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Non-Clinical Factors Associated with International Normalized Ratio Control in Patients on Warfarin Therapy: A Review Paper

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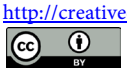

Abstract

Warfarin is a coumarin derivative oral anticoagulant with a narrow therapeutic international normalized ratio (INR) range. Regular and accurate INR monitoring is essential for optimal anticoagulation management and to reduce the risk of adverse events. However, achieving and maintaining the therapeutic INR range are still a challenge as it is affected by several clinical and non-clinical factors. In this review paper, we analyzed how the non-clinical factors like socio-demographic, modifiable risk and protective factors affect the INR control in patients receiving warfarin therapy. We conducted an extensive literature search in Pubmed, Embase, Scopus and Web of Science for original articles or review papers published from 2016 to 2020. Finally, we included 20 articles in this review which fulfilled the selection criteria. Multiple factors such as female gender, ethnicity difference, lower education level, living alone, activities of daily living dependency, smoking, alcohol abuse, fasting and low body mass index along with poor access to medical facilities are associated with poor INR control. Patient self-management and weight elevation are known to be protective factors against poor INR control. Physicians managing patients on warfarin therapy are encouraged to identify and recognize these factors before prescribing warfarin to achieve and maintain the therapeutic INR.

Subject Areas

Pharmacology

Keywords

Non-Clinical, Risk Factor, International Normalized Ratio, Control, Warfarin

1. Introduction

Warfarin, a coumarin derivative oral anticoagulant, is widely prescribed globally for the prevention of venous thromboembolism and thromboembolic stroke in patients with either Non-Valvular Atrial fibrillation (AF) or chronic atrial fibrillation [1] [2]. A study has shown that warfarin initiation period bears the highest risk of poor anticoagulation, although long-term warfarin management also has higher chances of over anticoagulation [3]. That is why it is essential to monitor the warfarin initiation and management doses which may be affected due to many reasons either clinical or non-clinical.

Warfarin dose adjustment is based on regular monitoring of international normalized ratio (INR), which is required to reduce the risk of adverse events. Very high or low doses of warfarin may lead to poor INR control as Okumura *et al.* (2011) have reported that higher warfarin doses are associated with poorer INR control whereas Palaretti *et al.* (2005) describe that lower warfarin doses are associated with poorer INR control [4] [5]. Henceforth, monitoring of warfarin efficacy and its complications is essential for the management of patients on warfarin therapy. Accurate INR monitoring is essential for optimal anticoagulation management. It is recommended by the professional society guidelines that INR needs to monitor in 4 weeks' intervals or once every month [6].

Time in therapeutic range (TTR) has been widely used to measure the quality of INR control as it reflects the percentage of time within a therapeutic INR range [7]. A minimum target of TTR ≥ 65% is recommended by the experts to ensure the effectiveness and safety of warfarin [8]. The general INR range recommended by the Western and recently published Malaysian guidelines is 2.0 - 3.0 for all age groups. In addition, an INR range of 2.5 - 3.5 is recommended for a patient with high thrombotic risk, for example, patients with mechanical prosthetic valves [9] [10]. On the other hand, Japanese Circulation recommended different INR ranges according to the age group. An INR range of 2.0 - 3.0 is used for patients < 70 years and a lower INR range of 1.6 - 2.6 is being used by the Japanese physicians for patients ≥ 70 years old. The J-RHYTHM Registry has shown that Japanese physicians tend to go with lower INR range than the usual 2.0 - 3.0 therapeutic range for 60% of patients aged < 70 years old [11].

There is still debate on the optimal INR range for Asian population due to limited evidence. Moreover, several factors affect the patients from achieving and maintaining therapeutic INR range, and these factors could be clinical and non-clinical. In this review paper, we analyzed how the non-clinical factors like socio-demographic, modifiable risk and protective factors affect the international normalized ratio (INR) control in patients who are receiving treatment with warfarin.

2. Method

2.1. Search Strategy

We conducted an extensive literature search in a very systematic way focusing

on the original articles or review papers published from year January 2016 to May 2020. The search was conducted in four different databases which include Pubmed, Embase, Scopus and Web of Science. While searching in the following databases, the Medical Subject Headings (MeSH) or free terms "Risk factor" OR "Factor" AND "International Normalized Ratio" OR "International Normalized Ratio Control" OR "INR control" AND "warfarin" were used.

