IJPSR (2023), Volume 14, Issue 4 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 16 August 2022; received in revised form, 30 September 2022; accepted 03 November 2022; published 01 April 2023

CODING FOR AN ANTICOAGULANT: SYSTEMATIC REVIEW OF PHARMACOGENETICS-GUIDED WARFARIN THERAPY ON THE THERAPEUTIC AND ADVERSE CLINICAL EVENTS ON PATIENTS WITH ATRIAL FIBRILLATION, PULMONARY EMBOLISM, AND DEEP VEIN THROMBOSIS

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Keywords:

Atrial Fibrillation (Afib), Pulmonary Embolism (PE), Deep Vein Thrombosis (DVT), Pharmacogenomics (PGx), Warfarin

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ABSTRACT: Background: Warfarin is an anticoagulant widely used to prevent thromboembolic events (TEs) in patients with various cardiovascular (CV) diseases. Pharmacogenomics (PGx)-guided testing is a growing method suggested to help predict warfarin dosing. A systematic review was performed to compare the incidence of thromboembolic events (TEs), bleeding events (BEs), time in therapeutic range (TTR), the proportion of time to therapeutic range (PTTR) and warfarin dose adjustments between PGx-guided warfarin therapy and standard of care (SOC) in patients with non-valvular atrial fibrillation (Afib), pulmonary embolism (PE), and deep vein thrombosis (DVT). **Methods:** Two reviewers independently searched MEDLINE, CINAHL, Web of Science, Embase, Cochrane Library and clinicaltrials.gov databases from October 2019-August2022 to identify studies. Abstracts were reviewed for outcomes of interest and patient demographics to identify patients present with International Normalized Ratio (INR) readings, TTR, PTTR, BEs and TEs. **Results:** From the database search, 28 articles were retrieved based on abstract screening. A total of 6 articles were ultimately selected for the systematic review. All articles found favor in the PGx-guided group in terms of TTR. There were findings favoring PTTR, decreased BEs, and fewer dose adjustments in the PGx-guided group. **Conclusion:** Results of the systematic review demonstrate that PGx-guided warfarin dosing may establish a longer TTR than SOC. In select patients, PGx-guided warfarin therapy may decrease PTTR, reduce BEs, and require fewer dose adjustments. There was no noted benefit in PGx-guided therapy to reduce TEs.

INTRODUCTION: Warfarin is an oral anticoagulant (OAC) or Vitamin K antagonist (VKA) that is widely used for the prevention and treatment of thromboembolic events (TEs) in the world [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(4).1703-13

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.14(4).1703-13

However, oral VKAs are challenging drugs to use since they interact with numerous other drugs, and food, and demonstrate wide interpatient variability in metabolism and sensitivity [2].

Adverse events due to increased warfarin sensitivity may harm patients by increasing the risks of serious bleeding, including hemorrhagic events (*i.e.* bleeding in the brain or intracerebral hemorrhage). About 5-12% of intracerebral hemorrhage is related to warfarin, leading to an estimated annual incidence in the US of nearly 3,000 cases [3-5].

These warfarin-induced intracerebral hemorrhages tend to happen most frequently during the first year of warfarin therapy, with the risk being most prominent during the first month of therapy. Additionally, warfarin therapy's significant bleeding risk entails 0.6, 3 and 9.6% incidence of fatal, major and minor bleeds on an annual basis, respectively [6]. The cost of warfarin compared to other oral anticoagulants known as direct oral anticoagulants (DOAC) (*i.e.,* dabigatran is an example of DOAC that does not require dose titration like warfarin) per se is low. Still, International Normalized Ratio (INR) monitoring is likely associated with large healthcare resources [7].

Warfarin is closely monitored with a laboratory parameter known as the INR, which measures how long it takes for blood to clot. High INR levels indicate that patients on warfarin are bleeding too much (or bleeding does not stop when necessary). Low INR levels indicate that patients with cardiovascular conditions are at risk of forming blood clots or TEs that can adversely affect different body organs (*i.e.,* pulmonary embolism (PE) for the lung, ischemic stroke for the brain). Although the benefits of warfarin for TE protection are supported by high evidence of patients with cardiovascular (CV) diseases such as atrial fibrillation (Afib) or a history of TE, warfarin is a double-edged sword as a medication because small interpatient variability in warfarin dosing can have adverse consequences. Warfarin is among the top 10 drugs with the largest number of serious adverse event reports and accounts for over 10% of hospital admissions related to adverse drug reactions [8].

