ≤ 1.5/1.5 < INR ≤ 1.8/ 1.9 ≤ INR < 3.2/ 3.2 ≤ INR < 5.0/INR ≥ 5.0	25% (04/16)	Yes
	1.0 ≤ INR <2.0/ 3.0 < INR < 6.0/ 6.0 ≤ INR < 10.0/ 10.0 ≤ INR ≤ 18.0/ INR > 18.0	69% (11/16)	
	INR ≤ 1.5/1.51 ≤ INR ≤1.99/ 2.0 ≤ INR ≤ 3.0/ 3.01 ≤ INR < 3.99/ 4.0 ≤ INR ≤ 4.99/5.0 ≤ INR ≤ 8.99/ INR ≥ 9.0	13% (02/16)	
	other	25% (04/16)	
	No answer	13% (02/16)	
Questions 10 to 16 refer to an outpatient whose therapeutic INR range is between 2 and 3, and in none of the cases the patient has shown evidence of hemorrhage.			
*10. If a patient shows an INR lower than or equal to 1.5; what would the dose adjustment be?	Increase 20%	38% (06/16)	No
	Increase 33%	31% (05/16)	
	Double the dose	06% (16/01)	
	other	25% (04/16)	

(*continues*)

TABLE 1 Questions contained in Q1, Q2 and Q3 and responses obtained from medical experts after their application in first, second and third rounds. The responses were classified according to their percentage of agreement.

Questions	First Round		
	Response	Amount (%) (responses/ doctors)	Consensus (> 70%)
10a. After how many days would you reassess patient status?	5-7 days	100% (16/16)	Yes
*11. What if 1.5 ≤ INR ≤ 1.8?	Increase 15%	38% (06/16)	No
	Increase 10%	31% (05/16)	
	Recollect after a week	06% (16/01)	
	Other	25% (04/16)	
11a. After how many days would you reassess patient status?	5 to 7 days	88% (14/16)	Yes
	14 days	13% (02/16)	
12. What if 1.8 ≤ INR ≤ 3.2?	Do not change the dose	81% (13/16)	Yes
	Reduce the dose by 25%	13% (02/16)	
*12a. After how many days would you reassess patient status?	7-10 days	44% (07/16)	No
	30 days	44% (07/16)	
	other	13% (02/16)	
*13. What if 3.2 ≤ INR <4.9?	Discontinue the next dose and reintroduce warfarin at a weekly dose reduced by 10 -20%.	50% (08/16)	No
	Discontinue the next dose and reintroduce warfarin at a weekly dose reduced by 33%.	44% (07/16)	
	Discontinue for three days and reintroduce warfarin at a dose reduced by 25-50%.	06% (16/01)	
13a. After how many days would you reassess patient status?	5-7 Days	88% (14/16)	Yes
	2-5 days	06% (16/01)	
	14 days	06% (16/01)	
*14. What if 5.0 ≤ INR <9.0, with no evidence of bleeding	Discontinue warfarin and assess the need to give vitamin K orally (2-4 mg). After 24 hours, if there is no more risk of bleeding, reintroduce warfarin with reduction of 15% in the weekly dose.	38% (6/16)	No
	Discontinue the next three doses and then restart the treatment at a dose 33% lower	38% (6/16)	
	Discontinue the next dose and then restart the treatment at lower doses until reach the therapeutic INR	06% (16/01)	
	Discontinue until desirable INR and reintroduce at reduced dose	06% (16/01)	
	Discontinue until desirable INR, reassess in 2-3 days, and reintroduce at reduced dose	06% (16/01)	
	Discontinue warfarin and assess the need to give vitamin K orally (2-4 mg). After 24 hours, if there is no more risk of bleeding, reintroduce warfarin with reduction of 50% in the weekly dose.	06% (16/01)	
*14a. After how many days would you reassess patient status?	3-7 days	56% (9/16)	No
	2 days	25% (04/16)	
	24 hours	13% (02/16)	
	No answer	06% (16/01)	

(*continues*)

TABLE 1 Questions contained in Q1, Q2 and Q3 and responses obtained from medical experts after their application in first, second and third rounds. The responses were classified according to their percentage of agreement.

