

# Effect of ABO blood groups on response to warfarin

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## Research article

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# Abstract

**Background:** Numerous studies have demonstrated that patients with non-O blood groups have higher risk for venous thromboembolism than those with O blood group. However, it has remained unknown about the effect of ABO blood groups on warfarin dose requirements in patients receiving anticoagulation in Chinese Han population. The study aimed to investigate the influence of ABO blood groups on warfarin dose requirements in Chinese Han population. **Methods:** A retrospective study was conducted in the First Affiliated Hospital of Shantou University Medical College in Southern China. Three hundreds and 58 patients with confirmed diagnosis of deep venous thromboembolism and atrial fibrillation were included. Frequency of blood groups and warfarin dose requirements were determined. **Results:** Of 358 patients with deep venous thromboembolism and atrial fibrillation, 111 patients had blood group A (31.01%), 104 patients had blood group B (29.05%), 20 patients had blood group AB (5.59%), and 123 patients had blood group O (34.36%). The patients with O blood group had a lower warfarin dose requirements compared with those with A, B and AB blood group. **Conclusion:** Our study showed that patients with non-O blood groups require higher doses of warfarin.

## Background

Warfarin is the most commonly prescribed oral anticoagulant drug since 1950s [1], which has been widely used to prevent embolic stroke in patients with atrial fibrillation (AF) [2] and treatment of thromboembolic disorders. Despite extensive experience with its use, warfarin still caused a variety of adverse effects because of its narrow therapeutic index [3]. The anticoagulant activity of warfarin is assessed by using the International Normalised Ratio (INR) [4]. Maintaining a patient in the therapeutic range is associated with improved outcomes, with target INR being between 2.0 and 3.0 for most indications. Subtherapeutic anticoagulation will lead to inadequate protection while supratherapeutic anticoagulation to life-threatening bleeding. Therefore it is important to identify the clinical and genetic predictors of warfarin dose-response in individual patients [5-7].

According to previous studies, various factors such as age, gender, body weight and genetic polymorphisms [8-11] have been reported to be major determinants of warfarin dose requirements. Recently some studies have addressed the potential role of ABO blood groups in deep vein thrombosis (DVT). Compared with O blood group, non-O blood groups have higher risk for DVT [12-14]. However, the influence of ABO blood groups on warfarin dose requirements was not well known. In present study we aimed to investigate the influence of ABO blood groups on warfarin dose requirements in patients with DVT and AF in Chaoshan District of Guangdong Province in South China.

## Methods

A retrospective descriptive study was carried out in the First Affiliated Hospital of Shantou University Medical College in Southern China. Patients with diagnosed DVT and AF between January 2015 and May 2019 were reviewed to detect data of patients. The patients with ABO blood group treated by warfarin

were enrolled in the present research, with target INR between 2.0 and 3.0. The diagnosis of DVT was done based on typical clinical symptoms and the ultrasonograph findings. The diagnosis of AF was documented via either ECG or Holter examination within admission. The patients with serious hepatic or renal insufficiency and abnormal coagulation function were excluded. The study profile was showed in the Fig 1. The study was approved by the ethics committee of Shantou University Medical College.

Data are presented as the number of patients or mean  $\pm$  SD. Differences between groups were assessed by Chi-square tests or by ANOVA for multiple comparisons using SPSS 16.0. P value  $< 0.05$  was considered significant.

## Results

As shown in the Table 1, there are 358 patients in this study, which include 270 patients with AF and 88 patients with DVT. 156 patients (43.58%) were male and 202 patients (56.42%) were female and. The frequency of ABO blood group in patients was as follows: 111 patients had blood group A (31.01%), 104 patients had blood group B (29.05%), 20 patients had blood group AB (5.59%), and 123 patients had blood group O (34.36%). Age, gender, weight, hemoglobin (HGB), red blood cell (RBC), platelet (PLT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), serum creatinine (Scr) and INR between different ABO blood groups were not significant. There was significant difference about weight between four groups. Primary clinical characteristics of patients with ABO blood groups are summarized in Table 2. The patients with O blood group had a lower warfarin dose requirements compared with those with A, B and AB blood groups ( $2.74 \pm 0.83$  mg versus  $3.19 \pm 0.97$  mg,  $3.32 \pm 0.97$  mg and  $3.14 \pm 0.93$  mg,  $P < 0.05$ ). There are no differences of warfarin dose requirements among A, B and AB blood group. The result suggested that the dose of warfarin for anticoagulation was affected by ABO blood groups.