Primarily, a total of 1202 articles were identified from the four databases: Pubmed (470 articles), Embase (402 articles), Scopus (164 articles) and Web of Science (166 articles). We identified the duplicates and removed those using EndNote software. After the removal of duplicates, there were 989 articles which were screened by the titles and abstracts. We screened the full text of articles that meet the eligibility criteria based on titles and abstracts. Further, we assessed the full-text articles based on the inclusion and exclusion criteria, and finally, we selected 20 articles (as shown in Figure 1 and Table 1) for this review.

2.2. Selection Criteria

Inclusion Criteria: We included studies in this review based on the following inclusion criteria:

1) Adult patients age 18 years and above.

2) Patients treated with warfarin medication.

3) Full text of the studies which should be accessible electronically and written in English only.

Exclusion Criteria: The following exclusion criteria were used to disregard the studies from this review:

1) Children age less than 18 years' old.

2) Case report as this type of medical literature has publication bias and possible to over-interpret the findings.

3) Study protocol or unpublished reports.

2.3. Data Extraction

Two reviewers (TR and NKJ[1]) independently extracted data from each selected article onto a standardized form developed for this review. The form includes study design, sample size, main study findings and conclusion. This process helps to minimize biases and human error. Extracted data were compared for accuracy before both the reviewers came to a general agreement. The third reviewer, either CGY or NKP[2], contributed to resolving when any discrepancies raised between two primary reviewers.

3. Result

1) Age: There is clear evidence on the benefits of warfarin for stroke and thromboembolism prevention in patients with Atrial fibrillation (AF), and the pre-

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valence of AF in patients > 70 years old and >85 years old is >5% and >10% respectively. Although the prevalence of AF is high, the concern on the risk of bleeding has limited these elderly patients from getting optimal anticoagulation prophylaxis [12] [13]. Cross-sectional study design though limits the establishment of causality but has shown that advanced age, especially elderly patients, have the highest risk of poor INR control which increases warfarin-related complications [14].

Advanced age is a non-modifiable risk factor of bleeding; hence it is essential to monitor the dose of warfarin [15]. Shendre *et al.* (2018) reported that the incidence rate of haemorrhage is significantly highest among the elderly patients on warfarin therapy compared to the young warfarin consumers [Incidence Rate Ratio (IRR) 1.8, 95% Confidence Intervals (CI): 1.12 - 3.0]. Although these elderly patients can achieve good INR control, they still have an increased risk of significant bleeding, which may happen due to either poor hypertension control or age-related frailty [16]. Cohen *et al.* (2019) described that 8% of their older study population has supra-therapeutic INR level with consequences of higher bleeding rate, a longer length of stay and elevated mortality rate. Approximately 33% of patients had INR overshoot of >3 after warfarin initiation, and 8% of these patients had INR elevations of ≥5 [17].

