



Warfarin resistance

Warfarin resistance is a condition in which individuals have a high tolerance for the drug warfarin. Warfarin is an anticoagulant, which means that it thins the blood, preventing blood clots from forming. Warfarin is often prescribed to prevent blood clots in people with heart valve disease who have replacement heart valves, people with an irregular heart beat (atrial fibrillation), or those with a history of heart attack, stroke, or a prior blood clot in the deep veins of the arms or legs (deep vein thrombosis).

There are two types of warfarin resistance: incomplete and complete. Those with incomplete warfarin resistance can achieve the benefits of warfarin treatment with a high dose of warfarin. Individuals with complete warfarin resistance do not respond to warfarin treatment, no matter how high the dose. If people with warfarin resistance require anticoagulant therapy and take the average warfarin dose, they will remain at risk of developing a potentially harmful blood clot.

Both types of warfarin resistance are related to how the body processes warfarin. In some people with warfarin resistance, their blood-clotting process does not react effectively to the drug. Others rapidly break down (metabolize) warfarin, so the medication is quickly processed by their bodies; these individuals are classified as "fast metabolizers" or "rapid metabolizers" of warfarin. The severity of these abnormal processes determines whether the warfarin resistance is complete or incomplete.

Warfarin resistance does not appear to cause any health problems other than those associated with warfarin drug treatment.

Frequency

Warfarin resistance is thought to be a rare condition, although its prevalence is unknown.

Causes

Many genes are involved in the metabolism of warfarin and in determining the drug's effects in the body. Certain common changes (polymorphisms) in the *VKORC1* gene account for 20 percent of the variation in warfarin metabolism due to genetic factors. Polymorphisms in other genes, some of which have not been identified, have a smaller effect on warfarin metabolism. The polymorphisms associated with warfarin resistance often differ by population and ethnic background.

The *VKORC1* gene provides instructions for making a vitamin K epoxide reductase enzyme. The *VKORC1* enzyme helps turn on (activate) clotting proteins in the pathway that forms blood clots. Warfarin prevents (inhibits) the action of the *VKORC1* enzyme by binding to the enzyme and preventing it from binding to and activating the clotting

proteins, stopping clot formation. Certain *VKORC1* gene polymorphisms lead to the formation of a *VKORC1* enzyme with a decreased ability to bind to warfarin. This reduction in warfarin binding causes incomplete warfarin resistance and results in a higher dose of warfarin needed to inhibit the *VKORC1* enzyme and stop the clotting process. If the *VKORC1* enzyme cannot bind to any warfarin, the result is complete warfarin resistance.

While changes in specific genes affect how the body reacts to warfarin, many other factors, including gender, age, weight, diet, and other medications, also play a role in the body's interaction with this drug.

Inheritance Pattern

The polymorphisms associated with this condition are inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to result in warfarin resistance. However, different polymorphisms affect the activity of warfarin to varying degrees. Additionally, people who have more than one polymorphism in a gene or polymorphisms in multiple genes associated with warfarin resistance have a higher tolerance for the drug's effect or are able to process the drug more quickly.

Other Names for This Condition

- coumarin resistance
- poor metabolism of coumarin

Diagnosis & Management

Formal Treatment/Management Guidelines

- Canadian Medical Association: Warfarin Therapy Management
https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/warfarinmgmt_2015_full.pdf
- Canadian Medical Association: Warfarin Therapy – Management During Invasive Procedures and Surgery
https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/warfarinsurg_2015_full.pdf

Genetic Testing Information

- What is genetic testing?
</primer/testing/genetic-testing>
- Genetic Testing Registry: Warfarin response
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0750384/>

Research Studies from ClinicalTrials.gov

- ClinicalTrials.gov
<https://clinicaltrials.gov/ct2/results?cond=%22warfarin+resistance%22+OR+%22coumarin+resistance%22+OR+%22warfarin+dosage%22+OR+%22warfarin+dosing%22>

Other Diagnosis and Management Resources

- American Society of Hematology: Antithrombotic Therapy
<https://www.hematology.org/About/History/50-Years/1523.aspx>
- MedlinePlus Drugs & Supplements: Warfarin
<https://medlineplus.gov/druginfo/meds/a682277.html>
- PharmGKB
<https://www.pharmgkb.org/guidelineAnnotation/PA166104949>

Additional Information & Resources

Health Information from MedlinePlus

- Drugs & Supplements: Warfarin
<https://medlineplus.gov/druginfo/meds/a682277.html>
- Encyclopedia: Deep Venous Thrombosis
<https://medlineplus.gov/ency/article/000156.htm>
- Health Topic: Bleeding
<https://medlineplus.gov/bleeding.html>
- Health Topic: Blood Clots
<https://medlineplus.gov/bloodclots.html>
- Health Topic: Blood Thinners
<https://medlineplus.gov/bloodthinners.html>

