International Journal of Pharmacy and Pharmaceutical Sciences

Print ISSN: 2656-0097 | Online ISSN: 0975-1491 Vol 15, Issue 1 2023

Original Article

DEVELOPMENT OF A PREDICTION TOOL FOR THE ASSESSMENT OF RISKS ASSOCIATED WITH ACENOCOUMAROL

V. SIVAKUMAR, SOWMIKA S.*, MADHUMITHA A., GOWTHAM KUMAR N., ANAS C. P.

Department of Pharmacy Practice, PSG College of Pharmacy, Coimbatore 641004, Tamil Nadu, India
Email: sowmikasuma@gmail.com

Received: 23 Sep 2022, Revised and Accepted: 19 Nov 2022

ABSTRACT

Objective: To develop a statistical predictive model to ensure the safest use of oral anticoagulant (Acenocoumarol) therapy.

Methods: It is a retrospective observational single-center study done at PSG Hospitals in Coimbatore, Tamilnadu, India. The data were collected from 2019 to 2020 from Hospital Information System (HIS). The statistical analysis was done using Chi-square and Multinomial logistic regression.

Results: The study includes 82 patients who were treated with Acenocoumarol. The results were calculated using a student t-test and the P-value was<0.0001, which is significant as it is less than 0.05, and the prediction tool is developed by using Multinomial Logistic Regression.

Conclusion: The Risk Assessment tool was developed. As the sample size increases, the accuracy of predictability also increases. So further validation of the tool is required for more accuracy and the data input should also be increased.

Keywords: Acenocoumarol, Risk assessment tool, Bleeding and clotting risks

DOI: https://dx.doi.org/10.22159/ijpps.2023v15i1.46434. Journal homepage: https://innovareacademics.in/journals/index.php/ijpps.

INTRODUCTION

Acenocoumarol compete with vitamin K for epoxide-reductase, thereby reducing the amount of reduced vitamin K required for the carboxylation of clotting factors II, VII, IX, and X. They are useful in the main and secondary prevention of thrombo-embolic disease conditions [1]. Oral anticoagulants are in place to treat various conditions such as Atrial fibrillation, Ischemic heart disease, Deep vein thrombosis, and Ischemic stroke, which help in the prevention of further disease and complications. Vitamin K antagonists (VKAs) are effective in the prevention of venous and arterial thrombosis, but their major complication is bleeding [2]. Still, bleeding is the most serious complication. Although many studies have tried to identify independent risk factors for bleeding, controversy still exists [4]. Acenocoumarol is generally given lifelong and its dosing management becomes complex in the presence of conditions such as atrial fibrillation, cerebrovascular disease, diabetes, hypertension, heart failure and rheumatoid heart disease, which leads to the notable increase in anticoagulants-induced bleeding and clotting risks. Some well-designed studies have shown evidence that the adverse effects associated with acenocoumarol are more difficult to control due to fluctuations in Pro-thrombin time (INR), Factor VII levels, and Protein C levels [5]. Currently, the dosing of acenocoumarol is based on INR which represents the bleeding and clotting risks even though the dosing is dependent upon INR, other factors such as co-morbidities and medications influence the INR, which makes the dosage adjustment difficult. Some studies show that increasing age is associated with bleeding risk [6, 7], and also studies show there is a significant association of bleeding risk with co-morbidities, co-medications (antiplatelets), and susceptibility to gastrointestinal bleeding [8]. Bleeding caused by anticoagulants is common and frequently significant. An individual patient's bleeding risk can be assessed, providing the primary-care physician with a quantitative basis for evaluating the risks and benefits of therapy and for enhancing patient management [9]. Since Acenocoumarol therapy is associated with serious adverse effect such as Bleeding and clotting. Therefore this study is intended to develop a risk prediction tool of acenocoumoral which helps in predicting the risk prior to the treatment. This tool can be used in the population between 18 to 75 y of age. Moreover, the tool predicts the risk by analysing all the factors beforehand and helps in further dose adjustment.

MATERIALS AND METHODS

Study design

This was a single-center Retrospective observational study. The approval (Ref. No: PSG/IHEC/2021/Appr/Exp/158) to conduct the study was obtained from the Institutional Ethics Committee of PSG College of Pharmacy before starting the study.