## Discussion

Warfarin, an anticoagulant with vitamin K antagonist, is widely used for treatment of venous thromboembolism and prevention of stroke in patients with atrial fibrillation. Though effectiveness in preventing embolic strokes [15], maintain anticoagulation within the target INR range and preventing devastating risk of intracranial hemorrhage (ICH) remain challenging. To be effectiveness and safety, an INR target of 2.0-3.0 is widely adopted. Owing to the multitude of factors interacting with warfarin, it is not easy to maintain INR values within the target range of 2.0 to 3.0. To predict warfarin doses, Gage et al proposed a warfarin-dosing algorithm by combining cytochrome P450 2C9 (CYP2C9) and vitamin K epoxide reductase complex subunit 1 gene (VKORC1) genotype status with relevant clinical factors, which can explain 53-54% of the variability in the warfarin dose [7]. In study by Ather et al [16], the algorithm explained only 30% of the variance, which suggested though many factors affecting warfarin dose requirements have been well described, determining more factors is important.

Recently the relationships between ABO blood groups and DVT have been demonstrated. Compared with O blood group, there is higher risk of venous thromboembolism in non-O blood groups [12-14]. Furthermore, the blood group remarkably affected the anesthetic effects of propofol [17]. However, the association of ABO-blood groups with warfarin dose requirements has not been addressed.

In present study, we investigated the possible connection between ABO phenotype and warfarin dose requirements. The study showed that there are lower warfarin dose requirements in patients with O blood type than non-O blood groups. There are no significant differences about warfarin dose requirements among A, B and AB blood group. To our knowledge, this is the first report to assess the influence of ABO blood group on warfarin dose requirements, the result suggested that ABO blood groups may be as a clinical factor to be included in predicting warfarin dose requirements.

The mechanisms that patients with O blood group had lower warfarin dose requirements have not been fully elucidated. It was reported that body weight contributed to the anticoagulant response to warfarin [10]. In present study the weight in O blood group is lighter than B blood group. However body weight only accounts for about 6.3% of the variability in warfarin dose requirements [10]. Other factors maybe play a role. The association between ABO blood groups and risk of thrombosis has been recognized for many years. A number of studies have demonstrated that there were higher levels of Factor VIIIc (FVIII) and von Willebrand factor (vWF) in non-O blood groups than O blood group [18-22]. The elevated levels of the vWF-FVIII complex are associated with increased risk of venous thromboembolism [23]. Additionally, there is a longer prothrombin time (PT) in patients of obst ructive jaundice with O blood group than non-O blood group [24]. But in present study, there was not significant difference about PT in different ABO blood groups (table 3, shown in the supplemental data). Based on these studies, we speculated that lower warfarin dose requirements in patients with O blood group might be associated with high levels of FVIII and vWF.

A few limitations were apparent in present study. First, though warfarin dose requirements are higher in non-O blood groups than O blood group, the population of the study is small, especially in AB blood group, large sample would be needed to verify the relations between ABO blood groups and warfarin dose requirements. Secondly, it is a retrospective study, which made it that the effects of some genetic factors such as CYP2C9 and VKORC1 on warfarin dose requirements were not excluded [8-10]. Lastly, owing to the geographic distribution difference of ABO blood groups, the association between ABO blood groups and warfarin dose requirement in Chinese Han population from Chaoshan region may be different from other regions in China.

