**Integrative Pharmacogenomics and Structural Equation Modeling Reveal Genetic Determinants of DOAC Therapy**

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**Background and aims.** Genetic variability plays a critical role in determining the pharmacokinetics and clinical efficacy of direct oral anticoagulants (DOACs), yet pharmacogenomic guidance is still lacking in clinical practice. This study systematically evaluates how specific gene polymorphisms influence DOAC therapy, aiming to advance precision medicine in anticoagulation.

**Methods.** A systematic review adhering to PRISMA-2020 guidelines (PROSPERO ID: CRD42024592412) analysed 31 studies. Structural Equation Modelling (SEM) in R Studio (v2024.12) was used to examine genetic variants related to DOAC pharmacokinetics and treatment outcomes. PCA clustering further strengthened the analysis.

**Results.** SEM result (see **Figure 1**) revealed that genetic factors positively influenced drug concentration dynamics (β = 0.24), which in turn strongly impacted clinical outcomes (β = 1.10), while higher drug exposure (Cmax/Cmin) was associated with increased bleeding risk (β = 1.00), and gene variants were inversely related to ischemic stroke (β = –0.17). The structural equation model demonstrated high fit (CFI = 0.997, RMSEA = 0.037, see **Table 1)**. Variants in ABCB1, CES1, ABCG2, CYP3A4, and SLCO1B1 were associated with altered drug exposure and bleeding or stroke risk. Specific alleles reduced clinical event risks to below 20 – 40%, depending on the DOACs and genotype (see **Figure 2**). PCA identified two patient clusters (see **Figure 3**): Low Risk (stable pharmacokinetics, minimal adverse events) and Moderate Risk (variable drug exposure, elevated complications).

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| **A diagram of a clinical**  **Figure 1.** SEM of Genetic Influence on DOACs Outcomes. | | **Table 1.** SEM Model Fit Summary   |  |  | | --- | --- | | **Parameter** | **Value** | | CFI / TLI | 0.996 / 0.986 | | RMSEA (90% CI) | 0.047 (0.000–0.104) | | p (RMSEA ≤ 0.05) | 0.445 | | SRMR | 0.031 | |
| A graph of dna sequence  AI-generated content may be incorrect.  **Figure 2.** Top Genotypes Associated with DOACs Clinical Effectiveness | **A diagram of a diagram  AI-generated content may be incorrect.**  **Figure 3.** PCA Plot with Cluster Annotations | |

**Conclusion/Discussion.** Genetic polymorphisms significantly influence DOACs response. Integrating pharmacogenomic testing with therapeutic drug monitoring can enhance treatment precision, paving the way toward more personalized anticoagulation strategies.

**References:**

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