Questions	First Round		
	Response	**Amount (%) (responses/ doctors)**	**Consensus (> 70%)**
15. And if INR > 10.0, with no evidence of bleeding?	Discontinue warfarin until INR reduction and give 5 to 10 mg of vitamin K orally.	75% (12/16)	Yes
	Other	31% (05/16)	
*15a. After how long would you reassess patient status?	24 hours	69% (11/16)	No
	Every 2 Days	31% (05/16)	
16. In case there is evidence of minor bleeding, what is the dose of vitamin K?	Discontinue warfarin, give vitamin K 10mg and, if necessary, supplement with fresh plasma or prothrombin concentrate.	94% (15/16)	Yes
	Discontinue warfarin, give vitamin K, and restart later	06% (16/01)	
16a. After how many days would you reassess patient status?	12 hours	75% (12/16)	Yes
	24 hours	25% (04/16)	
The question below refers to the case of a patient showing evidences of major bleeding:			
17. Sugiro: How would you manage warfarin therapy?	Discontinue warfarin, give prothrombin complex and vitamin K 10mg 75% (12/16)		Yes
	other	25% (04/16)	
17a. After how long should the patient be reassessed?	12 hours	81% (13/16)	Yes
	1 day	19% (3/16)	
The question below refers to the case of a patient experiencing life-threatening bleeding: 18. Sugiro: How would you manage warfarin therapy?	Discontinue warfarin, give prothrombin complex and vitamin K 10mg	75% (12/16)	Yes
	Other	25% (04/16)	
18a. After how many days would you reassess patient status?	12 hours	81% (13/16)	Yes
	1 day	19% (3/16)	
Questions	Second Round		
	Response	Amount (%) (responses/ doctors)	Consensus (> 70%)
**1. How many days after taking the initial dose should the first INR testing be done to assess the patient?	3 days	27% (3/11)	No
	5 days	55% (6/11)	
	1 week	18% (2/11)	
**2. What should be the frequency of INR monitoring until the desired range is reached?	Every 2-3 days	36% (4/11)	No
	Weekly	64% (7/11)	
**3. Is there a preferable period within the day to collect blood for INR testing?	Yes, morning	36% (4/11)	No
	No	64% (7/11)	
4. When should dose adjustment be done (tick all possible alternatives)?	If the INR is out of therapeutic range after 4-6 days from the beginning of the therapy.	100% (11/11)	Yes
The following questions refer to an outpatient whose therapeutic INR range is between 2 and 3, and in none of the cases the patient shows evidence of hemorrhage.			
**5. If a patient shows INR lower than 1.5, which would be the dose adjustment?	Increase by 20%	27% (3/11)	No
	Double the daily dose	9% (1/11)	
	Increase by 33%	55% (6/11)	
	Other	9% (1/11)	

(*continues*)

TABLE 1 Questions contained in Q1, Q2 and Q3 and responses obtained from medical experts after their application in first, second and third rounds. The responses were classified according to their percentage of agreement.

Questions	First Round		
	Response	**Amount (%) (responses/ doctors)**	**Consensus (> 70%)**
**6. What if 1.5 ≤ INR ≤1,8	Increase by 15%	64% (7/11)	No
	Increase by 25%	36% (4/11)	
7. After how many days would you reassess the status of a patient showing 1.9 ≤ INR ≤ 3.4?	7-14 days	73% (8/11)	Yes
	30 days	27% (3/11)	
**8. What if 3.4 ≤ INR ≤ 5.0	Suspend the next dose and reintroduce warfarin with a weekly dose reduced by 10-20%	55% (6/11)	No
	Suspend the next dose and reintroduce warfarin with a weekly dose reduced by 33%	45% (5/11)	
**9. What if 5.0 ≤ INR ≤ 9.0 with patient under risk to develop hemorrhage in the next 30 days?	Discontinue treatment for the 3 next doses and then restart therapy at a dose 33% lower	45% (5/11)	No
	Discontinue warfarin treatment and assess the need for oral administration of vitamin K (2-4 mg). After 24 hours, if there is no more risk of bleeding, reintroduce warfarin with 15% reduction	45% (5/11)	
	Other	9% (1/11)	
**9a. After how many days would you reassess patient status?	24h	55% (6/11)	No
	2 days	9% (1/11)	
	3-7 days	36% (4/11)	
10. What if 9.0 ≤ INR ≤ 20.0?	Discontinue warfarin therapy until reduction of INR. Reintroduce therapy at low-dose of warfarin and restart dose titration. If required, give vitamin K (5-10mg)	73% (8/11)	Yes
	Other	27% (3/11)	
**10a. After how many days would you reassess patient status?	Daily	64% (7/11)	No
	Every 2 Days	36% (4/11)	
Questions	Third Round		
	Response	Amount (%) (responses/ doctors)	Consensus (> 70%)
1. Is there a preferable period during the day to collect blood for INR testing?	Yes, morning	50% (4/8)	No
	No, but always in the same period	50% (4/8)	
Questions 2 to 5 refer to an outpatient whose therapeutic INR range is between 2 and 3, and in none of the cases the patient shows evidence of hemorrhage.			
2. If a patient shows INR lower than 1.5, which would be the dose adjustment?	Increase by 20%	38% (3/8)	No
	Increase by 33%	62% (5/8)	
3. What if 1.5 ≤ INR ≤1.8	Increase by 15%	38% (3/8)	No
	Increase by 25%	50% (4/8)	
	Other	12% (1/8)	
4. What if 3.2 ≤ INR ≤ 4.9	Suspend the next dose and reintroduce warfarin with a weekly dose reduced by 10-20%	62% (5/8)	No
	Suspend the next dose and reintroduce warfarin with a weekly dose reduced by 33%	25% (2/8)	
	Other	12% (1/8)	