Study duration

The duration of the study was 6 mo.

Study setting

The study was conducted at PSG Hospitals, a tertiary care teaching hospital Coimbatore, Tamil Nadu. The study was conducted during the period of 6 mo from July 2019 to April 2020.

Study subjects

Patients who were treated with Acenocoumarol.

Study tool and data collection

The information from the data collection form during a period of 6 mo, from July 2019 to April 2020 and was scrutinized and evaluated. The collected data were analyzed statistically to obtain the results of the probability of the clotting and bleeding risk of patients treated with Acenocoumarol.

Inclusion and exclusion criteria

Patients between the age group of 18 to 75 y who were treated with Acenocoumarol. Pregnant women and patients with other co-morbidities such as Cancer and renal failure, were excluded from the study.

Statistical Analysis

The whole data collected were entered into an MS spreadsheet and the data were analyzed using IBM SPSS version 26.0. The relation between variables was found by testing the p-value<0.05. Descriptive statistics such as mean and median were used to describe demographic characteristics. Pearson's correlation was used to analyze the relationship between bleeding and clotting

events; and demographic variables (Age, Gender, Co-morbidities), Therapeutic variable (INR), and Clinical variable (co-medications and platelet level). Multinomial logistic regression was used to develop a Risk assessment tool.

RESULTS

A total of 82 Patient's data were included in the study; among them, 46(56.1%) were male and 36(43.9%) were female. A large proportion of patients were below the age group of 60 y and the least proportion of patients was above the age group of 60 y. In this, the majority of patients were having co-morbidities of hypertension and Diabetes Mellitus. Patients with co-morbidities such as Hypertension (n=38) and Diabetes mellitus (n=27). Patients were taking co-medications, Aspirin (n=26) and Clopidogrel (n=36). The study interpreted the data and analyzed the factors that are associated with bleeding and clotting risks. Both the influencing and non-influencing factors were analyzed using the chi-square test with evidence of p-value. The chi-square test shows a significant association with the risks and it is considered an influencing factor and factors which does not have a significant association are considered non-influencing factors.

Table 1: Study population data

Factors		Frequency
Age	Below 60	54
	Above 60	28
Gender	Male	46
	Female	36
Comorbidities	Hypertension	38
	Diabetes mellitus	27
Comedications	Aspirin	26
	Clopidogrel	36

The risk assessment tool is developed by interpreting and analyzing the data which were collected from the Hospital Information System. The statistics used for developing the risk assessment tool is multinomial logistic regression.

Development of a risk assessment tool

The Risk Assessment Tool is designed to predict the future risk of acenocoumarol therapy. The dependent factor (Dose) and independent factors (Age, Gender, Co-morbidities, and Co-medications) were entered and analyzed for developing this tool. The factors that are associated with the risk of bleeding, clotting and no event were analysed. The prediction data is a percentage value representing the probability of a particular complication that is bleeding and clotting risk and the approximate percentage of dose adjustment.

The goodness of fit describes how well it fits the set of observations. It summarizes the discrepancy between observed values and predicted values. The significant value determines whether observed sample frequencies differ significantly from expected frequencies. The significance value of 1.000 defines that this data is fit to develop a tool.

Table 2: Statistical tool

Goodness-of-Fit		
	Chi-Square	Significance
Pearson	39.725	1.000
Deviance	41.049	1.000

ACENOCOUMORAL RISK ASESSMENT TOOL		
Age	Below 60	
	Above 60	
Platelet range	Normal	
	Increase	
	Decrease	
Co-morbities	Hypertension	
	Diabetes Mellitus	
Co-medication	Aspirin	
	Clopidogrel	
INR	1 to 2	
	2 to 3	
	3 to 4	
	Above 4	
Dose	1mg	
	2mg	
	3mg	
	4mg	
Predicted value	No event	
	Bleeding	
	Clotting	
	dosage adjustment	