In January 2015, the Obama administration launched the Precision Medicine Initiative (PMI) to accelerate the translation of scientific discoveries into individual treatments [9]. In addition, the 21st Century Cures Act provides funding to extend precision medicine to all diseases through PMI and allows the Food and Drug Administration (FDA) to review evidence regarding usage, or the potential benefits and risks of a drug from sources other than randomized clinical trials for new drug approvals [10, 11]. Data sources include electronic health records, claims, billing data, and health applications [12]. Precision medicine relies on complex laboratory tests to identify specific chromosomal, DNA, RNA, protein, or metabolite abnormalities in patients' blood or tissue [13]. PGx is the study of how genes affect an individual's response to drugs. Commercially available since 2006, the development of next-generation sequencing offered a cost-efficient and time-effective method for sequencing DNA, which served a significant step forward in personalized medicine [14]. Pre-emptive PGx testing remains at the forefront of precision medicine as an individual's genetic makeup is analyzed [15, 16]; pre-emptive approaches seek to optimize drug therapy by screening patients for multiple PGx variants before an indication for pharmacotherapy [17, 18].

One example of a pre-emptive approach to drug therapy optimization is PGx-guided warfarin dosing. This may prove more beneficial than a reactive approach, as an out-of-range INR may indicate that a patient is not receiving their appropriate dose of warfarin and places said patient at a higher risk of coagulation- or bleeding-associated harm. Indeed, a pre-emptive PGx-guided approach minimizes clinicians' trial and error method for therapy optimization in patients with CV diseases such as Afib, PE, and deep vein thrombosis (DVT).

CV diseases are the leading cause of death worldwide, accounting for 31% of all deaths (17.9 million people in 2016) [19]. Approximately, $555 billion in CV-related direct and indirect healthcare costs were incurred in the United States of America (USA) in 2016. These costs are projected to increase to $1.1 trillion by 2035 [20]. CV treatment is at the forefront of PGx-guided therapy due to significant variation in treatment response. To achieve therapeutic anticoagulation, daily doses of warfarin can vary up to 20-fold among patients [21]. In addition to the variation that can be attributed to various sociodemographic characteristics, genetic determinants have been identified as a risk factor affecting drug metabolism, absorption, and distribution mechanisms [22]. Hence, PGx-guided warfarin dosing algorithms are hypothesized to help patients to maintain appropriate therapeutic INR levels and lower the risk of adverse events. Since the half-life of warfarin is about 17 hours in patients without PGx variants, the therapeutic anticoagulant effects of warfarin take, on average, 3 days to reach a stable value if warfarin concentrations are constant [23]. However, 3 days

may not be a completely adequate predictor of warfarin's effects and INR interpretation for some patient populations with PGx variants; therefore a number of days for adequate control of warfarin dosing might not be definitive. Because warfarin has a very narrow therapeutic range as well as patients' variability of genes such as cytochrome P450 (CYP) 2C9 and Vitamin K epoxide reductase complex subunit 1 (VKORC1), finding the optimal initial/maintenance warfarin dose can be challenging. In recognition of these variants, the FDA changed the warfarin package insert label in 2007 for physicians to consider VKORC1 and CYP2C9 genetic testing for safety and efficacy of warfarin use [24, 25].

Recent studies suggest pharmacogenomic (PGx)-guided therapy improves various pharmacologic outcomes, such as time in therapeutic range (TTR), the proportion of time to therapeutic range (PTTR), dosage adjustments, TEs and bleeding events (BE), in relation to anticoagulation therapy in warfarin-naive patients [21, 26, 27]. However, the extent to which PGx-guided therapy improves outcomes amongst different populations is inconsistent in terms of therapeutic range in ethnicity, with certain populations benefiting more than others. Specifically, in an article by Syn *et al.,* ethnically diverse Asian patients from various hospitals in Southeast Asia did not have significantly improved PTTR or BEs findings with PGx use. However, PGx-guided warfarin therapy reduced the dosage adjustments needed within his same population [28].

In a study by Kimmel *et al.*, a subgroup analysis of PGx-guided warfarin therapy on Black and non-Black populations suggested that these ethnicities may respond differently to therapy with certain PGx testing in place. However, the study was underpowered in its ethnicity comparison, and further research is needed on this topic [29]. This literature inconsistency of PGx-guided warfarin therapy is also true for patients suffering from CV diseases since those who suffer from CV diseases are at a higher risk of recurrent adverse CV events, and anticoagulation therapy is imperative. With warfarin being the most affordable and accessible anticoagulant on the market, there is a high demand for its use [8]. Due to warfarin's nature for adverse BEs, patients who are most likely to use warfarin, such as those with a CV event history, are at the greatest risk of experiencing the aforementioned adverse effects, including potential uncontrolled coagulation. PGx-guided therapy offers a solution to this problem by providing pre-determined prescription suggestions on how to dose warfarin properly before initiation. Unfortunately, due to varying results and lack of cumulative evidence for specific patient populations, collecting and implementing genomic information on everyone in the general practice setting is up for debate as to whether it is worthwhile or not [21, 26, 27]. As mentioned earlier, the double-edged sword of warfarin therapy is a clinical consideration for implementing PGx-guided warfarin testing to minimize trial-and-error compared to the standard of care (SOC). Hence, there is an evident knowledge gap on how PGx-guided therapy can improve warfarin initiation for patients who suffer from select CV diseases that warrants a systematic review. The objectives were to:

1. To compare the incidence of TEs and BEs in relation to safety outcomes between the PGx-guided warfarin therapy group versus the SOC group in the cardiovascular disease population.

2. To examine the impact of PGx-guided warfarin therapy on TTR, PTTR and dosing adjustments by comparing efficacy outcomes (therapeutic outcomes) in these two groups of interest.

Materials & Methods:

Systematic Review: This systematic review was performed according to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [30]. Articles were identified from MEDLINE, CINAHL, Web of Science, Embase, the Cochrane Library and clinicaltrials. gov database for studies on PGx-guided warfarin therapy compared to an SOC in patients. The search terms were a combination of the following: "warfarin," "pharmacogenomics," "anticoagulation," "cardiovascular disease," "atrial fibrillation," "pulmonary embolism," and "deep vein thrombosis." Articles were further reviewed and identified based on the inclusion of a combination of the key terms. Both RCTs and observational studies were taken into consideration. Identified articles were of the English language, including international studies initially written in

other languages which were then translated into the English language.

Inclusion and Exclusion Criteria: Abstracts were reviewed for the outcomes of interest and appropriate transitions of care protocol. Demographics were reviewed to identify patients present in the study who had previous CV events of interest. These studies worked independently and measured outcomes based on INR readings, such as TTR and PTTR and adverse effects, such as the occurrence of bleeding and TEs. Articles that reported one or more of these clinical outcomes, possessed a standard of care control protocol for the control group, focused on the aforementioned CV events of interest, utilized PGx testing and selected warfarin as the treatment of choice, met the inclusion criteria for the systematic review. Articles were excluded if the study was not PGx related, warfarin was not the anticoagulant of choice, not CV related, or the patient population experienced a heart valve replacement. If the population of interest had non-human subjects, such as animals, the study was excluded. Additionally, articles which were meta-analysis or systematic review, displayed lack of power or control group, had heterogeneous outcomes, or expressed bias such as promotional funds, were also excluded. Articles which received funding from PGx or warfarin-related corporations were classified as biased. If the presence of bias was unclear, the article was eliminated to assure only unbiased work was represented. Randomized controlled trials (RCTs) as well as retrospective and prospective cohort studies were considered for outcome of interest. All articles considered had to be no earlier than 2006 to reflect when PGx testing platforms became commercially available for clinical practice. A total of two independent reviewers evaluated each study to determine if the inclusion criteria were met and to verify no exclusion criteria were overlooked.

Data Extraction: The main search and the screening of abstracts were conducted independently by two authors (AG and SK). Differences were resolved by consensus between the two reviewers. The literature review and selection of articles were conducted from October 2019 to August 2022.

RESULTS: Of the articles produced in the database search, 28 articles were retrieved for possible inclusion in the systematic review based on abstract screening. Through the initial review of the 28 articles, 16 articles were identified for the systematic review due to the inclusion of relevant topics, such as PGx, CV and warfarin use. Of those 16 articles, only a total of 6 articles met the specific inclusion criteria and were ultimately included, accumulating a total of 2,278 enrolled patients. The exclusion criteria were primarily due to unspecified control standards, lack of power, and not meeting this systematic review's specific criteria. **Fig. 1** shows a flow diagram of the search strategy and review process [6, 27, 29, 30-33].