(*continues*)

TABLE 1 Questions contained in Q1, Q2 and Q3 and responses obtained from medical experts after their application in first, second and third rounds. The responses were classified according to their percentage of agreement.

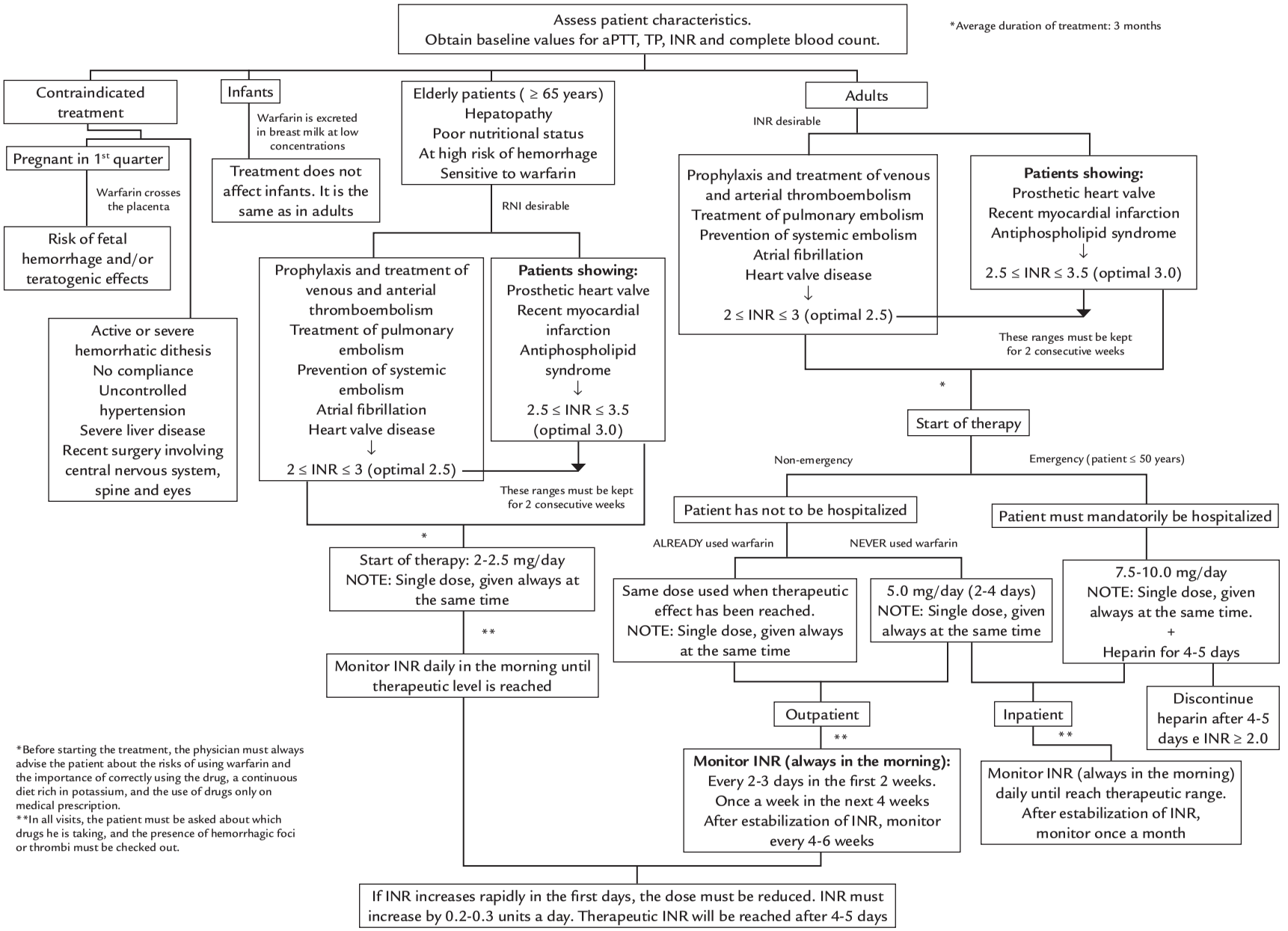
Questions	First Round		
	Response	**Amount (%) (responses/ doctors)**	**Consensus (> 70%)**
5. What if 5.0 ≤ INR ≤ 9.0 with no evidences of bleeding?	Discontinue the next 3 doses and then restart the therapy at a dose 33% lower	50% (4/8)	No
	Discontinue warfarin treatment and assess the need for oral administration of vitamin K (1-2 mg). After 24 hours, if there is no more risk of bleeding, reintroduce warfarin with 15% reduction	38% (3/8)	
	Other	12% (1/8)	
6. In case there is evidence of bleeding, classified as minor, what should the management be?	Suspend the next dose, give vitamin K according to INR (1-2 mg for INR> 4.5; p 1-2,5mg/5.0 <INR <9.0; 2,5-5,0mg for INR> = 9.0), monitor, and repeat if necessary, the dose of vitamin K, and restart warfarin therapy	50% (4/8)	No
	Discontinue and give vitamin K 1-2 mg, monitor, and repeat if necessary vitamin K, and restart therapy	38% (3/8)	
	Other	12% (1/8)	
7. In case there is evidence of bleeding, classified as minor, what should the management be?	Discontinue, give 5-10mg of vitamin K by slow intravenous infusion plus 25-50U/kg of prothrombin complex concentrate or 15ml/kg of fresh plasma, and reassess	100% (8/8)	Yes
8. In case there is evidence of a life-threatening bleeding, what should the management be?	Discontinue, give 10mg of vitamin K by slow intravenous infusion and 25-50U/kg of prothrombin complex concentrate OR 150 to 300 ml of fresh plasma, and reassess	75% (6/8)	Yes
	Discontinue, give 10mg of vitamin K by slow intravenous infusion, 25-50U/kg of prothrombin complex concentrate and 15ml/kg of fresh plasma, and reassess	25% (2/8)	

