

# Warfarin maintenance dose in Iranian patients

## *A cross sectional study in 5 cities of Iran*

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### ABSTRACT

**الأهداف:** تحديد الجرعات المناسبة والانتظامية من عقار الوارفارين (warfarin) لدى مجموعة من المرضى الإيرانيين.

**الطريقة:** أُجريت هذه الدراسة المتعددة المراكز (دراسة مشتركة) في خمسة مدن كبيرة في إيران وذلك خلال الفترة من يناير 2007م إلى يناير 2008م، وشملت 150 مريضاً ممن تفوق أعمارهم 12 عاماً ويتلقون عقار الوارفارين. لقد قمنا بتحديد وقت البروثرومبين بواسطة المقياس الموحد لمدى سيولة الدم (International normalized ratio) وذلك يومياً خلال الأيام الأولى من بدء تلقي العقار، ومن ثم كل أسبوع إلى كل أسبوعين لمدة شهر واحد على الأقل. ولقد اعتبرنا جرعة الوارفارين مستقرة ومناسبة وذلك عند ثبات مقياس مدى سيولة الدم عند المستوى 2-3 في ثلاثة فحوص متتالية، وبعد ذلك قمنا بتقدير متوسط جرعة الوارفارين التي تم أخذها خلال المرات الثلاثة الأخيرة.

**النتائج:** أشارت نتائج الدراسة إلى أنه لم يكن هناك اختلافاً واضحاً من الناحية الإحصائية بين المدن الخمسة التي تضمنتها الدراسة، وكذلك بين الذكور والإناث ( $p=0.228$ )، حيث لم تظهر جرعات عقار الوارفارين اليومية وما ترتب عليها من مستويات مقياس سيولة الدم أي فروق إحصائية بين الجنسين. ولقد قلت الجرعة اليومية من الوارفارين بنحو واضح لدى المرضى الذين تزيد أعمارهم عن 60 عاماً ( $p=0.004$ ) وللأعمار التي تتراوح ما بين 45-60 عاماً، و ( $p=0.002$ ) للأعمار 30-45 عاماً. أظهرت هذه الدراسة أن الجرعة الموصى بها من عقار الوارفارين هي تقريباً 4 مليغرام وذلك من أجل تحقيق مستوى ثابت من مقياس سيولة الدم والذي يتراوح ما بين 2-3.

**خاتمة:** أثبتت هذه الدراسة أنه يجب تحديد الجرعة المناسبة من عقار الوارفارين، فذلك يعد ضرورياً عند اعتبار الاختلافات الجغرافية والعرقية بين المرضى الإيرانيين.

**Objective:** To determine the warfarin maintenance dose in Iranian patients.

**Methods:** This multicenter study was conducted between January 2007 and January 2008 in 5 different large cities of Iran. Patients older than 12 years receiving warfarin were included. During the first days of warfarin use, international normalized ratio (INR) was measured daily and after that every 1-2 weeks, with a duration of at least one month. The warfarin dose was considered to be stabilized if the INR remained unchanged on 3 consecutive measurements at a level between 2-3. Then mean dose of the last 3 warfarin doses was calculated.

**Results:** One hundred and fifty patients receiving warfarin took part in this study. No significant differences were noted in the mean warfarin dosage among the 5 cities, and between men and women ( $p=0.228$ ). The warfarin daily dose and INR did not show any statistical difference between men and women. The warfarin dose statistically decreased in patients older than 60 years old ( $p=0.004$  versus 45-60 years, and  $p=0.002$  versus 30-45 years). This study showed that the required mean warfarin dose in Iranian patients was approximately 4 mg to achieve an INR between 2-3.

**Conclusion:** Considering geographic and ethnic differences of Iranian patients, attention to the dose determination of warfarin is of importance.

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Warfarin is one of the most widely prescribed anticoagulants and is administered clinically as a racemic mixture of 2 enantiomers, (R)-warfarin, and (S)-warfarin that needs active monitoring to improve outcomes of oral anticoagulation therapy.<sup>1-3</sup> The dosing of warfarin is difficult because of many known and unknown factors that influence an individual's response.<sup>4,5</sup> Many different factors are responsible for the variable effect of warfarin including the VKORC1-1639 G>A polymorphism, body weight, age, and serum albumin alterations, diet, drug and herbal interactions, co-morbidity, and social habits such as smoking or alcohol consumption.<sup>6,7</sup> Ethnic differences in warfarin dose required for an international normalized ratio (INR) between 2 and 3 well described in the literature, but do not appear to be extensively appreciated by clinicians. For example, in the anticoagulation consensus guidelines that relate specifically to warfarin no attention is paid to the influence of ethnicity on the typical maintenance dose.<sup>8</sup> The purpose of this investigation is to determine the maintenance dose of warfarin in Iranian patients.

