

## ORIGINAL ARTICLES

## FREQUENCY OF DIFFERENT DISORDERS REQUIRING WARFARIN THERAPY AND ITS OUTCOME IN TERMS OF DOSAGE AND INR VALUE IN PAKISTANI POPULATION

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### ABSTRACT

**Objective:** To determine the frequency of different disorders requiring warfarin therapy and to see the target INR and warfarin dose requirement in Pakistani population.

**Study Design:** Descriptive study.

**Setting and Duration of Study:** The study was carried out at Armed Forces Institute of Cardiology (AFIC) Rawalpindi, Military Hospital Rawalpindi and National Institute of Cardiovascular Diseases (NICVD), Karachi, Pakistan from October 2010 to March 2012.

**Patients and Methods:** Stable patients taking warfarin therapy were recruited after detailed medical history, physical examination and laboratory tests. The demographic and clinical data of individuals were entered in a pre-structured proforma. Patients suffering from hepatic and renal disease, any co-morbid disease or taking any concurrent medication or diet which would have affected warfarin therapy, were excluded. Data was analyzed using SPSS version 20.0.

**Results:** A total of 607 stable patients fulfilling the eligibility criteria, participated in the study. There were 297 (48.9%) male and 310 (51.1%) female patients. The mean age was  $37.93 \pm 12.23$  years (range 18–65 years). The most common indication for warfarin therapy was valvular heart diseases (93.4%) followed by atrial fibrillation (2.3%) whereas other indications for warfarin use are less commonly seen in our study population. Patients had mean international normalized ratio (INR) value of  $2.3 \pm 0.8$  (range 1.5–3.5). Mean daily dose of warfarin calculated in 607 patients was  $5.62 \pm 1.98$  mg with the range of 0.36–15 mg whereas mean weekly dose was  $39.36 \pm 13.8$  mg with the range of 2.5–105 mg.

**Conclusion:** In Pakistani population the most common indications for warfarin use are valvular heart diseases followed by atrial fibrillation. The mean INR values were within recommended range of 2–3. The mean daily dose observed in long-term therapy is comparable to the empirical dose of 5 mg routinely started in clinical practice.

**Keywords:** Atrial fibrillation, INR, Valvular heart diseases, Warfarin.

### INTRODUCTION

Warfarin has been the most commonly prescribed oral anticoagulant since its approval in 1954<sup>1-3</sup>. It has been used for prophylaxis and treatment of various venous and arterial thromboembolic disorders. Patients with valvular heart diseases, prosthetic heart valves, atrial fibrillation, myocardial infarction, pulmonary embolism, deep vein thrombosis and recurrent strokes require anticoagulant therapy<sup>1,4-5</sup>.

Management of warfarin therapy is difficult because of significant intra- and inter-individual variability, low therapeutic index and highly variable pharmacokinetics<sup>5-7</sup>. Warfarin dose requirement varies considerably among individuals and also in the same person at different times due to wide range of food and drug interactions. The environmental factors may be more important for intra-individual variations<sup>8-10</sup>. Many factors like age, sex, weight, ethnicity, genetic factors, dietary intake, concurrent diseases and medications have been reported to affect the warfarin dose requirements. Inadequate or supra-therapeutic anticoagulation may result in substantial morbidity and mortality

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Received: 23 Dec 2013; Accepted: 30 Jan 2014

due to failure to prevent thromboembolism or bleeding complications respectively. Clinicians may avoid prescription of warfarin, due to fear of risk of complications, in patients, who may be benefited from this therapy<sup>2,10-15</sup>.

Warfarin is usually administered with an initial dose of 5 mg daily. The dose is titrated with repeated laboratory monitoring through prothrombin time (PT) and international normalized ratio<sup>16-18</sup>.

The present study was the first comprehensive study conducted in Pakistani population to evaluate the frequency of various conditions leading to thrombo-embolism in which warfarin therapy is indicated. The study also demonstrated the target INR and dose requirement in our population.