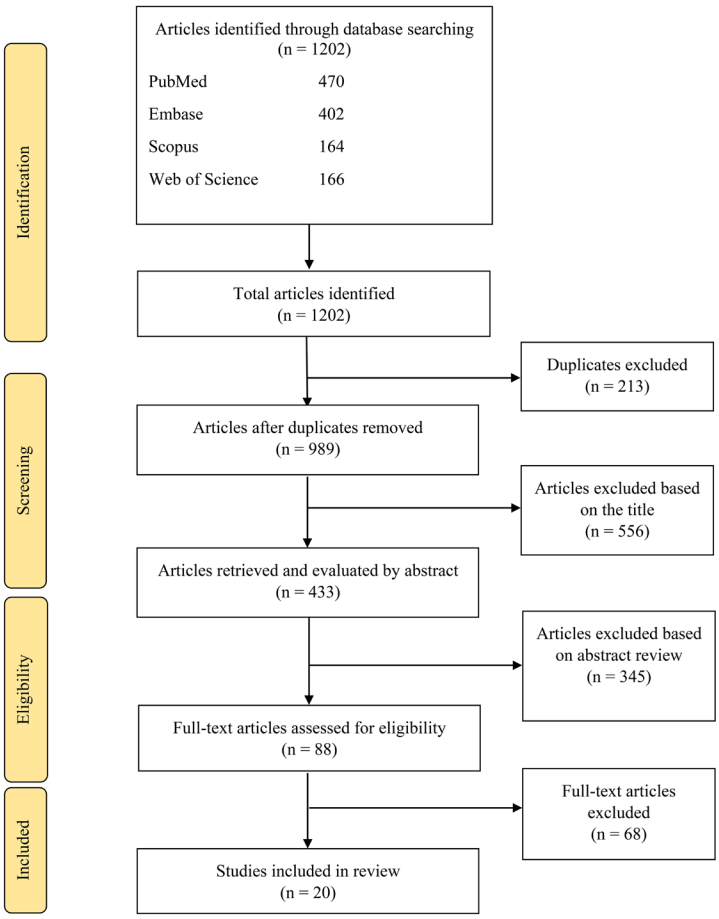

Figure 1. PRISMA chart used for the selection of articles.

Table 1. List of selected articles which are included in review with the main findings and conclusion.

Article; Study country; Year of Publication [Reference no]	Type of study	Sample size	Main Findings	Conclusion
Abohelaika *et al.*; UK; 2016 [21]	Longitudinal study	2094	- Warfarin dose changes and INR monitoring frequency decrease until the age of 67 and increases as they get older - TTR according to age was significantly lower - Females have a higher probability of TTR ≤ 65% compared to male - Patients under domiciliary service have a higher probability of TTR ≤ 65% compared to those in general practice and hospital-based clinics	Anticoagulation control is influenced by age, gender and physical dependence
Al-Momany *et al.*; Jordan; 2019 [58]	Cohort study	2788	- Factors such as concurrent medication use (46.9%), smoking cigarettes and shisha (17%), non-balanced vitamin K dietary intake (16.88%) lower the INR value - Herbal supplements (Hawthorn and Ginseng) are associated with supratherapeutic INR value.	Smoking shisha and cigarettes, concurrent medication use, herbal use and increased vitamin K consumption are associated with non-therapeutic INR value.
Bernaitis *et al.*; Australia, Singapore; 2017 [20]	Retrospective cohort study	4366	- Mean TTR is significantly higher in Australia than Singapore - Anemia and age < 60 years influence the INR control in Australia - The INR control in Singapore is influenced by factors such as vascular disease, concurrent platelet inhibitor therapy and CHA_2DS_2-VASc score of 6	Multiple patient factors influence the INR control in both these countries
Bjorck *et al.*; Sweden; 2019 [62]	Retrospective cohort study	28,011	- The prevalence of excessive alcohol consumption is higher in patients with iTTR < 60% - Concomitant comorbidities are associated with poor INR control - Patients with previous stroke have iTTR > 70%	Excessive alcohol consumption is the most significant predictor of poor INR control. Concomitant disorders are associated with poor INR control.
Bourgeois *et al.*; UK; 2016 [59]	Prospective cohort study	711	- CYP2C9 and VKORC1 are the major genetic determinants of warfarin dosing - Age, height, weight, alcohol consumption and concomitant drugs influence the warfarin dosing and initial response to warfarin.	Genetic and other multiple factors such as age, height, weight, concomitant drugs use, and alcohol consumption are important determinants of warfarin dosing.
Chalachew *et al.*; Ethiopia; 2019 [53]	Cross-sectional study	73	- Educational level of less or equal to primary school, decrease in check-up visit frequency, distance of more than 300km from the follow-up medical facility and public health institution as a source of free warfarin supply are associated with subtherapeutic INR control.	Distance from follow-up facility, educational level, follow-up visits number and source of warfarin supply are significantly associated with subtherapeutic INR control.
Cohen *et al.*; USA; 2019 [17]	Retrospective cohort study	4556	- Peripheral vascular disease, chronic obstructive pulmonary disease (COPD), non-black race, mild liver disease, no statin use and low weight are associated with supratherapeutic INR value. - The prevalence of INR overshoot in older adults on newly initiated warfarin therapy during acute hospitalization is 8%. - Patients with INR overshoot experienced a significantly higher rate of mortality, bleeding events and length of stay in hospital.	Peripheral vascular disease, chronic obstructive pulmonary disease (COPD), non-black race, mild liver disease, no statin use and low weight are sensitivity markers of INR overshoot.