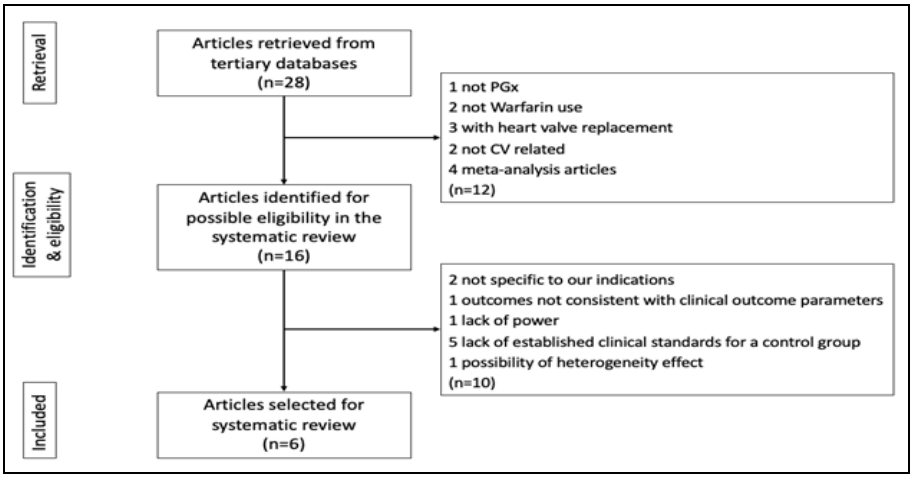

FIG. 1: PRISMA FLOWCHART REPRESENTING THE RESULT OF THE SEARCH STRATEGY AND THE NUMBER OF ARTICLES EXCLUDED AND ELIGIBLE FOR REVIEW

The study methods, baseline practice characteristics and findings of each study are summarized in **Table 1**, where "favor" indicates the numerical superiority of desired outcomes in one study group

to another, with or without statistical significance [6, 27, 29, 30-33]. Within the 6 selected articles, common characteristics included clear SOC protocols, large populations of enrollees with the specific CVs of interest, the use of PGx-guided techniques to initiate warfarin therapy, and identical means to measure coagulation rates. Despite the common design of therapy provision and goals, the methods in each study differed in select ways. This can be observed primarily in the various follow-up periods, design of the trials, as well as in populations of interest.

TABLE 1: ANALYSIS OF INCLUDED TRIALS

Study, year	Design	Details of Research/Article	Patient CV hx	Findings	INR Goal	Follow Up
Pengo *et al*, 2015	RCT	Study aims to determine whether PGx testing (CYP2C9, VKORC1, CYP4F2) based therapy for warfarin is superior to SOC.	Afib	TTR favors PGx group over SOC in terms of time outside of INR*	Not falling outside of the range of <2 and 3<	All patients had a minimum for 30 days follow-up. 397 median days for PGx group and 359 median days for SOC group for follow up
Kimmel *et al*, 2013	RCT	Study aims to compare PGx (CYP2C9, VKORC1) and SOC for warfarin dosing strategies	Afib, DVT, PE	TTR favors PGx group with African American race over SOC*	INR 2-3	All patients were followed for a total of 6 months.
Makar-Ausperger *et al*, 2018	RCT	Study aims to determine efficacy and safety of PGx testing (CYP2C9, VKORC) based therapy for warfarin use compared to SOC.	Afib, DVT, PE	TTR favors PGx group over SOC for patients with Afib*	INR 2-3	All patients were followed up the first 5 days of initiating therapy then to the end of the 4th week
Jorgensen *et al*, 2019	Cohort	Study aims to determine whether PGx (CYP2C9, VKORC1) based therapy for warfarin could translate into routine clinical practice for Afib or VTE patients compared to SOC	Afib, DVT, PE	TTR favors PGx group over SOC*; PGx testing less likely for INR >4 occurrences	INR 2-3	All patients remained in the project for follow up for at least 2 weeks. A large majority of patients were followed up for a max of 12 weeks (84 days)
Caraco *et al*, 2008	RCT	Study aims to determine if PGx testing (CYP2C9) prior to warfarin therapy for safety and efficacy compared to SOC	Afib, DVT, PE	TTR favors PGx group over SOC*; PTTR favors PGx group over SOC*; INR favors PGx group over SOC* and with an average interval of consecutive INR tests being greater in PGx group	INR 2-3	All patients were followed up for daily monitoring for the first 8 days and then until therapeutic INR range was reached for >2 days, which was around 22.1 days for PGx and 40.2 days for SOC
Pirmohamed *et al*, 2013	RCT	Study aims to compare the level of anticoagulation in PGx (CYP2C9*2, CYP2C9*3, VKORC1) and SOC for warfarin therapy	Afib, VTE	TTR favors PGx group over SOC*; PTTR favors PGx group over SOC; Thromboembolic events did not happen in the PGx group; Fewer dose adjustments in PGx group*	INR 2-3	All patients were followed for 3 months of therapy

RCT randomized control trial, PGx pharmacogenomic intervention, SOC standard of care, Afib atrial fibrillation, PE pulmonary embolism, VTE venous thromboembolism, PTTR time to reach therapeutic range, TTR time in therapeutic range, hx history, * statistically significant finding