## MATERIAL AND METHODS

It was a descriptive study. The clinical data collection and laboratory investigations were done at Armed Forces Institute of Cardiology (AFIC) Rawalpindi, Military Hospital Rawalpindi and National Institute of Cardiovascular Diseases (NICVD), Karachi. The study was carried out from October 2010 to March 2012. The study was conducted in accordance with the current Good Clinical Practices<sup>19</sup> and the Declaration of Helsinki<sup>20</sup>. The study protocol was approved by ethical committees of Centre for Research in Experimental and Applied Medicine (CREAM), Army Medical College and National Institute of Cardiovascular Diseases.

Study subjects were adults of either sex between the ages of 18 to 65 years who were receiving warfarin as anticoagulation therapy. Stable patients taking warfarin were recruited in the study after informed consent. A stable patient was defined as the one whose warfarin dose had been constant for at least three previous clinical visits over a minimum period of three months, and had an international normalized ratio (INR) of the prothrombin time (PT) within the range of 1.5-3.5<sup>8,21-23</sup>. The patients suffering from hepatic and renal disease, any co-morbid disease (like thyroid disease, malignancy) or taking any

concurrent medication or diet (like food rich in vitamin K) which would have affected warfarin therapy, were excluded. All participants were Pakistani citizens belonging to different regions

**Table-1: Distribution of study population undergoing oral warfarin therapy by region of origin (n=607).**

Province / Region	n %
Punjab	306 (50.4)
Sindh	139 (22.9)
Khyber Pakhtunkhwa	106 (17.5)
Balochistan	28 (4.6)
Gilgit Baltistan	6 (1.0)
Azad Jammu & Kashmir	22 (3.6)

of Pakistan to provide representation from all areas. The number of patients enrolled from different regions like Punjab, Khyber Pakhtunkhwa, Sindh, Balochistan, Gilgit-Baltistan, Azad Jammu and Kashmir, were in proportion to the population of that region. Each subject was evaluated by detailed medical history, physical examination and laboratory tests. The demographic and clinical data of individuals was entered in a pre-structured proforma. Demographic data included age, gender and ethnicity whereas clinical data included indications for warfarin use, warfarin dose, present and previous INR values. Data had been analyzed using SPSS version 20.0 (IBM Corporation, USA). Descriptive statistics was used to describe the data. Mean and standard deviation (SD) were calculated for quantitative variables like age, warfarin dose, present and previous INR values. Frequency and percentages were calculated for qualitative variables like gender, ethnicity and indications for warfarin use.

## RESULTS

A total of 607 stable patients fulfilling the eligibility criteria, participated in the study. There were 297 (48.9%) male and 310 (51.1%) female subjects. The mean age was 37.93 ± 12.23 years (range 18-65 years). The frequency of patients belonging to different provinces and regions of Pakistan are given in table-1. The indications for

warfarin therapy and number of patients suffering from these, are summarized in table-2. Patients recruited in the study had mean INR value of  $2.3 \pm 0.8$  (range 1.5–3.5). Mean daily dose of warfarin calculated in 607 patients was  $5.62 \pm 1.98$  mg with the range of 0.36–15 mg whereas mean weekly dose was  $39.36 \pm 13.8$  mg with the range of 2.5–105 mg.

## DISCUSSION

Warfarin has been used for prophylaxis and treatment of many thromboembolic disorders<sup>2, 24</sup>. Individuals with valvular heart diseases are at higher risk of developing thromboembolism. There is also risk of cardio-embolic stroke after prosthetic heart-valve replacement. Patients with these valvular conditions are placed on long-term anticoagulation therapy with warfarin<sup>25</sup>. Most of the patients in our study population on long-term therapy were suffering from valvular heart diseases. The other common use of warfarin is atrial fibrillation which is associated with high risk of thromboembolic events, stroke, heart failure and premature death<sup>26-27</sup>. Many clinical trials have shown effectiveness of warfarin therapy in attenuating the risk of stroke in such patients<sup>28</sup>. The incidence of paroxysmal atrial fibrillation following coronary artery bypass graft has also been reported to be reduced with use of warfarin<sup>29</sup>. A number of patients (1.6%) with coronary artery bypass graft in our study were also on warfarin therapy.