Continued

Garcia-Sempere *et al.*; Spain; 2019 [38]	Cross-sectional study	22,629	- 53% of women and 49.3% of men had poor INR control with TTR ≤ 65%. - Women, long-term antiplatelet users, use of alcohol and concomitant comorbidities are associated with poor INR control.	Women are with a higher risk of poor INR control.
Jaakkola *et al.*; Finland; 2017 [3]	Clinical trial	13,618	- Chronic medical conditions such as heart failure, chronic kidney disease, mechanical heart valve prosthesis and active cancer are permanent risk factors of excessive warfarin anticoagulation. - Chemotherapeutic agents, antibiotic and antifungal treatment are temporary risk factors of excessive warfarin anticoagulation - Active smoking and alcohol abuse are risk factors of excessive warfarin anticoagulation.	Identifying these risk factors is helpful in the early detection and prevention of supratherapeutic INR.
Katada *et al.*; Japan; 2019 [68]	Retrospective observational study	58	- The maximum INR of prothrombin time (PT-INR) and warfarin sensitivity index (WSI) are significantly higher in patients who are fasting during the postoperative period compared to those with no dietary intake reduction.	Postoperative fasting is significantly associated with INR control.
Liang *et al.*; China; 2019 [24]	Prospective registry study	1895	- Age ≥ 70 years, use of a single drug, bleeding history and lack of assessment of bleeding risk is associated with TTR < 70%. - Peripheral arterial disease, coronary artery disease and diabetes mellitus are associated with increased variability of INR.	Warfarin anticoagulation in Chinese patients with NVAF is associated with lower TTR than in current guidelines and affected by multiple risk factors.
Martin-Perez *et al.*; Spain; 2019 [35]	Nested case-control study	12,506	- Multiple factors, including low socioeconomic status and residency in rural areas are associated with poor INR control.	Low socioeconomic status and residency in rural areas are associated with poor INR control.
Numao *et al.*; Japan; 2017 [22]	Cohort study	626	- Older age ≥ 75 years is an independent predictor of high INR variability	Identifying the factors related to high INR variability in AF patients may assist the clinician in identifying patients likely to show unstable INR control.
Ohara *et al.*; Japan; 2019 [50]	Prospective cohort study	309	- African American patients have 30% lower S-warfarin clearance [CL(S)] compared to Asian and White patients - Half maximal effective concentration (EC50) showed a greater racial difference than CL(S). - Age, weight, sex and African American ethnicity are significant predictors of INR	African American has higher warfarin requirement than Asian and White patients
Praxedes *et al.*; Brazil; 2019 [54]	Retrospective cohort study	312	- Assistance for warfarin administration, female gender, absenteeism and non-compliance are associated with TTR ≤ 60%	Patient's behaviour towards treatment influence the TTR.
Prochaska *et al.*; Germany; 2019 [29]	Cohort study	760	- Female sex and living alone are independent risk factors of INR control - Self-management of warfarin therapy is a protective factor.	Women and living alone patients have a higher risk of low-quality warfarin therapy.
Schaefer *et al.*; Switzerland; 2016 [80]	Cohort study	15,834	- High intensity of therapeutic range, female sex, intervals of more than 14 days between measurements and management other than PSM are predictors of poor INR control.	Several factors influence poor INR control in PSM cohort.

Continued

Schein *et al.*; USA; 2016 [28]	Review Paper	NA	- Female gender, younger age and smoking are associated with poor INR control. - Male gender and PSM are associated with TTR ≥ 65%.	Sustainability of INR within the therapeutic range is influenced by multiple factors and careful evaluation of patients prior to warfarin initiation is essential.
Shendre *et al.*; UK; 2018 [16]	Prospective cohort study	1498	- Warfarin dose requirement is 10.6% lower for middle-aged and an additional 10.6 % lower for elderly patients compared with young patients - Middle-aged and elderly patients spend more time in therapeutic INR range compared to young patients. - Absolute haemorrhagic risk is marginally higher in middle-aged patients and significantly higher in elderly patients compared to young patients.	Elderly patients have a higher risk of haemorrhagic events despite optimal INR control.
Yong *et al.*; USA; 2016 [42]	Retrospective cohort study	184,161	- TTR was highest in whites and lowest in blacks - One-year warfarin persistence was lower in blacks compared to the whites	Differences in INR control is most evident among blacks.

