Systemic Review and Meta-Analysis of CYP2C9 Genotype-Guided Therapy on Warfarin in Medicare-Aged Adults

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Abstract

- Warfarin is a commonly prescribed vitamin K antagonist used for prophylactic anticoagulation in the setting of stroke, atrial fibrillation, valve replacement, heart failure, and myocardial ischemia.
- The cytochrome p450 enzyme isoform CYP2C9 is well known for its influence on warfarin metabolism, and patients with variants of this gene have unpredictable responses to the drug because of a narrow therapeutic index.
- The aim of this study is to utilize bibliometric analysis to identify gaps in the literature on *CYP2C9* genotype-guided warfarin therapy and subsequently conduct a systematic review and meta-analysis to evaluate its impact on major adverse events in Medicare-aged adults.

Methods and Statistical Analysis

Bibliometric Analysis

- Constructed search queries were created based on *CYP2C9* and genotype-guided warfarin therapy, focusing on clinical outcomes from studies between Jan 2010–Jul 2025.
- Bibliometric mapping were performed to identify publication trends, clusters, and gaps utilizing VOSviewer.
- Visualized clusters (“bubbles”) were created highlight paucity of data.

Evidence Gap Translation

- Underrepresented areas were prioritized and identified in bibliometric analysis.
- Defined focus for systematic review/meta-analysis.

Systematic Review

- Conducted according to PRISMA guidelines.
- Databases mined: PubMed, EMBASE, Web of Science (Jan 2010–Jul 2025).
- Studies were included if they compared *CYP2C9* genotype-guided versus conventional warfarin dosing in adults with a mean age of ≥65 years, and reported major bleeding (per International Society on Thrombosis and Haemostasis (ISTH) criteria) or other clinical outcomes.
- Two reviewers independently screened, extracted data, and assessed study quality.

Results

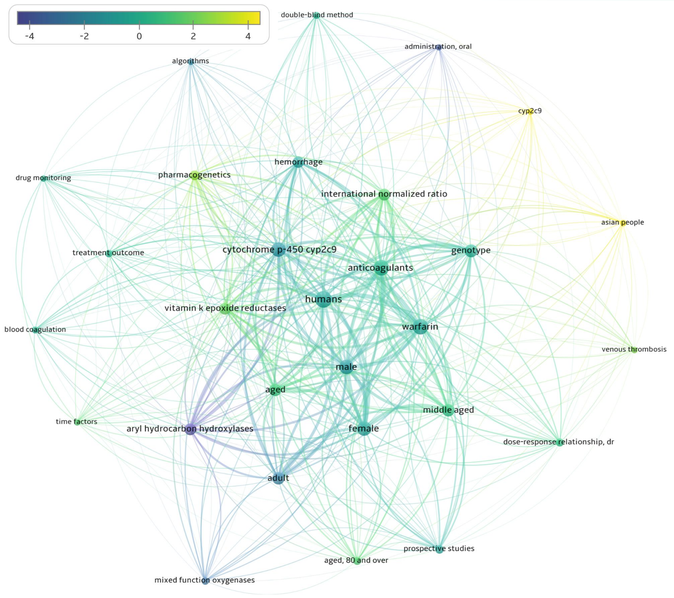

Figure 1. Network analysis of CYP2C9-warfarin pharmacogenetics by research topic. VOSviewer legend: Indicates relative differences via subtracted means after baseline removal.

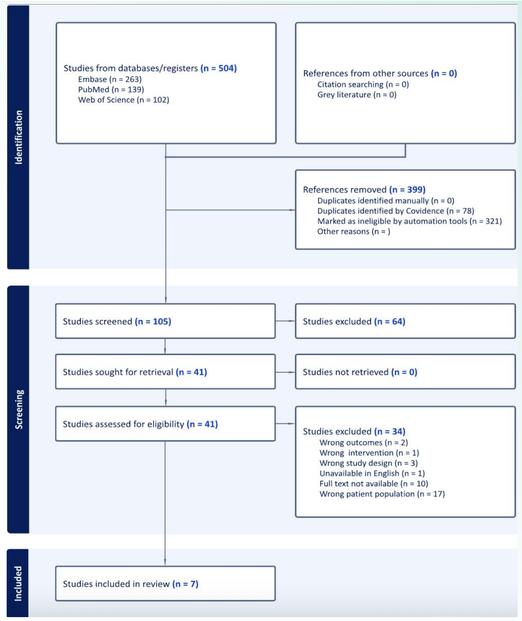

Figure 2. PRISMA-style schematic of article search, screening, and inclusion process.