Venous thrombembolism involving deep vein thrombosis and pulmonary embolism has been reported in 1 in 1000 persons annually leading to serious morbidity and mortality. Patients at high risk of deep vein thrombosis and pulmonary embolism are prescribed warfarin<sup>30-31</sup>. In our study, only one such patient was seen.

Warfarin reduces the risk of death, re-infarction and developing thromboembolic conditions like stroke and systemic embolism after myocardial infarction. So in selected case of myocardial infarction warfarin is used<sup>32</sup>. Patients with heart failure are at higher risk of developing atrial fibrillation, stroke and thromboembolic

events. Some studies have advocated the use of warfarin in such patients<sup>33-34</sup>. Only one patient

**Table 2: Percentage of patients with various indications for oral warfarin therapy**

Indications	n (%)
Mitral valve replacement	340 (56)
Aortic valve replacement	108 (17.8)
Double valve replacement	91 (15)
Mitral stenosis	18 (3)
Atrial fibrillation	14 (2.3)
Coronary artery bypass grafting	10 (1.6)
Mitral regurgitation	4 (0.7)
Left ventricular clot	3 (0.5)
Cerebrovascular accident	3 (0.5)
Aortic regurgitation	2 (0.3)
Ventricular septal defect closure	2 (0.3)
Aortic stenosis	2 (0.3)
Triple valve disease	2 (0.3)
Percutaneous transvenous mitral commissurotomy (PTMC)	2 (0.3)
Dilated cardiomyopathy	1 (0.2)
Atrial septal defect closure	1 (0.2)
Deep vein thrombosis	1 (0.2)
APLA syndrome (Anti phospholipid antibody syndrome)	1 (0.2)
Patent ductus arteriosus	1 (0.2)
Rheumatic heart disease	1 (0.2)

with dilated cardiomyopathy was seen in our patients.

The patients undergoing orthopedic surgical procedures like fixing hip fracture and prosthetic total hip or knee joint replacement are at higher risk of developing thromboembolic events. Anticoagulation therapy with warfarin is prescribed in such patients<sup>35-36</sup>. There was no patient in our study with this indication. It may be due to the fact that our patients were those on long-term therapy and such surgical patient may be offered short-term therapy after surgery.

Patients recruited in the study had mean INR value of  $2.3 \pm 0.8$  (range 1.5-3.5). According to international guidelines on anticoagulation, in most of the cases INR is maintained between 2 and 3 but in some cases between 2.5 and 3.5 particularly with prosthetic heart valve<sup>24,37</sup>. Some studies have advocated lower INR range of 1.5-2 to reduce the chances of bleeding. An INR below 1.5 is likely to cause thromboembolism whereas above 3.5 has a risk of bleeding. Mean daily dose of warfarin in our patients was  $5.62 \pm 1.98$  mg which is comparable to the empirical dose of 5 mg routinely started in clinical practice<sup>38,39</sup>. Now-a-days dosing algorithm based on demographic variables along with common CYP2C9 and VKORC1 genotyping are in use instead of dosage based on clinical assessment in some parts of the world. Such individualized approach has offered better outcome in warfarin response<sup>40</sup>.

## CONCLUSION

In our Pakistani study population the most common indication for warfarin use is valvular heart disease (93.4%) followed by atrial fibrillation (2.3%). The mean INR values were within international recommended range. The mean daily dose observed in long-term therapy was comparable to the empirical dose of 5 mg routinely started in clinical practice.

## Conflict of Interest

The project was funded by Higher Education Commission (HEC) of Pakistan.

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