*NA = Not Applicable.

Regarding time in therapeutic range (TTR), the Veterans Affairs Study to Improve Anticoagulation (VARIA) reported that elderly patients have better TTR level [18]. Similarly, Shendre *et al.* (2018) described that elderly patients (>70 years) have significantly higher TTR compared to younger warfarin user ($p < 0.0001$). However, the risk of major bleeding is still higher among older patients despite achieving better INR control [16], which is because as there is no association between high TTR (>70%) and warfarin adverse events [19].

A study conducted in Australia also found that patients < 60 years have low TTR [20]. On the other hand, Abohelaika *et al.* (2016) demonstrated that increasing age of >70 years is associated with lower TTR of ≤65% [21]. Also, Numao *et al.* (2017) reported that older age is associated with increased INR variability, which highlights the increased risk of poor anticoagulation [22]. The TTR value is also low in older age [23] [24]. The possible cause could be the convenience of polypharmacy, low body mass index (BMI) and renal or liver dysfunction that may lead to unstable pharmacokinetics [25].

In contrast, several studies have shown that younger age < 45 years or <60 years is associated with poor INR control [26] [27] [28]. Abohelaika *et al.* (2016) reported that patients < 60 years have poorer INR control compared to elderly patients, and this could be due to their employment issue, alcohol abuse, poor compliance and comorbidities [21]. In contrast, Prochaska *et al.* (2019) found that age is not a risk factor of sub-therapeutic control [29].

Age has been integrated into a few risk scores of bleeding. Anyhow, this incorporation has only able to improve the predicting ability to bleed moderately. Different risk scores use different age cut-off, which makes it harder to set the age threshold for determining the risk of bleeding [30]. Worsening of normal body function due to age-related frailty could accelerate the adverse events in the

elderly [31]. Maximum effectiveness cannot be achieved with a lower INR target range of 1.6 - 2.6 in elderly patients (>70 years), although it might decrease the bleeding risk [32]. Therefore, current evidence recommended the INR target of 2.0 to 3.0 in the elderly as the benefits still outweigh the risk [33].

2) Gender: Various studies identified the associations between gender and INR control. Marie *et al.* (2012) found that female gender is highly associated with excessive anticoagulation whereas Martin-Perez *et al.* (2019) did not find any statistically significant association between gender of the patients and INR control [34] [35]. Prochaska *et al.* (2019) reported that female is associated with sub-therapeutic INR control which is in line with an epidemiology report released in the United States by Rose *et al.* (2009) [29] [36]. The possible speculated explanation for this gender-specific variation could be due to non-compliance, poor dietary vitamin K intake, different physiological response to warfarin or treatment variation by clinicians [29] [37]. Concerning time in therapeutic range (TTR), the female has been found to be more vulnerable than male as they act as an independent predictor of poor TTR [26] [38].

Abohelaika *et al.* (2016) reported that females have lower mean TTR by 1.3% and they spent marginally more time below the therapeutic range compared to males; though there is no significant difference in mean time spends beyond the INR target between different genders. More women are monitored domiciliary than men which could be a contributing factor of this TTR variation [21]. In contrast, Bernaitis *et al.* (2017), Gallagher *et al.* (2011) and Okumura *et al.* (2011) reported that there is no association between gender difference and TTR [4] [20] [39].

3) Ethnicity: The warfarin maintenance doses, which required to attain the optimal INR control significantly, are different among patients from different ethnicities (African American > White > Asian) [40]. A study described that African American patients have a lower TTR and an increased risk of bleeding compared to European American patients; this suggests that INR control could be affected by racial difference [41]. Yong *et al.* (2016) reported that black patients have lower first-year and long-term TTR compared to all other races in the study despite similar INR monitoring frequency intensity. They found different mean TTR among different racial groups. The white racial group had the highest mean TTR after accounting their socio-demographic, clinical and site-level factors. The study also found that the difference in anticoagulation control among different racial groups is not associated with the accessibility to medical facilities as the blacks stay near to the medical facilities and have greater opportunity to utilize the cardiology care after the new-onset of atrial fibrillation compared to other racial groups [42].