*Questions contained in the questionnaire of the second round.

**Questions contained in the questionnaire of the third round.

A

Recommendations for the use of warfarin in anticoagulation therapy



*Before starting the treatment, the physician must always advise the patient about the risks of using warfarin and the importance of correctly using the drug, a continuous diet rich in potassium, and the use of drugs only on medical prescription.
**In all visits, the patient must be asked about which drugs he is taking, and the presence of hemorrhagic foci or thrombi must be checked out.

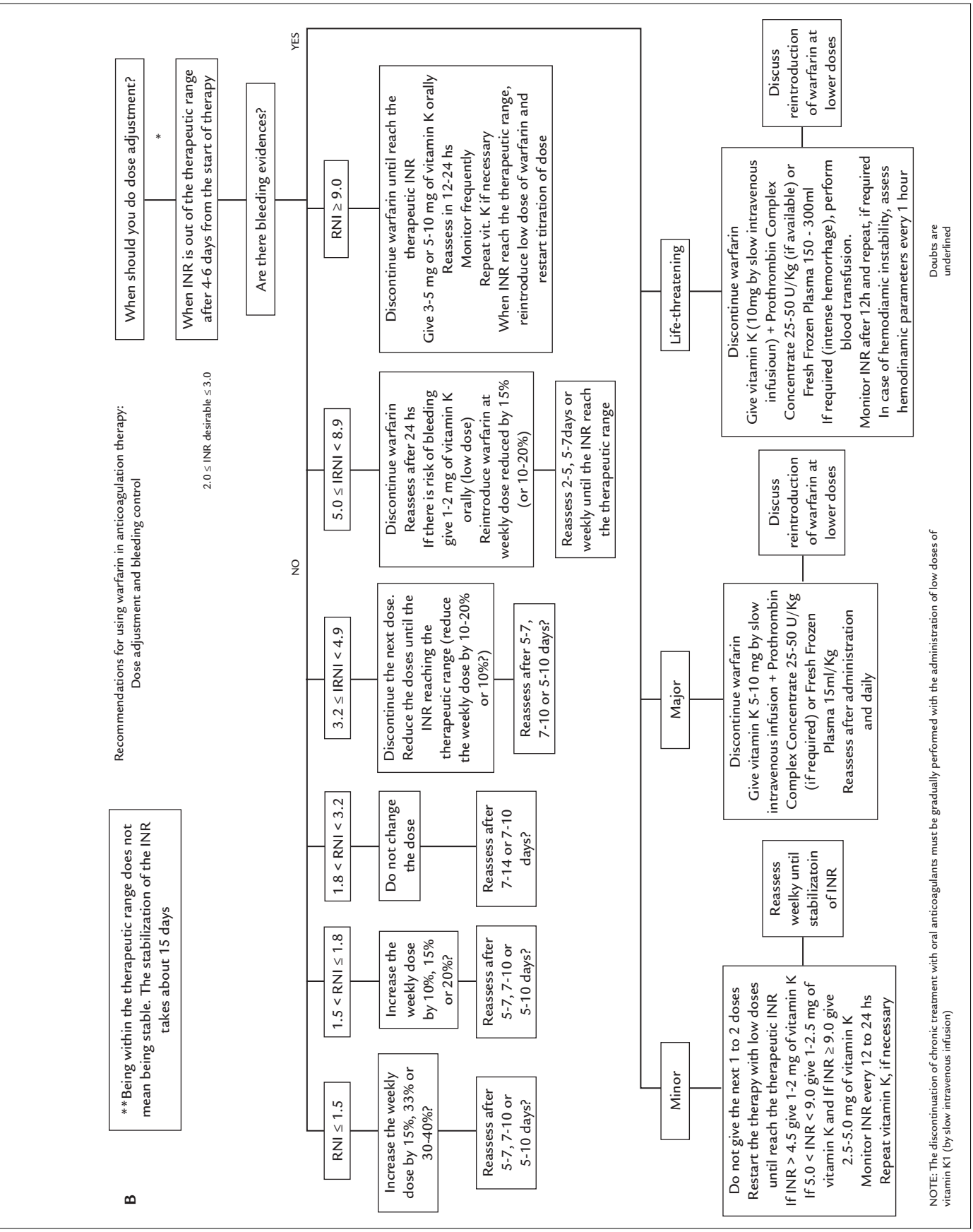


FIGURE 1 (A) Algorithm "Recommendation for the use of warfarin in anticoagulation therapy." (B) Algorithm "Recommendations for the use of warfarin in anticoagulation therapy: dose adjustment and bleeding control" (before the application of the Delphi Method).