However, the core principles behind each program focused on the instances of TE and BE as well as the measured TTR and PTTR following protocols which best suited their practice [6, 27, 29, 30-33]. The

definition of statistical significance remained fairly consistent between each study, where significance was defined as either a p-value of equal to or less than 0.05 [6, 27, 29, 30-33]. The only study which diverged from this Kimmel *et al.,* which defined significance as a p-value equal to or less than 5.5% [29]. In addition, only 2 articles, Kimmel *et al.* and Makar-Ausperger *et al.,* indicated that the intention-to-treat method was applied to their respective studies [29, 31]. Follow-up time was largely variable between the studies, ranging from days to months, with the longest documented follow-up time being 1037 days [27, 31]. Three of the 6 studies had unfixed follow-up periods; 2 of which provided a minimum number of days to follow up, while the remaining 1 set a therapeutic goal to discontinue follow up [6, 27, 31]. During each follow up, the same therapeutic goal was shared in each study: an INR ranging from 2 to 3. Each study also shared one common gene to genetically test, which was CYP2C9. Another shared aspect was that each study included warfarin-naive individuals with a history of Afib [6, 27, 29, 30-33]. The reported patient characteristics are summarized in **Table 2** [6, 27, 29, 30-33]. Based on the 6 articles, the typical patient were aged from mid-50s to mid-70s and had a former cardiovascular event, including one or a combination of Afib, PE, or DVT. Patients primarily were of European, Black, non-Black and Israeli descent based on geographical location and documented ethnicities. The studies' subjects were drawn from populations in Europe, the USA, and Israel [6, 27, 29, 30-33].

TABLE 2: PATIENT CHARACTERISTICS OF INCLUDED TRIALS

Study, year	Number of Enrollees	Typical Age: PGx, SOC (mean, median, not specified)	Male Sex: PGx%, SOC%	Where Study was Conducted (Ethnicity)	Afib % of total patients in study	DVT % of total patients in study	PE % of total patients in study	VTE % of total patients in study
Pengo *et al*, 2015	200	71, 75 (median)	65.9, 65.2	Italy (Caucasian)	100	0	0	N/A
Kimmel *et al*, 2013	1015	59, 57 (median)	53, 49	USA (non-Black and Black)	21.8 (Afib only)	Unknown total	Unknown total	58.0 (PE or DVT only)
Makar-Ausperger *et al*, 2018	205	70, 73 (not specified)	51.9, 43.4	Croatia	30.2	60	19.5	N/A
Jorgensen *et al*, 2019	212	72.14, 69.65 (mean)	52.94, 54.84	England (parents and grandparents of White ancestry)	78.8	9.9	11.3	N/A
Caraco *et al*, 2008	191	57.6, 59.7 (not specified)	48.4, 43.8	Israel	34	27.2	21.5	N/A
Pirmohamed *et al*, 2013	455	67.8, 66.9 (mean)	64.2, 57.9	Sweden and UK	72.1	Unknown total	Unknown total	27.9

PGx pharmacogenomic intervention, SOC standard of care, Afib atrial fibrillation, DVT deep vein thrombosis, PE pulmonary embolism, VTE venous thromboembolism, USA United States of America, UK United Kingdom

Pengo *et al.,* Kimmel *et al.,* Makar-Ausperger *et al.*, and Pirmohamed *et al.* had the greatest number of patients with a history of Afib, with Pengo *et al.* having only Afib as the population of interest [27, 29, 31, 33]. Pengo *et al.*, Jorgensen *et al.*, and Pirmohamed *et al.* had the highest percentage of Afib patients in their studies, ranging from 72.1-100% [27, 32, 33]. Makar-Ausperger *et al.*, Jorgensen *et al.*, Caraco *et al.,* and Kimmel *et al.* each studied Afib, DVT and PE, whereas Pirmohamed *et al.* only studied Afib and venous thromboembolism (VTE) [6, 29, 31-33]. Makar-Ausperger *et al.* and Caraco *et al.* both have the highest documented percentage and highest count of DVT patients, ranging from 27.2-60% and 52-127 patients, respectively. Makar-Ausperger *et al.* and Caraco *et al.* also documented PE patients' highest percentages and counts, ranging from 19.5-21.5% and 40-52 patients, respectively [6, 31]. Unfortunately, the quantity of DVT and PE participants in Pirmohamed et al' study is inconclusive due to VTE being inclusive of DVT and PE. The exact counts of DVT and PE were also unclear in the studies by Kimmel *et al.* due to only a total count

of the two being provided, which totaled 589 subjects with DVT or PE only, accounting for 58% of the total population [29]. The specific CV event counts were based on primary indication for warfarin or clinical characteristics and history, with the latter being prioritized when both were provided [6, 27, 29, 30-33].