There are multiple potential explanations for the variation in the anticoagulation effect among different racial groups. Different racial groups have different pharmaco-genetics which affects the metabolism of warfarin and dose-response. Studies found that Asian and whites have lower warfarin dose requirements

compared to blacks, and this is potentially due to the variation in genotype frequencies among the races [43] [44]. The geographic and cultural differences could be the primary driving source for this kind of variation more than the race itself [45]. Srivastava *et al.* (2008) have reported that the awareness of their atrial fibrillation medical condition is lower in blacks compared to other races [46]. Multiple factors such as age, gender, socioeconomic status, region, alcohol abuse, pill burden, comorbidities, bipolar disorder and hospitalizations influence 69% difference between whites and blacks [18] [47].

There are two methods in predicting the warfarin doses for different races; these are the race-specific and race-adjusted dosing algorithms. Limdi *et al.* (2015) demonstrated that the race-specific algorithm is better than the race-adjusted algorithm, and this is because the race-specific algorithm can explain the higher degree of dose variability better than that of the race-adjusted [48]. African American racial group has a lower degree of warfarin dose variability, and both the algorithms can explain this. However, the race-adjusted algorithm is considered further convenient to be used clinically as it can estimate the warfarin dosing for all patients irrespective of their race [49].

Ohara *et al.* (2019) reported that >50% of Asian patients with VKORC 1-1639G/G or G/A genotypes have sub-therapeutic INR control. Minor allele frequencies of genetic predictors may vary significantly among three racial groups. Asian patients have less INR variability compared to that of the White population, and this could be due to the high prevalence of VKORC1-1639A/A genotypes among this population [50]. CYP2C9*8 is a genotype which is more common among African American patients compared to Asian and White patients, and this may lead to significant INR variability in this specific race [51]. A clinical trial has shown that the mean TTR is lower in genotype-guided dosing compared to clinically guided dosing among black patients, and this indicates that genotype-guided dosing is not always better than the latter [52].

4) Education and other social factors: Chalachew *et al.* (2019) found that non-clinical factors such as >300 km to medical facility for follow-up, less frequent clinic visits, lower educational level and free warfarin supply source from public institutions were significantly associated with sub-therapeutic INR control. Patients with lower education may have difficulty understanding the nature of the clinical condition, the importance of regular follow-up and INR monitoring [53]. Hospitalizations and outpatient emergency visits may influence INR elevation, and this may be due to adjustment of the warfarin dose with the incidental INR without prior knowledge about the long-term dosing or compliance.

Patients who are dependent on someone's help for their daily living also have a higher risk of excessive anticoagulation [3] [54]. Patients living in a rural area are very likely to have supra-therapeutic INR control compared to those living in urban areas, and this could be because of lack of accessibility to medical facilities, poverty and social exclusion [35]. In addition, living alone significantly increases the risk of sub-therapeutic INR control by 53% [29]. Individuals who are living alone are very likely to have a poor diet which may affect their vitamin K

consumption [55]. This reduction in vitamin K dietary intake increases the risk of poor INR control [56].

5) Smoking and Alcohol: A systemic review has shown that smoking significantly increases the warfarin clearance, which eventually reduces the effect of warfarin [57]. There is no evidence on the interaction between warfarin and nicotine. However, the body absorbs other chemical compounds of the smoke and transports to the liver. The liver produces more enzymes to excrete these toxic chemical compounds. During this process, the liver eliminates more warfarin as well, which eventually increases the warfarin requirements in active smokers. Quitting smoking may also affect the warfarin dosing as these ex-smokers require lower warfarin dose [58]. Therefore, smoking relapses must be questioned to those patients with smoking history plus poor INR control.

Al-Momany *et al.* (2019) also reported that shisha smoking, as harmful as cigarette smoking, is associated with poor INR control. Smoking shisha is often not consistent, which makes the situation difficult to adjust the warfarin dose and maintains the optimal INR value. In addition, some patients think that smoking shisha is not considered as smoking and prefer not to provide related information to the doctors. Therefore, physicians need to ask the patients specifically on shisha smoking [58].