## Conclusions

In summary, the present study demonstrated that patients with non-O blood groups required higher doses of warfarin to maintain an INR target of 2.0-3.0.

## Abbreviations

Atrial fibrillation (AF); International Normalised Ratio (INR); Deep vein thrombosis (DVT)

## Declarations

### Acknowledgements

Not applicable.

### Funding

None.

### Availability of data and materials

Raw data supporting the obtained results are available at the corresponding author.

### Authors' Contributions

SZ and LSW drafted the manuscript. ZLC, XHL and XRT were involved in data collection. HJC performed the statistical analysis. MY conceived of the study. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

The study was approved by the ethics committee of Shantou University Medical College. The need for consent was waived because of the retrospective data.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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## Tables

Table 1 Primary characteristics of patients with atrial fibrillation and deep venous thromboembolism

Variable	Patients (n=358)
Age (years, mean±SD)	
Male	62.63±13.47
Female	62.14±11.93
Gender [n (%)]	
Male	156 (43.58)
Female	202 (56.42)
Weight (Kg, n=252)	58.49±10.45
Primary reason for anticoagulation [n (%)]	
AF	270 (75.42)
DVT	88 (24.58)

AF, Atrial fibrillation; DVT, deep vein thrombosis;

Table 2 Characteristics of patients with ABO blood groups

Blood group	A	B	AB	O	P Value
Total Number	111	104	20	123	
Age (years, mean ± SD)	62.25±11.21	60.50±14.42	61.95±15.43	64.09±11.54	0.203
Gender					0.572
Female	67	55	13	67	
Male	44	49	7	56	
Weight (Kg, n=252)	59.46±11.14	60.30±10.33	60.17±8.47	55.68±9.73 #	0.025
HGB (g/L)	125.96±21.22	126.93±22.40	124.00±20.52	127.75±20.30	0.857
RBC (×10 <sup>9</sup> /L)	4.26±0.71	4.29±0.80	4.21±0.57	4.38±0.70	0.569
PLT (×10 <sup>9</sup> /L)	203.86±73.99	212.67±78.43	217.00±61.70	214.23±88.77	0.744
ALT (U/L, n=355)	30.85±32.84	27.88±24.47	53.47±83.58	35.46±44.06	0.054
AST (U/L, n=355)	30.34±19.86	35.41±41.64	41.37±34.15	41.35±65.06	0.319
BUN (mmol/L)	6.39±2.95	5.85±2.21	5.74±2.20	6.72±3.25	0.104
Scr (μmol/L)	103.42±36.54	105.23±42.65	90.60±19.35	104.28±32.51	0.425
NR	2.37±0.28	2.37±0.25	2.34±0.25	2.34±0.27	0.765
Warfarin dose (mg)	3.19±0.97	3.32±0.97	3.14±0.93	2.74±0.83 Δ*	0.000

# O blood group vs B blood group P < 0.05

Δ O blood group vs B blood group P < 0.01

\* O blood group vs A, B blood group P < 0.05

Table 3 Coagulation function of patients with different blood groups

Group	A	B	AB	O	P Value
Number	57	48	10	71	
PT (s)	13.37±2.83	12.98±2.57	12.88±2.20	13.19±2.19	0.857
PT (%)	75.13±25.03	79.85±26.50	81.44±28.22	73.50±19.74	0.451
INR	1.16±0.25	1.13±0.22	1.12±0.19	1.15±0.19	0.827
APTT (s)	31.13±5.99	29.27±5.62	30.06±4.99	31.26±5.43	0.242
TT (s)	18.03±1.96	17.72±1.97	17.99±1.58	18.11±1.83	0.734
Fib (g/L)	3.35±1.35	3.16±1.39	3.07±1.34	2.95±0.97	0.347

Of 358 patients, 186 patients had tests for coagulation function before treatment with warfarin. There were no significant differences in PT, PT%, INR, APTT, TT and Fib among four groups.

PT=prothrombin time. INR=International Normalised Ratio. APTT=activated partial thromboplastin time. TT=thrombin time. Fib= fibrinogen.