ACENOCOUMORAL RISK ASESSMENT TOOL		
Age	Below 60	NO
	Above 60	YES
Platelet range	Normal	YES
	Increase	NO
	Decrease	NO
Co-morbities	Hypertension	YES
	Diabetes Mellitus	NO
Co-medication	Aspirin	YES
	Clopidogrel	NO
INR	1 to 2	NO
	2 to 3	NO
	3 to 4	YES
	Above 4	NO
Dose	1mg	NO
	2mg	NO
	3mg	NO
	4mg	YES
Predicted value	No event	25%
	Bleeding	72%
	Clotting	3%
	dosage adjustment	53%

Fig. 1: Risk assessment tool

According to the tool, it gives the predicted value for risk associated with acenocoumoral: Bleeding, Clotting and No event. Patients with co-morbidities such as Hypertension (n=38) have a 57.8% of bleeding risk and 5.2% of clotting risk and Diabetes mellitus (n=27) has a 66.6% of bleeding risk and 3.7% of clotting risk. Patients taking co-medications, Aspirin (n=26) have a 57% of bleeding risk and Clopidogrel (n=36) has a 21% of bleeding risk. This tool can be used for analysing the factors of the patients who are treated with acenocoumoral to reduce the risk prior the treatment. Accordingly, the dose adjustment can be done, if the percentage of bleeding risk is>50% then the dose should be reduced and if clotting risk is >50% then the dose should be increased. By using this tool, the risk can be assessed earlier and further dose adjustments can be done without switching to other treatment options.

VALIDATION

The developed risk assessment tool is validated with 20 samples in patients who were been treated with acenocoumarol, and with the help of the tool, the samples are validated and result shows 75% accuracy. On validation, the tool helped in the prior prediction of risks. The advantage of developing this tool helps in close monitoring and the prediction rate leads to the cautious use of acenocoumarol in cardiac patients. However, there are some limitations, where other factors could be considered such as Pharmacokinetics and Pharmaco-dynamics (PKPD) data of the drug for more accuracy of the tool.

DISCUSSION

Using an administrative healthcare database, we identified that 5 variables were associated with major bleeding and clotting risk; and so a tool has been developed that estimates bleeding and clotting risk in patients taking Acenocoumarol. In the derivation data set, the discrimination of the tool was adequate. We validated the tool in a second data set, showing similar tool discrimination and adequate calibration. Our tool has a certain level of predictive ability than existing ones. The tool's performance decreased in those >75 y. Therefore, quantifying an individual's risk of major haemorrhage is a vital component of effective anticoagulation and management. There have been several risk stratification tests developed to assess bleeding and clotting risk; however, our tool has certain advantages compared to current schemes. With the introduction of Direct Oral Anticoagulants (DOACs), there is a need for a tool that provides clinicians and patients with more quantitative information to evaluate the risk-benefit ratio of anticoagulation therapy, which goes beyond the binary aspect of a positive or negative recommendation. Developed in a database that includes patients on DOACs, our tool describes bleeding risk by type of OAC initiated and takes into account the described lower risk of bleeding in DOACs. Using the predictive tool, clinicians can facilitate the decision-making process. For example, predicted bleeding risk based on our tool could be automatically calculated using available prior clinical information and shown to providers as part of a patient dashboard or clinical decision support system. The Risk Assessment tool was developed and validated in datasets with a large number of major bleeding events, allowing the identification of predictors and a more precise inference. The database also includes clinical information on co-morbidities and prescription medications that were considered risk factors for major bleeding and clotting risks.

In this study, elderly patients aged above 60 y have increased bleeding even; there is a significant association between age and bleeding events. A study conducted by Hilde A M Koositra in Groningen in 2016 [25] compared the bleeding event between age groups. Patients 90 y or older had a mildly increased risk of bleeding compared with patients aged 70 to 79 y. The risk of bleeding for patients aged 80 to 89 y was comparable with that for patients in their 70s. The higher bleeding risk in the elderly makes physicians reluctant to prescribe VKAs. However, the clinical decision to initiate anticoagulation should be as a balance between the risks of bleeding and thrombosis [26].