Alcohol abuse highly increases the risk of over anticoagulation [3] [59]. Excessive alcohol consumption dysregulates liver enzymes production and functions; thus inhibits the warfarin breakdown and also leads to poor compliance to medications [60]. Alcohol abuse also potentially may induce hepatic microsomal enzymes which elevate the warfarin metabolic elimination. As alcohol consumption increases, coagulation factor VII decreases as well [61].

A study of 28,011 patients on warfarin therapy showed that alcohol abuse is significantly associated with poor INR control of iTTR < 60% (Odds Ratio: 2.72, CI: 2.27 - 3.24, $p < 0.001$) [62]. Excessive alcohol consumption is also a risk factor of bleeding in HAS-BLED score but not included in SAMe-TT_2R_2 and PROSPER scores [63]. ROCKET-AF study showed that alcohol abuse reduced the TTR in patients on warfarin [64]. A critical assessment of the benefits of anticoagulation compared to risk should be conducted before prescribing warfarin. Novel oral anticoagulants (NOAC) could be beneficial for these patients, but there is limited evidence on the efficacy and safety of NOAC in patients with excessive alcohol consumption which suggests further investigation in this issue.

6) Fasting: Fasting can affect the metabolism of warfarin and the volume of warfarin distribution. Studies found a 20% reduction in systemic clearance and central volume of S-warfarin distribution in healthy individuals with 36-hours of fasting. They also identified the area under the concentration curve of S-warfarin, which increased by 20% with fasting at unchanged warfarin therapy. Furthermore, they have shown that the level of the fatty acids in plasma increases after fasting. This increase in plasma fatty acids influences the S-warfarin protein binding [65] [66]. Lai *et al.* (2014) demonstrated that the risk of supra-therapeutic INR control increases in Muslim patients on warfarin therapy

during Ramadan fasting [67].

Katada *et al.* (2019) also found that patients who were fasting had significantly higher INR value compared to non-fasting patients. The maximum warfarin sensitivity index values were significantly different between these fasting and non-fasting patients. The intra-individual variability of warfarin therapy is significantly affected by fasting [68]. A similar study also described that reduction in dietary intake in critically ill patients increases the hypersensitivity to warfarin. Intravenous infusion of vitamin K_2 had played a vital role to reduce the INR value in these patients [69]. Besides, patients on warfarin therapy with cardio-vascular diseases require more attention during fasting as these patients often have poor nutritional status [70].

7) Weight: Martin-Perez *et al.* (2019) reported that a lower body mass index (BMI) is associated with an elevation of INR ≥ 5 [35]. A case-control study also found that a BMI < 20 kg/m^2 increase the risk of supra-therapeutic INR of ≥6. This study identified that a recent loss of a minimum of 2 kg weight is a risk factor of poor INR control [71]. Besides, it has been previously proposed that the clotting factors VII and X reduce with the decrease in weight [72]. Cohen *et al.* (2019) demonstrated that as the weight increases, INR overshoot decreases which indicates that weight elevation particularly > 90 kg is a protective factor against supra-therapeutic INR [17].

8) Self-management and INR Control: Like weight, patient self-management (PSM) similarly acts as a protective factor as it is an essential strategy in managing the patients with chronic illness including hypertension, diabetes and chronic obstructive pulmonary disease [73]. Multiple PSM programs have been established to assist the management of these diseases. Several randomized control trials have found that PSM is effective and safe to be used to manage a patient [74] [75]. Moreover, PSM is considered as more cost-effective and economical. Hence, channelling more financial resources to educate patients on anticoagulation therapy would be a wise strategy [76]. Self-management via telemedicine programs will be beneficial for well-controlled patients compared to face-to-face appointments in the anticoagulation clinic [77].

PSM significantly reduces the risk of thromboembolism, bleeding and mortality compared to the routine management [78]. Therefore, scientific societies recommended PSM to be used for eligible patients on anticoagulation therapy [79]. PSM correspondingly helps the patients to self-care of their long-term anticoagulation, including INR monitoring and warfarin dose adjustments. The patients can do self-tests and self-adjust the warfarin therapy according to the INR values. Thus, PSM may aid physicians in managing the increasing number of patients on oral anticoagulants [80].