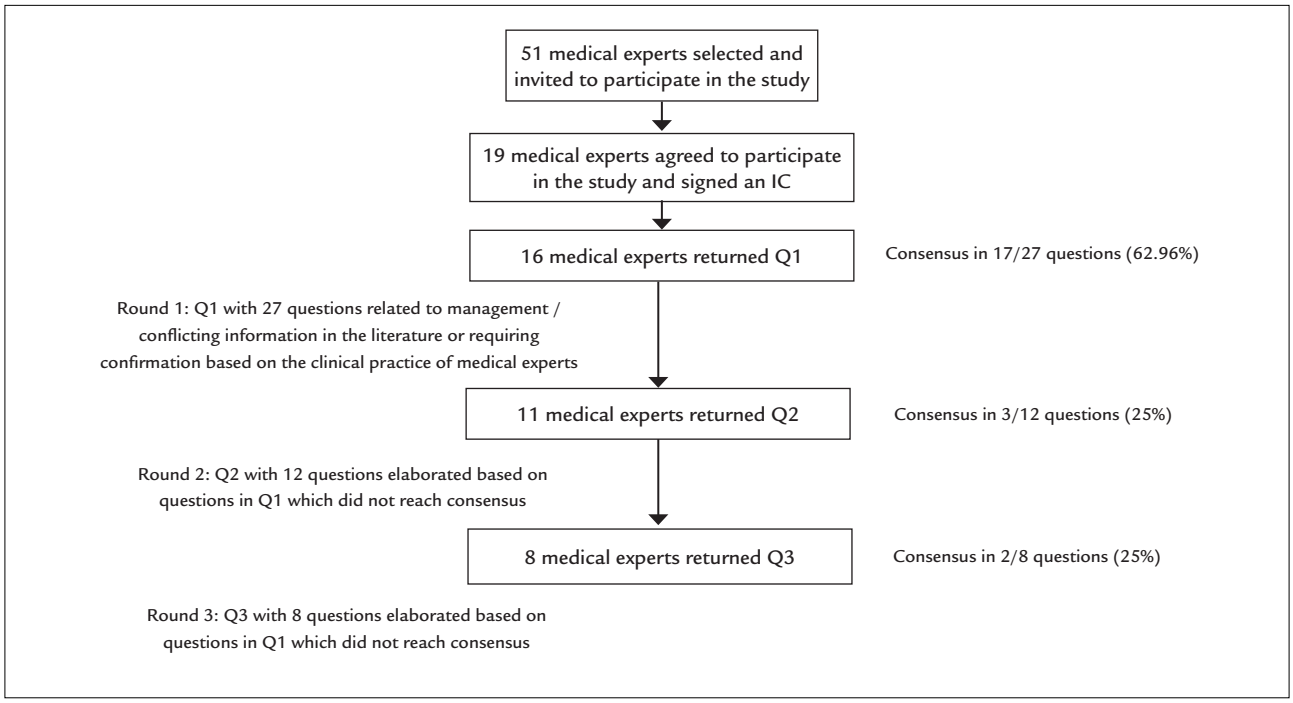


FIGURE 2 Flowchart of Delphi Method for the application of questionnaires to medical doctors specialized in anticoagulation with warfarin.

Discussion

Even with the introduction of new oral anticoagulants,[10] warfarin still stands as the oral anticoagulant of choice for thromboembolic events due to several factors: (i) deep knowledge of various clinical indications; (ii) accumulation of safety data; (iii) availability of antidote; (iv) possibility of monitoring with a simple blood sample; (v) low cost of treatment; (vi) free distribution by the Brazilian public health system; (vii) availability of pharmacogenetic studies for optimization of drug therapy.

Pharmacotherapy with warfarin requires careful and continuous monitoring of the patient to minimize the risk of bleeding and thrombosis, since the dose required for proper anticoagulation is highly variable. One measure to minimize the risks and enhance patient safety is the application of clinical and pharmacogenetic algorithms to establish the optimal dose.

The use of algorithms based on pharmacogenetics for individualization of dose regimen for warfarin is described by several authors,[22-25] since genotype is the main determinant of the required warfarin dose and the risk of bleeding, especially in the early months of therapy.[26]

Clinical studies have shown that the use of genotype to determine warfarin dose generates variability of results, especially because of the complexity of interrelations between genetic and non-genetic factors.[3,23] Meta-analyses have shown that the dose-adjustment strategy guided by genotype does not improve anticoagulation control at the beginning of therapy compared to adjustments based on clinical data.[24,27] Thus, studies conducted by Johnson and Cavallari[3] indicated that the algorithms based on pharmacogenetics to warfarin are "population-specific" and generally achieve better responses in European populations, and cannot be extrapolated for mixed samples. The Brazilian population is highly heterogeneous and this scenario is challenging for pharmacogenetic studies.[23]

Additionally, the amount of information related to pharmacogenomics of warfarin, especially from well-conducted studies, still remains poor and inconsistent.[2,28]

In times of cost reductions and patient-centered care, clinical practice must always aim at reducing adverse events and improving patient quality of life, as well as optimize the use of financial resources. Cost-effectiveness analyses of dose adjustment guided by genotype for warfarin are inconclusive. In this context, it seems unlikely that a dose adjustment guided by genotype for patients who will start treatment with warfarin will become the standard in the near future.[27] For Stergiopoulos and Brown,[27] it is more feasible to allocate financial resources for the establishment of better infrastructure for INR testing, implementation of validated clinical protocols of anticoagulation and promotion of patient compliance.