**Methods.** This study was conducted in 5 different cities of Iran (Tehran, Tabriz, Ahwaz, Mashhad, and Hamadan) from January 2007 to January 2008. The main reason for selecting these cities was geographical distribution to design a multicenter study. The Ethics Committee of Tabriz University of Medical Sciences approved this research. Patients older than 12 years of age receiving warfarin, and attending as outpatients in the clinics were enrolled. They might have been admitted in the selected hospitals recently, but they were followed up for at least one month out of hospital to ensure good stabilization of warfarin dose. Each patient was screened for normal hepatic and renal function and for drugs deemed to interfere with warfarin and any concurrent therapy with such drugs was excluded.<sup>9,10</sup> Patients with target INR ranges of 2-3 were included. Both the British Society for Hematology (BSH) and the American College of Chest Physicians (ACCP) recommend a target INR range of 2-3 (moderate-intensity anticoagulation) for most indications of warfarin, such as prophylaxis, and treatment of venous thrombosis, treatment of pulmonary embolism, and prevention of systemic embolism.<sup>11</sup> Patients with target INR ranges outside these values were excluded. During the early days of warfarin consumption, the INR was measured daily, and after that every 1-2 weeks. The warfarin dose was considered to be stabilized if the INR

remained unchanged on 3 consecutive measurements at a level between 2-3.<sup>12</sup> Finally, the mean dose of the last 3 warfarin doses was calculated.

We collected the following data: age, gender, present INR, and recommended dosage. Height (without shoes) and weight (light indoor clothing) was measured by clinic nurses to calculate body mass index (BMI). In every visit, probable bleeding events were enquired about and considered.

All data were expressed as mean±SD. The significance of the difference among variables was assessed using Student's t-test or analysis of variance (ANOVA) where appropriate. A *p*-value less than 0.05 was considered statistically significant. The data were analyzed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA).

**Results.** One hundred and fifty Iranian patients (75 male, 75 female) receiving oral anticoagulation took part in this study, 30 patients from each city. The characteristics of patients and treatment indications are shown in Table 1. Women were heavier than men, but the differences in BMI were not meaningful. This study showed that 45.3% of subjects required 2-4 mg of warfarin daily, and 42.7% of them received more than 5 mg warfarin every day during the treatment period. Table 2 shows some of the patients' characteristics based on gender, and there were no statistically significant differences between men and women considering age, BMI, mean daily warfarin dose and INR. One-way analysis of variance (ANOVA) showed that the mean daily warfarin dose and BMI in each city were not significantly different (Table 3). In addition, 22.7% of

**Table 1** - The characteristics of the study patients and treatment indications.

Characteristics	n (%)
Age (Mean ± SD) (range)	49.77±15.36 (20-80)
Gender F/M	75/75
Body mass index (kg/m <sup>2</sup> )	24.43±4.34
<b>Treatment indication</b>	
Deep vein thrombosis	92 (61.3)
Pulmonary thromboembolism	29 (19.3)
Cardiovascular disease (including atrial fibrillation)	16 (10.7)
Cerebral venous thrombosis	13 (8.7)
Mean warfarin daily dose (mg) (range)	1.52±4.11 (1.26-7.5)
Mean international normalized ratio	0.29±2.51

**Table 2** - Patients' characteristics according to gender.

Characteristics	Men	Women	<i>P</i> -value
Age (years)	50.15±15.81	49.4±14.94	0.767
Body mass index (kg/m <sup>2</sup> )	24.03±4.04	24.83±4.61	0.261
Daily warfarin dose (mg)	4.77±1.43	4.08±1.24	0.167
International normalized ratio (mg)	2.53±0.29	2.49±0.29	0.372

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**Table 3** - Relation of the 5 cities to warfarin dose and body mass index.