Prochaska *et al.* (2019) similarly reported that self-management is associated with a reduction in risk of sub-therapeutic INR control by 78%, and this established that self-management acts as a protective factor against poor INR control [29]. This study finding is also consistent with the findings published in the

Cochrane database [75]. However, the effectiveness of self-management is questionable in a recurrent sub-therapeutic INR. Grunau *et al.* (2011) have conducted a study comparing physician management with PSM over a period of 4 months. The mean TTR in physician management and PSM groups is 82% and 80% respectively. During the self-management period, no thromboembolism or major bleedings occur, which shows a promising outcome with PSM [81]. Self-management with active participation in dose adjustments of warfarin will be beneficial for patients with TTR ≥ 75% [82]. Studies have reported that patients, who self-manage, have equal or higher TTR compared to conventional management [83].

Another study has also demonstrated that self-management is associated with lower complications, including thromboembolism compared to conventional management (Odds Ratio: 0.51, 95% CI: 0.31 - 0.85) [84]. In addition, patient self-testing (PST) allows the patients to measure their INR values. However, the warfarin dose-adjustment will be done by physicians [80]. However, Ward *et al.* (2015) proposed that patients under self-management are more likely to attain better TTR compared to patients under self-testing [85]. Both these PSM and PST can be facilitated by point-of-care testing.

Study Limitations: We did not find any article where the randomized controlled trial has been conducted to analyze how the non-clinical factors affect the INR control in patients receiving warfarin therapy. Hence, we could not conduct any risk of bias assessment to establish transparency of evidence which were synthesized in this review paper.

4. Conclusions

Though various studies have evaluated the effect of increasing age on the INR control, yet there is no clear unanimous establishment of the association between advanced age and poor INR control or low TTR. That is why careful warfarin dosing and INR monitoring are essential in older patients as they have a higher risk of bleeding. We also found the evidence that female gender is associated with poor INR control, and this gender-specific variation as a non-clinical factor needs to be tackled to ensure their optimal clinical outcomes. The variation in genotype frequencies impacts the warfarin dosing and quality of INR control among different ethnicities. Hence, a race-specific dosing algorithm would be helpful for physicians in prescribing warfarin.

Besides, proper healthcare strategies are required as multiple social factors such as lower education level, living alone, and accessibility to medical facilities may lead to poor INR control. Smoking and alcohol abuse are always being the risk factors of multiple chronic illnesses; poor INR control is not exceptional. Fasting is responsible for increasing the risk of supra-therapeutic INR control, as it affects warfarin metabolism and clearance. Therefore, more attention should be provided to patients on warfarin therapy during any types of fasting, including Ramadan fasting.

A low BMI is associated with supra-therapeutic INR although a high BMI is a protective factor against supra-therapeutic INR, this suggests that the other clinical consequences of excessive weight gain should not be neglected. Like high BMI, PSM acts as a protective factor against poor INR control. Since PSM is more cost-effective, managing eligible patients using self-management would be ideal as PSM is equally or more effective than conventional management.

That is why we recommended that multiple non-clinical factors which influence the INR control in patients on warfarin therapy should not be neglected. Identifying and recognizing these factors before prescribing warfarin would be quintessential to achieve and maintain therapeutic INR. Hence, physicians managing patients on warfarin therapy are encouraged to identify and recognize these non-clinical factors before prescribing warfarin to achieve and maintain the therapeutic INR. Also, a critical assessment of warfarin dosing and the benefits of anticoagulation compared to risk is essential before prescribing warfarin to these patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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List of Abbreviations

AF: Atrial Fibrillation
BMI: Body Mass Index
CI: Confidence Intervals
INR: International Normalized Ratio
IRR: Incidence Rate Ratio
MeSH: Medical Subject Headings
NOAC: Novel Oral Anti-Coagulants
TTR: Time in therapeutic range
PSM: Patient Self-Management
PST: Patient Self-testing
VARIA: Veterans AffaiRs Study to Improve Anticoagulation