Traditionally, pharmacotherapy with warfarin starts with a non-standardized dose, which is adjusted based on

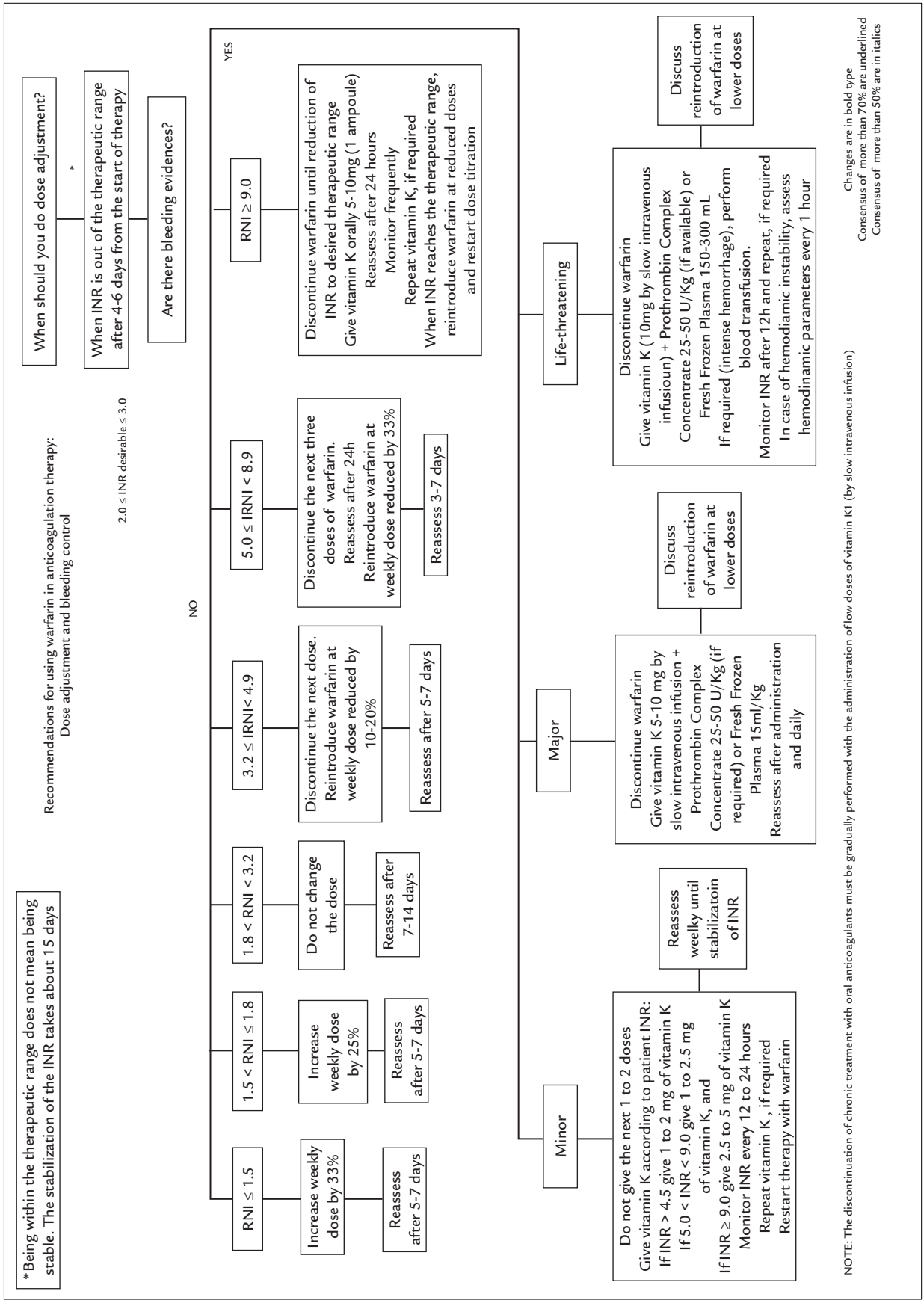


FIGURE 3 Algorithm "Recommendations for the use of warfarin in anticoagulation therapy: dose adjustment and bleeding control" (after the application of the Delphi Method).

the INR of prothrombin time. A literature search indicated that there are disagreements regarding the initial dose, the time and frequency of INR monitoring, and dose adjustment in case of some adverse event. These issues were evaluated in our study by means of Delphi Method.

In our study, experts were judiciously selected from different specialties and linked to private and/or public hospitals to ensure group diversity. According to Keeney et al.,[29] the selection of experts (or panelists) is one of the critical points of this method, since the result of the study will critically depend on the opinion of the respondents. They must be really involved with the subject of the panel and represent the opinion of a population.

Regarding panel size, the literature does not determine the ideal number of panelists, since the result does not depend on the statistical power of the sample size. Nevertheless, it suggests the inclusion of 10-18 experts.[30] Furthermore, the size and composition of the panel depends on the nature of the research.[31] Our study started with 19 panelists, which is a number higher than the recommended considering potential dropouts.