In our study, the bleeding event is higher in patients who have received the co-medications (Anti-platelet therapy). Same way, a cross-sectional study was performed in patients undergoing Vitamin K antagonists (VKA) therapy, followed in the cardiology department of the University Hospital of Sidi Bel Abbes (2018) conducted by Malika Belkacemi *et al.* [27]. The study constitutes one hundred patients and recorded 22 cases of bleeding. Overdose and concomitant use of drugs that interfere with the acenocoumarol effect are significant risk factors for bleeding. Another study conducted by Jose Miguel *et al.*, in 2018, reveals that the risk of bleeding is higher when anti-platelet therapy is combined with acenocoumarol than when patients take only acenocoumarol.

Hence, knowledge of predictive factors for VKA-related excessive anticoagulation seems to be of the utmost importance for improving patient management. There is a need for a national registry to assess the efficacy and safety of drug use in the short and long term. Vitamin K antagonists (VKAs) are effective in the prevention of venous and arterial thrombosis, but their major complication is bleeding.

This study has several limitations intrinsic to administrative claims data that should be considered. As such, the predictive ability of our tool depends on the ability to ascertain accurately both outcomes and covariates from administrative data. These variables, however, were defined according to validated algorithms with Positive Predictive Values between 80–100%. Second, our assessment of predictors of major bleeding is dependent on risk factors available in the database. Variables, including potentially relevant information, such as genetic susceptibility, were not available. Caution should therefore be taken when interpreting results for this tool due to the lack of availability, in our data, of variables needed to reconstruct this as originally defined. Third, in this analysis, a patient's follow-up did not end if there were changes in anticoagulation therapy or concerns with medication compliance or discontinuation following initiation. Fourth, OAC prescriptions were included independently of dosage strength. The data does not have adequate information to determine the appropriateness of the dosage; however, we included clinical indications for dosage reduction as candidate predictors in the tool. Since these variables were not selected for inclusion in the final tool, it may be reasonable to assume that they do not have an impact on the risk of bleeding or that physicians are prescribing appropriate doses to patients. Fifth, caution should be taken when applying this tool to those patients having co-morbidities other than Hypertension and Diabetes Mellitus. Sixth, we considered modifiable and non-modifiable predictors. Future work should evaluate the impact of modifying bleeding risk factors on the rates of bleeding in anti-coagulated patients.

CONCLUSION

To the best of our knowledge, this study aimed for the safest use of acenocoumarol and a decrease in the risks associated with the treatment. Therefore, a Risk assessment tool is developed, which helps in the prior prediction of risks and further dosage adjustments. The tool has been developed by interpreting and analyzing the factors which have a significant effect on bleeding and clotting risks.

LIMITATIONS OF THE STUDY

Due to the nature of administrative databases, we lack information. Specifically, the tool only reflects the risk of bleeding and clotting events in patients who are managed similarly to individuals in these databases and for those for whom anticoagulants are considered safe to use. It will be important to evaluate prospectively the ability of the proposed predictive tool to take into account potential changes in the quality of anticoagulation management by clinicians. We assume that it will perform well in a general population of patients. To improve the accuracy of this tool, the sample size should be large. This tool will be of future use with limitations such as use in pediatrics and large population.

ACKNOWLEDGEMENT

Authors take it as a privilege to acknowledge the Medical Record Department (MRD) for allowing us to collect patient data from Hospital Information System (HIS), PSG Hospitals.

FUNDING

No source of funding

AUTHORS CONTRIBUTIONS

Dr. V. Sivakumar and Madhumitha. A planned and designed the concept of the manuscript; Sowmika. S contributed to drafting the manuscript and reviewed the manuscript. Gowtham Kumar. N and Anas CP supported in designing and drafting the manuscript and literature search. Dr. V. Sivakumar and Sowmika. S reviewed the manuscript and contributed to designing the final version to be published.

CONFLICTS OF INTERESTS

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AF-Atrial Fibrillation; APT-Anti-Platelet Therapy; CAD-Coronary Artery Disease; HIS-Hospital Information System; INR-International Normalized Ratio; OAC-Oral Anti-Coagulants; PT-Prothrombin Time; HTN-Hypertension; DM-Diabetes Mellitus.