Safety Outcomes (Objective 1): Pengo *et al.*, Jorgensen *et al.*, Caraco *et al.*, Kimmel *et al.*, and Pirmohamed *et al.* all studied TE and BEs. These studies found no statistically significant differences between the PGx group and SOC for TE outcomes. Also, only Caraco *et al.* noted statistically significant outcomes for Bes [6, 27, 29, 32, 33]. Pengo *et al.* and Kimmel *et al.* stated that, although no statistically significant findings were associated with BEs and TEs in either control group, the trial was not adequately powered to detect possible differences in these outcomes. Jorgenson *et al* noted a similar limitation in TE and BE measurements, stating that time in the therapeutic INR range rather than clinical events of TE or BE as an outcome measure, concluding statistical power to assess for occurrence differences was not established. However, Jorgenson *et al.* documented that the PGx group was less likely to have an INR >4 and more likely to have an INR <2 [32]. Pirmohamed *et al.* noted a TE event occurring in the SOC group and none in the PGx group, although not statistically significant [33]. Caraco *et al.* determined a statistically significant finding for fewer incidences of minor BE favoring the PGx group; however, they did not find statistically significant outcomes only with the average interval of consecutive INR tests [6]. Only Pengo et al. and Pirmohamed et al investigated this topic in terms of dosage adjustments. Based on their findings, only Pirmohamed *et al.* found statistically significant fewer dosage adjustments were necessary to achieve a therapeutic INR range for the PGx-guided group compared to SOC. This study found that 4.9 adjustments were necessary in the PGx-guided therapy compared to 5.4 dosage adjustments in the SOC [33]. As for Pengo *et al.*, the number of dose adjustments was not different between PGx-guided therapy and SOC [27].

Therapeutic Outcomes (Objective 2): All articles studied TTR and expressed statistically significant findings in TTR in favor of the PGx-guided warfarin if sub-group analysis is considered. However, in the Makar-Ausberger study, only the Afib population showed a statistically significant difference in TTR favoring the PGx-guided group [31]. The population in Kimmel *et al.* was pooled from the USA. The population was further sub-analyzed into Black and non-Black, with the Black population showing statistically significant favor for TTR in the PGx group [29].

PTTR was evaluated in Pengo *et al.*, Caraco *et al.*, Kimmel *et al.*, Makar-Asperger *et al.*, Pirmohamed et al., Pengo *et al.*, Kimmel *et al.*, and Makar-Asperger *et al.* found no statistical significance [6, 27, 29, 31, 33]. However, Caraco *et al.* and Pirmohamed *et al.* found favor for the PGx-guided groups [6, 33]. Caraco *et al.* found the PTTR was established earlier in the PGx group compared to SOC, by an average of 2.73 days earlier [6]. As for Pirmohamed *et al.*, statistical significance was determined with PTTR in the PGx group, achieving a therapeutic range of 21 days, whereas the SOC group averaged 29 days [33]. In the study by Kimmel *et al.*, the Black population was indicated to have a superior PTTR in the SOC group [29].

DISCUSSION: Warfarin is a challenging drug to dose due to its narrow therapeutic index, whereas PGx offers insight into warfarin dosing before initiation [2, 8, 21, 24-27]. Due to warfarin being frequently used in patients with various CV diseases, these populations will likely benefit from improved warfarin dosing techniques, specifically those with Afib, PE, and DVT [1, 24]. This systematic review suggests PGx-guided warfarin therapy improves TTR therapy and can have beneficial outcomes for PTTR, decreased BEs, and fewer dose adjustments. No articles indicated a statistically significant reduction in TE when comparing the SOC and PGx-guided therapies, suggesting no therapeutic benefit. Additionally, patients with Afib, PE, and DVT all displayed benefits in PGx-guided therapy, whereas patients with Afib suggested the strongest benefit from PGx-guided therapy. Previous studies noted that warfarin contributes to fatal, major, and minor bleeds globally [3-6].