The loss of follow-up by panelists along the rounds may restrict the application of the Delphi Method. Considering this, some care has been taken in our study, such as providing speedy feedback of the results of each round, and encouraging non-respondents to respond through systematic follow-up contacts. The peak loss in our study was recorded in the second round, 31.25%, and according to Keeney et al.[29] the optimal maximum loss of respondents at follow-up must be 30% in each round of the questionnaire.

Regarding the number of questions that composed the questionnaire, the first round, which included the largest number of questions, contained 27 items, which is an adequate number to ensure the compliance of respondents. According to Wright and Giovinazzo,[20] questions should be mainly composed of alternatives, so that the total time to answer them does not exceed 30 minutes.

The number of rounds in the studies published in the literature varies from 1 to more than 5 and most of them include 2-3 rounds.[32] In our study, a 3-round design was adopted.

The responses obtained from the questionnaires must be evaluated based on the agreement or consensus among the consulted experts, but the definition of whatever constitutes consensus is controversial. Some authors suggest as consensus 51% of agreement among respondents regarding a certain answer, but others suggest 70%, or 50%.[33-35] In our study, most of the questions reached a consensus ≥ 70%, and all of them had a consensus ≥ 50%.

In the first round, there was no consensus in 37% of the questions, which shows a high degree of disagreement among the consulted experts. Most of the questions that did yield consensus were related to dose adjustment based on the results of patients' INR without evidence of hemorrhage and time for reassessment. On the other hand, consensus was reached in all questions related to clinical management whenever the patient has hemorrhage, demonstrating agreement to procedures among health professionals when the patient experiences a serious adverse event.

By resubmitting the questions, consensus was reached in only 25%, related to procedure and period for dose adjustment. This low agreement rate in the responses was expected since those were questions that depended greatly on the clinical experience of each medical expert.

In the third round, including eight questions, consensus was reached in two questions. Unfortunately, questions related to procedure and period for dose adjustments did not reach consensus. However, if a 50% agreement rate was considered in the third round, a consensus would be reached for all questions.

Therefore, out of 27 initial questions, only six questions failed to reach ≥ 70% consensus, which proves the applicability of this method for developing algorithms for monitoring the use of warfarin, in which the main questions about the pharmacotherapy of this drug could be solved.

Study limitations

Our study was conducted based on the subjective reasoning of the experts. Thus, besides the frequent disagreement in responses between the consulted health professionals, other experts who were not included in our study may not agree with the results obtained.

Conclusion

We were able to develop algorithms for monitoring the use of warfarin by medical experts using the Delphi Method. Since this method is inexpensive and involves the participation of experts, it has proved adequate for the intended purpose.

Further studies are needed to validate the algorithms developed in our research, enabling them to be used in clinical practice.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

Resumo

Algoritmos para monitorar o uso de varfarina: resultados do método Delphi

A varfarina é o anticoagulante oral mais prescrito. Novos anticoagulantes orais foram recentemente aprovados; porém, o uso é restrito e as técnicas de reversibilidade do efeito anticoagulante ainda são pouco conhecidas. Assim, este estudo propõe o desenvolvimento de um algoritmo para o monitoramento terapêutico de pacientes em uso de varfarina, com base na opinião de médicos que utilizam esse fármaco na prática clínica. O desenvolvimento do algoritmo foi realizado em dois estágios: (i) revisão da literatura e (ii) avaliação do algoritmo por médicos, segundo o método Delphi. Com base na análise dos artigos, dois algoritmos foram desenvolvidos: "Recomendações para o uso de varfarina na terapia anticoagulante" e "Recomendações para o uso de varfarina na terapia anticoagulante: ajuste de dose e controle de sangramento". Posteriormente, os algoritmos foram analisados por 19 médicos que responderam ao convite e aceitaram participar da pesquisa. Desses, 16 responderam a primeira rodada, 11, a segunda e oito, a terceira. Houve um consenso de 70% ou mais na maioria das questões e 50% para seis questões. Assim, foi possível desenvolver algoritmos para o monitoramento do uso de varfarina por médicos, utilizando o método Delphi. O método proposto é de baixo custo e envolve a participação de médicos especialistas, revelando-se adequado para o fim pretendido. Mais estudos são necessários para validar esses algoritmos, permitindo que eles sejam usados na prática clínica.

Palavras-chave: técnica Delfos, varfarina, tomada de decisões, conduta do tratamento medicamentoso.

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