Genetic and Rare Diseases Information Center

- Warfarin resistance
<https://rarediseases.info.nih.gov/diseases/12721/warfarin-resistance>

Educational Resources

- American Heart Association: What Are Anticoagulants and Antiplatelet Agents?
https://www.heart.org/-/media/data-import/downloadables/pe-abh-what-are-anticoagulants-and-antiplatelet-agents-ucm_300338.pdf
- American Society of Hematology: Blood Clots
<https://www.hematology.org/Patients/Clots/>

- Food and Drug Administration Medication Guide
https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/009218s116lbl.pdf#page=32
- MalaCards: coumarin resistance
https://www.malacards.org/card/coumarin_resistance
- Merck Manual Consumer Version: How Blood Clots
<https://www.merckmanuals.com/home/blood-disorders/blood-clotting-process/how-blood-clots>
- National Health Service (UK)
<https://www.nhs.uk/medicines/warfarin/>
- UC San Diego Health: Anticoagulation Clinic: Warfarin Frequently Asked Questions
<https://health.ucsd.edu/specialties/anticoagulation/Pages/faq.aspx>

Patient Support and Advocacy Resources

- American Heart Association: A Patient's Guide to Taking Warfarin
<https://www.heart.org/en/health-topics/arrhythmia/prevention--treatment-of-arrhythmia/a-patients-guide-to-taking-warfarin>
- National Blood Clot Alliance
<https://www.stoptheclot.org/>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28warfarin+resistance%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D>

Catalog of Genes and Diseases from OMIM

- COUMARIN RESISTANCE
<http://omim.org/entry/122700>

Medical Genetics Database from MedGen

- Warfarin response
<https://www.ncbi.nlm.nih.gov/medgen/148193>

Sources for This Summary

- Azzam H, Elwakeel H, Awad I, El-Farahaty R, El-Gilany AH, El-Sharawy S. VKORC1 and CYP2C9 genotypes in Egyptian patients with warfarin resistance. *Blood Coagul Fibrinolysis*. 2016 Mar;27(2):121-6. doi: 10.1097/MBC.000000000000168.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/24978953>
- Issac MS, El-Nahid MS, Wissa MY. Is there a role for MDR1, EPHX1 and protein Z gene variants in modulation of warfarin dosage? a study on a cohort of the Egyptian population. *Mol Diagn Ther*. 2014 Feb;18(1):73-83. doi: 10.1007/s40291-013-0055-2.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/24092646>
- Kurnik D, Qasim H, Sominsky S, Lubetsky A, Markovits N, Li C, Stein CM, Halkin H, Gak E, Loebstein R. Effect of the VKORC1 D36Y variant on warfarin dose requirement and pharmacogenetic dose prediction. *Thromb Haemost*. 2012 Oct;108(4):781-8. Epub 2012 Aug 7.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/22871975>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3461592/>
- Oldenburg J, Müller CR, Rost S, Watzka M, Bevans CG. Comparative genetics of warfarin resistance. *Hamostaseologie*. 2014;34(2):143-59. doi: 10.5482/HAMO-13-09-0047. Epub 2013 Nov 29. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/24287886>
- Rost S, Fregin A, Ivaskevicius V, Conzelmann E, Hörtnagel K, Pelz HJ, Lappegard K, Seifried E, Scharrer I, Tuddenham EG, Müller CR, Strom TM, Oldenburg J. Mutations in VKORC1 cause warfarin resistance and multiple coagulation factor deficiency type 2. *Nature*. 2004 Feb 5;427(6974):537-41.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/14765194>
- Sinxadi P, Blockman M. Warfarin resistance. *Cardiovasc J Afr*. 2008 Jul-Aug;19(4):215-7. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/18776969>
- Watzka M, Geisen C, Bevans CG, Sittinger K, Spohn G, Rost S, Seifried E, Müller CR, Oldenburg J. Thirteen novel VKORC1 mutations associated with oral anticoagulant resistance: insights into improved patient diagnosis and treatment. *J Thromb Haemost*. 2011 Jan;9(1):109-18. doi: 10.1111/j.1538-7836.2010.04095.x.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/20946155>
- de Oliveira Almeida VC, Ribeiro DD, Gomes KB, Godard AL. Polymorphisms of CYP2C9, VKORC1, MDR1, APOE and UGT1A1 genes and the therapeutic warfarin dose in Brazilian patients with thrombosis: a prospective cohort study. *Mol Diagn Ther*. 2014 Dec;18(6):675-83. doi: 10.1007/s40291-014-0121-4.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/25312789>

Reprinted from Genetics Home Reference:

<https://ghr.nlm.nih.gov/condition/warfarin-resistance>

Reviewed: September 2018

Published: May 14, 2019

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services