REFERENCES

1. Barcellona D, Vannini ML, Fenu L, Balestrieri C, Marongiu F. Warfarin or acenocoumarol: which is better in the management of oral anticoagulants? Thromb Haemost. 1998 Dec;80(6):899-902. doi: 10.1055/s-0037-1615385, PMID 9869157.
2. Hirsh J. Oral anticoagulant drugs. N Engl J Med. 1991 Jun 27;324(26):1865-75. doi: 10.1056/NEJM199106273242606, PMID 1801769.
3. Fihn SD, Callahan CM, Martin DC, McDonell MB, Henikoff JG, White RH. The risk for and severity of bleeding complications in elderly patients treated with warfarin. The national consortium of anticoagulation clinics. Ann Intern Med. 1996 Jun 1;124(11):970-9. doi: 10.7326/0003-4819-124-11-199606010-00004, PMID 8624064.
4. Poli D, Antonucci E, Testa S, Tosetto A, Ageno W, Palareti G. Bleeding risk in very old patients on vitamin K antagonist treatment: results of a prospective collaborative study on elderly patients followed by Italian Centres for anticoagulation. Circulation. 2011 Aug 16;124(7):824-9. doi: 10.1161/circulationaha.110.007864. PMID 21810658.
5. Palareti G, Cosmi B. Bleeding with anticoagulation therapy-who is at risk, and how best to identify such patients. Thromb Haemost. 2009 Aug;102(2):268-78. doi: 10.1160/TH08-11-0730, PMID 19652877.
6. Hilkens NA, Algra A, Greving JP. Prediction models for intracranial hemorrhage or major bleeding in patients on antiplatelet therapy: a systematic review and external validation study. J Thromb Haemost. 2016 Jan;14(1):167-74. doi: 10.1111/jth.13196. PMID 26563743.
7. Selak V, Jackson R, Poppe K, Wu B, Harwood M, Grey C. Predicting bleeding risk to guide Aspirin use for the primary prevention of cardiovascular disease: a cohort study. Ann Intern Med. 2019 Mar 19;170(6):357-68. doi: 10.7326/M18-2808. PMID 30802900.
8. Landefeld CS, Beyth RJ. Anticoagulant-related bleeding: clinical epidemiology, prediction, and prevention. Am J Med. 1993 Sep;95(3):315-28. doi: 10.1016/0002-9343(93)90285-w, PMID 8368229.
9. Yeh RW, Secemsky EA, Kereiakes DJ, Normand SL, Gershlick AH, Cohen DJ. Development and validation of a prediction rule for benefit and harm of dual antiplatelet therapy beyond 1Y after percutaneous coronary intervention. JAMA. 2016 Apr 26;315(16):1735-49. doi: 10.1001/jama.2016.3775. Erratum in: JAMA. Erratum. 2016 Jul 19;316(3):350. PMID: 27022822; PMCID: PMC5408574.
10. Burgess S, Crown N, Louzada ML, Dresser G, Kim RB, Lazo Langner A. Clinical performance of bleeding risk scores for predicting major and clinically relevant non-major bleeding events in patients receiving warfarin. J Thromb Haemost. 2013 Sep;11(9):1647-54. doi: 10.1111/jth.12352, PMID 23848301.
11. Froom P, Miron E, Barak M. Oral anticoagulants in the elderly. Br J Haematol. 2003 Feb;120(3):526-8. doi: 10.1046/j.1365-2141.2003.04110.x. PMID 12580973.
12. Klok FA, Hosel V, Clemens A, Yollo WD, Tilke C, Schulman S. Prediction of bleeding events in patients with venous thromboembolism on stable anticoagulation treatment. Eur Respir J. 2016 Nov;48(5):1369-76. doi: 10.1183/13993003.00280-2016. PMID 27471209.
13. van der Meer FJ, Rosendaal FR, Vandenbroucke JP, Briet E. Bleeding complications in oral anticoagulant therapy. An analysis of risk factors. Arch Intern Med. 1993 Jul 12;153(13):1557-62. doi: 10.1001/archinte.153.13.1557, PMID 8323419.
14. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. Chest. 9th ed. 2012 Feb;141(2) Suppl:e44S-88S. doi: 10.1378/chest.11-2292, PMID 22315269, PMCID PMC3278051.