With Caraco *et al.* also noting that warfarin-induced major hemorrhages tend to occur most frequently during the first year of therapy,

indicating the need for further exploration in PGx-guided warfarin therapy for reducing BEs. As mentioned in the results of Caraco *et al.*, there were significantly more BEs in the SOC group compared to the PGx-guided group for warfarin dosing. Specifically, BE occurred in 12.5% of the SOC group and 3.2% in the PGx-guided group, accumulating 15 BEs, with 14 of said BEs being minor. A total of 5 of these BEs occurred during the first 8 days of induction, with 4 in the SOC and 1 in the PGx-guided groups. The 1 instance of a major BE concerning a serious lower gastrointestinal bleed occurred after 9 days of therapy in the SOC group, which interestingly occurred with an INR value of 1.74. Unfortunately, the study was not designed to identify differences in the rate of bleeding complications or was defined as a primary study endpoint. However, the risk of bleeding was measured using two surrogate markers: the number of days with an INR >3 and the extent of deviation from the therapeutic range of 2-3. According to these surrogate markers, the risk of bleeding was significantly higher in the SOC group [6].

Since the power was limited in the other 4 studies which evaluated BEs, which suggested no statistical significance between the SOC and PGx-guided groups, more research is necessary to establish the true effects of PGx-guided warfarin therapy in managing Bes [27, 29, 32, 33]. Nevertheless, the findings from these studies may offer some preliminary insight for future research. For instance, Kimmel *et al.* noted that major BEs, as defined by the Italian Study on Complications of Oral Anticoagulant Therapy (ISCOAT), occurred more frequently in the SOC group.

Namely, 10 subjects in the SOC group compared to 4 in the PGx-guided group experienced a major BE, where the INR was elevated to >3 in 1 SOC subject and 3 PGx-guided subjects [29]. As for Pirmohamed *et al.*, no major BEs were reported in either group; however, 3 clinically-significant minor BEs requiring hospital admission and 1 TE event all happened in the SOC group, none in the PGx-guided group [33]. In an interesting contrast to this, the study by Jorgensen *et al.* reported no subjects in the SOC experienced BEs and 1 subject in the PGx-guided group experienced a bladder bleed and had to withdraw from the study [32]. Another study that may offer further insight into PGx-guided warfarin therapy and BEs is a study by Panchenko *et al.*, which was conducted in Russia in 2020. In this study, both the SOC and PGx-guided groups started on 5mg of warfarin. However, on day 3 the SOC group made dosage adjustments based on INR, and the PGx-guided group adjusted on day 5 using the Gage algorithm to interpret the genetic findings. Using the ISCOAT definition for major BEs, there were 6 major bleeds in the SOC group, with 5 of these instances developing in carriers of at least 1 genetic polymorphism for increased warfarin sensitivity.

Interestingly, with BEs being the highest in the first month of therapy, PGx-guided therapy was found to significantly reduce the number of BEs with an INR ≥4 in this time frame, with instances in 4.8% in the PGx-guided group and 23.7% in the SOC group. It is important to note that, although the outcomes of this study are similar to this systematic review, this study was ultimately excluded due to inconsistencies in the INR goals, which was a lower target range than the recommended 2-3 INR therapeutic range implemented in Western society [34].

Concerning all the findings evaluated in this systematic review, more research is necessary to establish the clear relevance of PGx-guided warfarin dosing and consequential BEs. Within this systematic review, the populations were predominantly Caucasian; however, there was some variance in ethnicities which offered additional insight into population-specific benefits. Based on the information provided by the included articles, it is suggested that patients with a European, non-Black, and Israeli heritage seem to display more beneficial therapeutic outcomes from the PGx-guided therapy [6, 27, 29, 30-33]. However, according to the study by Kimmel *et al.*, Blacks using PGx-guided warfarin therapy show both risk due to a delayed PTTR and benefit in achieving a longer TTR with PGx-guided warfarin therapy. Although, it is important to note that the study did not test for the CYP2C9 variants that frequently occur in the Black population. Specifically, the common CYP2C9 variants in Blacks would include *5, *6, *8, and *11; however, the study only tested *2 and *3, which are most common in the Caucasian populations [29]. This systematic review

recommends a risk versus benefit consultation of PGx-guided warfarin therapy and provider judgment when recommending PGx-guided warfarin therapy for the Black population until more information is gathered to provide adequate guidance. Overall, those of European, non-Black, or Middle-Eastern descent in their 50s or older with Afib are the ideal populations likely to benefit the most from PGx-guided warfarin therapy to achieve sooner PTTR and likely a longer TTR, decreased BEs, and fewer dose adjustments.