Study	Sample Size (n)	Published Year	Country	Population	Intervention	Primary Outcomes	Key Findings
GIFT RCT	1650	2017	U.S.	Orthopedic surgery patients	Genotype-guided dosing	ISTH major bleeding, INR ≥4, composite adverse events	↓ Major adverse events, improved safety in genotype-guided group
XY3-WAR Trial	660	2020	China	AF/DVT patients	Genotype-guided dosing	TTR, INR control, adverse events	↑ TTR and faster INR control; no significant difference in adverse events
Croatia RCT	209	2018	Croatia	AF, DVT, PE patients	Genotype-guided dosing	TTR, thromboembolic/bleeding events	Benefit only in AF subgroup; no difference in DVT/PE
Pengo et al.	200	2015	Italy	AF patients	Genotype-guided dosing	TTR, INR >4, adverse events	No superiority over pharmacodynamic dosing; slight ↓ INR >4 events
Ruzickova et al.	103	2019	Czech Republic	Cardioembolic stroke patients	PGx-guided loading dose (2× estimated maintenance)	TTR (10d, 30d), INR control, adverse events	↑ Early TTR, faster INR control; no ↑ adverse events
Wen et al.	318	2017	Taiwan	Han-Chinese patients, mixed indications	Genotype-guided dosing (IWPC/Taiwan algorithms)	TTR, INR stability, bleeding, thromboembolism	No clear benefit of PGx dosing; frequent INR monitoring mitigated effect
Zhu et al.	507	2020	China	Elderly NVAF patients	Genotype-guided dosing	TTR (90d), bleeding, ischemic stroke	↑ TTR (+17%), ↓ ischemic stroke risk; no ↑ bleeding events

Table 1. Randomized controlled trials evaluating genotype-guided warfarin dosing (CYP2C9/VKORC1).
This table summarizes key features of seven RCTs included in the systematic review. Populations ranged from elderly orthopedic patients to atrial fibrillation (AF), deep vein thrombosis (DVT), pulmonary embolism (PE), and cardioembolic stroke cohorts across the U.S., Europe, and Asia. Primary outcomes included time in therapeutic range (TTR), major bleeding (as defined by the International Society on Thrombosis and Haemostasis, ISTH), thromboembolic events, and mortality. NVAF = non-valvular atrial fibrillation; PGx = pharmacogenetics; INR = international normalized ratio.

Discussion

- Evidence gaps identified by bibliometric analysis indicated limited randomized controlled trials (RCT) data exist specifically in Medicare-aged adults (≥65 years) with major bleeding outcomes, justifying the present systematic review and meta-analysis.
- RCTs demonstrated mixed results with large trials (e.g., GIFT) found reduced adverse events; smaller studies often showed no clear benefit.
- Benefit more evident in older atrial fibrillation patients; frequent international normalized ratio (INR) monitoring reduced added value of Pharmacogenetic-guided (PGx) dosing.
- PGx dosing may offer greatest utility in settings with high variability in response, limited INR monitoring capacity, and in older high-risk populations.
- Consistent improvement in anticoagulation control: Several trials (XY3-WAR, Ruzickova, Zhu) reported improved time in therapeutic range (TTR) and faster INR stabilization with genotype-guided dosing.
- Clinical outcome benefits remain variable: Reduction in ischemic stroke risk (Zhu et al.) and fewer supratherapeutic INR events (Pengo et al.) suggest possible clinical impact, though other studies reported no significant differences in bleeding or thromboembolic outcomes.

Conclusions and Future Directions

- Evidence across RCTs is mixed, but several demonstrate improved anticoagulation control with genotype-guided dosing.
- This systematic review addresses partially the gap of data related to Medicare-aged adults focusing on major bleeding and adverse events.
- Meta-analyses will be performed as permitted by the data. Primary outcomes will include major bleeding, thromboembolic events, time to stable dose, and over-anticoagulation (INR >4).
- Data will be synthesized using random-effects meta-analysis. Mean differences (MDs) or standardized mean differences (SMDs) with 95% confidence intervals (CIs) will be calculated for continuous outcomes, and risk ratios (RRs) for dichotomous outcomes. Heterogeneity assessed using the I^2 statistic.

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