15. Claxton JS, MacLehose RF, Lutsey PL, Norby FL, Chen LY, O'Neal WT. A new model to predict major bleeding in patients with atrial fibrillation using warfarin or direct oral anticoagulants. Plos One. 2018 Sep 10;13(9):e0203599. doi: 10.1371/journal.pone.0203599. PMID 30199542, PMCID PMC6130859.
16. Beshir SA, Aziz Z, Yap LB, Chee KH, Lo YL. Evaluation of the predictive performance of bleeding risk scores in patients with non-valvular atrial fibrillation on oral anticoagulants. J Clin Pharm Ther. 2018 Apr;43(2):209-19. doi: 10.1111/jcpt.12634. PMID 29030869.
17. Asiimwe IG, Waitt C, Sekaggya Wiltshire C, Hutchinson C, Okello E, Zhang EJ. Developing and validating a clinical warfarin dose-initiation model for black-African patients in South Africa and Uganda. Clin Pharmacol Ther. 2021 Jun;109(6):1564-74. doi: 10.1002/cpt.2128. Erratum in. Clin Pharmacol Ther. 2021 Aug 16;109(6):1564-74. doi: 10.1002/cpt.2128, PMID 33280090.
18. Nielsen PB. Tooling in oral anticoagulation treatment. Medical Informatics Group. Department of Health Science and Technology; 2010 Aug. p. 1-34.
19. Palareti G, Leali N, Coccheri S, Poggi M, Manotti C, D'Angelo A. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Italian study on complications of oral anticoagulant therapy. Lancet. 1996 Aug 17;348(9025):423-8. doi: 10.1016/s0140-6736(96)01109-9, PMID 8709780.
20. Trailokya A, Hiremath JS, Sawhney J, Mishra YK, Kanhere V, Srinivasa R. Acenocoumarol: a review of anticoagulant efficacy and safety. J Assoc Physicians India. 2016 Feb;64(2):88-93. PMID 27730796.
21. Rathore SS, Agarwal SK, Pande S, Singh SK, Mittal T, Mittal B. Therapeutic dosing of acenocoumarol: proposal of a population specific pharmacogenetic dosing algorithm and its validation in North Indians. Plos One. 2012;7(5):e37844. doi: 10.1371/journal.pone.0037844. PMID 22629463, PMCID PMC3358293.
22. van der Meer FJ, Rosendaal FR, Vandenbroucke JP, Briet E. Bleeding complications in oral anticoagulant therapy. An analysis of risk factors. Arch Intern Med. 1993 Jul 12;153(13):1557-62. doi: 10.1001/archinte.153.13.1557, PMID 8323419.
23. Rivera Caravaca JM, Marin F, Esteve Pastor MA, Valdes M, Vicente V, Roldan V. Antiplatelet therapy combined with acenocoumarol in relation to major bleeding, ischaemic stroke and mortality. Int J Clin Pract. 2018 Mar;72(3):e13069. doi: 10.1111/ijcp.13069. PMID 29436121.
24. Cesar JM, Garcia Avello A, Navarro JL, Herraez MV. Aging and oral anticoagulant therapy using acenocoumarol. Blood Coagul Fibrinolysis. 2004 Oct;15(8):673-6. doi: 10.1097/00001721-200412000-00007, PMID 15613922.
25. Kooistra HA, Calf AH, Piersma Wichers M, Kluin Nelemans HC, Izaks GJ, Veeger NJ. Risk of bleeding and thrombosis in patients 70 Years or older using vitamin k antagonists. JAMA Intern Med. 2016 Aug 1;176(8):1176-83. doi: 10.1001/jamainternmed.2016.3057, PMID 27379731.
26. Teichert M, van Noord C, Uitterlinden AG, Hofman A, Buhre PN, De Smet PA. Proton pump inhibitors and the risk of over anticoagulation during acenocoumarol maintenance treatment. Br J Haematol. 2011 May;153(3):379-85. doi: 10.1111/j.1365-2141.2011.08633.x. PMID 21418179.
27. Belkacemi M, Merad Y, Berber A. Frequency of bleeding complications in Algerian patients treated with the vitamin K antagonist acenocoumarol and associated factors. Int J Basic Clin Pharmacol. 2021 Nov;10(11):1. doi: 10.18203/2319-2003.ijbcp20214062.