## Figures

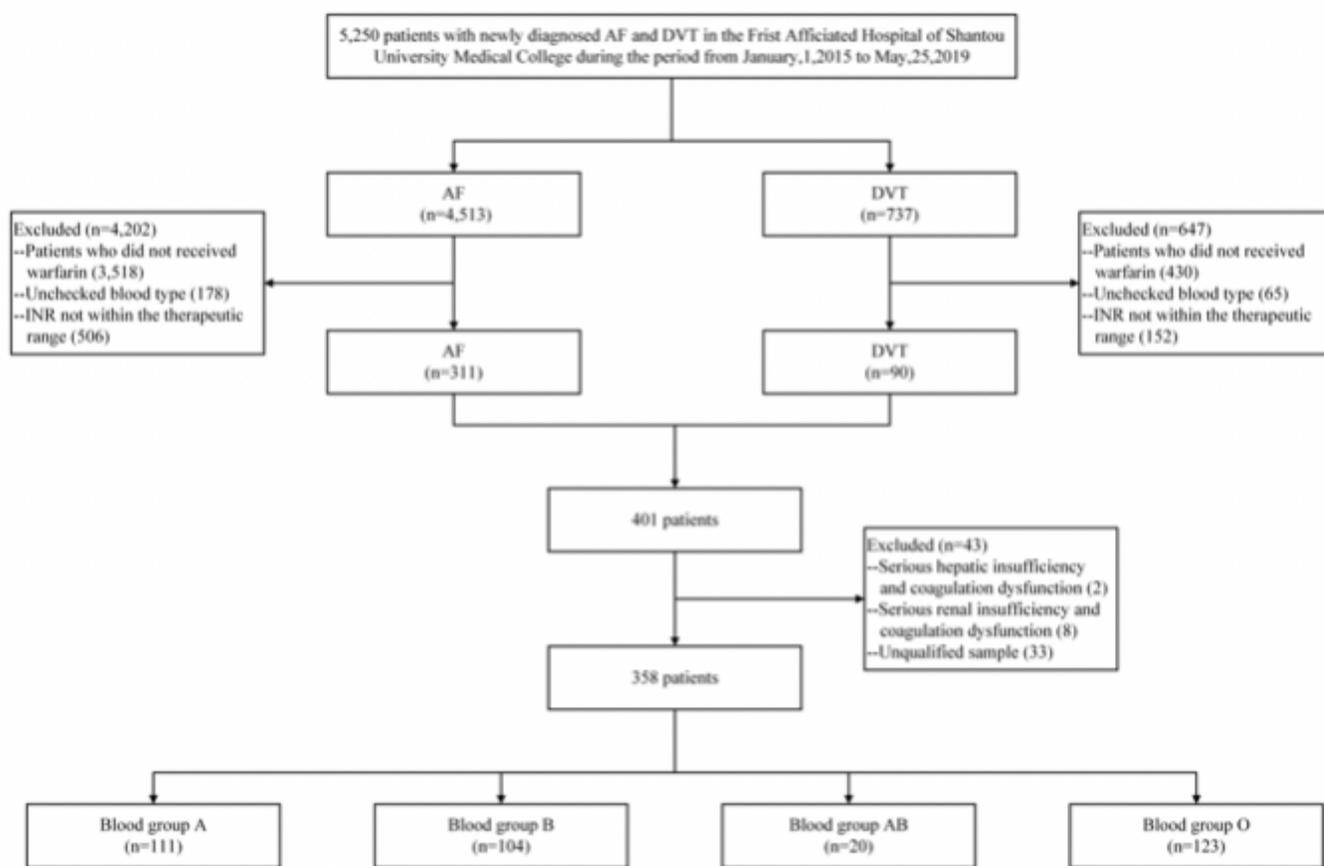


Figure 1

Study profile. AF=atrial fibrillation. DVT=deep vein thrombosis. INR=International Normalised Ratio.