Variable	City name					P-value
	Tehran	Tabriz	Ahwaz	Hamadan	Mashhad	
Daily warfarin dose (mean±SD)	4.23±1.63	4.13±1.59	4.08±1.56	3.98±1.35	4.13±1.55	>0.05
Body mass index (kg/m <sup>2</sup> )	24.26±3.85	25.73±5.3	24.36±4.58	24.6±4.21	23.16±3.3	>0.05

**Table 4** - Summary of published information on mean daily warfarin doses in different countries.

Investigator	Ethnicity/race	Age	Number	International normalized ratio	Warfarin dose (mg)
Miura et al <sup>15</sup>	Japanese	70.7±10.5	102	1.6-2.6	2.66
Blann et al <sup>13</sup>	Asian	61 (58-64)	72	2.28-2.42	5.5
	Afro-Caribbean	64 (61-67)	58	2.26-2.44	6.7
	Caucasians	70 (69-71)	737	2.30-2.34	4.1
Garwood et al <sup>4</sup>	European ancestry	78±1	49	2-3	4.2
	African ancestry	79±1	170	2-3	5.45
Yu et al <sup>10</sup>	Chinese	52.0±12.1	151	2-2.5	3.3

our study population (n=34) had a BMI lower than 20, 38.7% (n=58) had a BMI of 20-25, and in 38.7% (n=58), the BMI was higher than 25. There is a weak correlation between BMI and daily warfarin dose, though it was not significantly difference ( $p=0.289$ ,  $r=0.088$ ).

**Discussion.** Warfarin is the most widely used oral anticoagulant agent worldwide. Clinical factors, demographic variables, and variations in genes contribute significantly to the variability among patients in dose requirements for warfarin.<sup>5</sup> Ethnic differences in the warfarin dose required for an INR between 2 and 3 are well documented in the literature.<sup>8</sup> Our study shows that the mean warfarin requirement in Iranian patients is around 4 mg to achieve an INR between 2-3. In contrast, patients from China and Japan require approximately 3 mg warfarin daily.<sup>10,13</sup> In a study conducted by Garwood et al al,<sup>4</sup> European ancestry patients required a dose of  $\leq 5$  mg to maintain the desired level of anticoagulation. In contrast, more than 40% of African ancestry patients required a daily dose greater than 5 mg, and almost 20% required a dose of 7 mg or more. Blann and Hewitt<sup>13</sup> showed that the mean dose of warfarin with target INR 2-3 was 4.1 (4.0±4.2) mg/d in Caucasians, 5.50 (4.9±6.1) mg/d in Asians, and 6.7 (5.8±7.6) mg/d in Afro-Caribbeans.<sup>13</sup> Briefly, several studies have shown that to achieve the same INR range, Asians require lower warfarin doses, Whites require intermediate doses, and Blacks require higher doses.<sup>14</sup> This review is summarized in Table 4. Cross-sectional studies are consistent in reporting that warfarin requirements are lower in the elderly than in younger patients to achieve the same degree of anticoagulation.<sup>15</sup> In our study, daily warfarin doses decreased in patients older than 60 years of age statistically ( $p=0.004$  versus

45-60 years, and  $p=0.002$  versus 30-45 years). There is no significant difference between other age groups in daily warfarin dose. This also agrees with the finding of Hamberg et al<sup>16</sup> that showed a decrease of warfarin dose requirement by ~6% per decade. Whitley and colleagues<sup>17</sup> found a small correlation, without statistical differences, between BMI and total weekly warfarin maintenance dose (TWD). Several other studies found a relationship between BMI or body weight and warfarin dose. Sconce and colleagues<sup>18</sup> found a significantly positive correlation of warfarin dose with body weight ( $r=0.21$ ;  $p=0.003$ ), height ( $r=0.38$ ;  $p=0.001$ ), and body surface area ( $r=0.21$ ;  $p=0.005$ ). Singla and colleagues<sup>19</sup> found that BMI influences TWD equally to gender ( $r^2=5.3$ ,  $p=0.001$ ). It is currently not clear how much of an effect, if any, BMI plays upon TWD.<sup>16</sup> In Caucasian subjects, the age of the patient rather than body weight is an important determinant of warfarin requirements.<sup>10</sup> The amount of warfarin required to maintain a given INR depends on age, with older patients requiring less warfarin, and on gender, with women requiring less warfarin. Although in our study the difference between men and women was not significant, several studies, but not all, report that gender is a determinant of warfarin dose; males require higher doses than females.<sup>4</sup> For example, Yu and colleagues<sup>10</sup> could not find any gender-related difference in daily warfarin dose.

This study had the limitation of sample size from the cities due to some problems in data collection, but the global sample size (150 patients) was comparable to other published articles (Table 4).

In summary, these results suggest that the mean warfarin daily dose in Iranian patients is higher than Chinese and Japanese, and lower than Afro-Caribbean patients. Therefore, ethnic variations in warfarin dose should be included in the related guidelines. The

number of elderly patients who are eligible to receive warfarin is steadily expanding all over the world,<sup>20</sup> and increasing use of warfarin in these patients should intensify attention to any probable problems in the dose determination of warfarin.

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