A strength of this study included a thorough literature search, which was conducted using various tertiary and secondary resources, especially with two independent researchers. Using this thorough search as well as clear inclusion and exclusion criteria allows more patient-specific related outcomes with more supporting evidence of aforementioned outcomes. Another strength of this study is that it is the first of its kind to evaluate PGx compared to a SOC for initial warfarin therapy about Afib, PE and DVT cases. Specifically, many other systematic studies focus on PGx overall outcomes on possibly one disease state with less elaboration on population differences. In contrast, this study prioritizes the populations and Afib, PE, and DVT disease states. Ultimately, this study helped fill the gap in knowledge of how PGx-guided warfarin therapy will likely affect patients with specific CV diseases. Additionally, this study collected and evaluated multiple sources of literature over an extended period of over 18 months, allowing a thorough search. Using two independent reviewers further limited any review bias when establishing article selection.

In terms of limitations to this systematic review, limited studies met the inclusion and exclusion criteria. Since only 6 articles were included in this systematic review, the outcomes patients may experience with PGx-guided warfarin therapy might not comprehensively represent all patients' clinical outcomes. Another limitation of this systematic review is that within the reviewed articles, there were limited observational studies available. Five of the 6 articles used in this systematic review were RCTs, which offered insight into PGx-guided warfarin therapy in an environment with limited confounding effects [6, 27, 29, 30-33]. However, RCTs have fewer confounding effects and minimize extraneous factors, creating an environment that limits real-world application. Furthermore, the limited number of cohort studies may limit the study's real-world application of PGx-guided warfarin dosing in an uncontrolled environment. Additionally, the use of RCTs can have limited insight from a chronological standpoint with a generally shorter follow-up period compared to cohorts which generally look at longer durations of time, which offers deeper insight for PGx-guided warfarin therapy.

Also, the genetic testing methods used within the studies included in this review varied, which may have implemented bias in initial warfarin dosing selection. Specifically, all articles tested the CYP2C9 genotype; however, not all articles tested the VKORC1 or CYP4F2 genotypes, which can be a limitation on what initial dose should be selected [6, 27, 29, 30-33]. For instance, studies that tested 3 genetic components may have executed a more advanced initial dosing regimen over studies that reviewed only 1 genetic component. This is especially true without the VKORC1 genetic test, due to its impact on the vitamin K cycle and consequential therapeutic effects as highlighted in the Coumadin package insert [25]. Because of this, it can be argued that studies without CYP2C9 and VKORC1 genetic testing would not be comparable to those with them. The lack of consistent and tailored genetic testing leaves an additional knowledge gap regarding the genetic testing interpretation and implementation. A final limitation to the study is that no included studies addressed the Asian population, which limits the recommendation for PGx-guided warfarin therapy use in this ethnic group.

The findings based on this systematic review may prompt future researchers to conduct a meta-analysis. However, this may pose a future challenge since the articles within this review had inconsistent outcomes of interest, and consistent outcomes of interest play a key role in forming a meta-analysis. The authors of this study took into consideration the possibility of a meta-analysis. They opted not to conduct one at this time due to the inconsistent outcomes and genetic testing approaches, making it difficult to assess the values quantitatively. An additional consideration for future research on the subject of PGx-guided

warfarin therapy could be the financial impact this implication has on hospitals, insurance, and patient outcomes since none of the included studies of this systematic review addressed this topic. Ultimately, further future research is necessary to understand the influence of PGx-guided warfarin amongst various patient populations from an ethnic, genetic, financial, therapeutic, and disease-oriented standpoint.

CONCLUSION: This systematic review demonstrates that patients using PGx-guided warfarin dosing are more likely to establish a longer TTR than SOC treatment in patients with a history of Afib, PE, and DVT. In select patient populations, it is suggested that PGx-guided warfarin therapy may decrease PTTR, reduce BEs, and require fewer dose adjustments. However, there is no statistically significant benefit in PGx-guided therapy to reduce TEs. Future research is needed to understand further the extent of PGx-guided warfarin therapy in populations with CV diseases.

ACKNOWLEDGEMENTS: We are grateful to the authors of the contributing works, Jaehee Lee and newborn Angelina Taeri Kim, for all the social support. We also thank Linda Marie Green and Patrick Anthony Green for their constant social support.

Funding: This research did not receive any specific grant from the public, commercial, or not-for-profit funding agencies.

Ethics Approval and Consent to Participate: Not applicable

Consent for Publication: Not applicable

Data Availability: Not applicable. We used only published articles.

CONFLICT OF INTEREST: The authors declare that they have no competing interests

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How to cite this article:
Green AM, Brackbill M, Harralson AF and Kim SH: Coding for an anticoagulant: systematic review of pharmacogenetics-guided warfarin therapy on the therapeutic and adverse clinical events on patients with atrial fibrillation, pulmonary embolism, and deep vein thrombosis. Int J Pharm Sci & Res 2023; 14(4): 1703-13. doi: 10.13040/IJPSR.0975-8232.14(4).1703-13.