



## 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 treatment with warfarin and take the average 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 with this resistance 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.

### Genetic Changes

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 *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 *VKORC1* by binding

to the complex 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 more warfarin being needed to inhibit the VKORC1 enzyme and stop the clotting process. If no warfarin can bind to the VKORC1 enzyme, 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  
[http://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/warfarinmgmt\\_2015\\_full.pdf](http://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  
[http://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/warfarinsurg\\_2015\\_full.pdf](http://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/warfarinsurg_2015_full.pdf)

### Genetic Testing

- Genetic Testing Registry: Warfarin response  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/CN078029/>

### Other Diagnosis and Management Resources

- American Society of Hematology: Antithrombotic Therapy  
<http://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/guideline/PA166104949>

### General Information from MedlinePlus

- Diagnostic Tests  
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy  
<https://medlineplus.gov/drugtherapy.html>
- Genetic Counseling  
<https://medlineplus.gov/geneticcounseling.html>
- Palliative Care  
<https://medlineplus.gov/palliativecare.html>
- Surgery and Rehabilitation  
<https://medlineplus.gov/surgeryandrehabilitation.html>

### **Additional Information & Resources**

#### 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 Society of Hematology: Blood Clots  
<http://www.hematology.org/Patients/Clots/>
- Disease InfoSearch: Warfarin response  
<http://www.diseaseinfosearch.org/Warfarin+response/9469>
- Food and Drug Administration Medication Guide  
[https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/009218s116lbl.pdf#page=32](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/009218s116lbl.pdf#page=32)
- MalaCards: coumarin resistance  
[http://www.malacards.org/card/coumarin\\_resistance](http://www.malacards.org/card/coumarin_resistance)
- Merck Manual Consumer Version: How Blood Clots  
<http://www.merckmanuals.com/home/blood-disorders/blood-clotting-process/how-blood-clots>

### Patient Support and Advocacy Resources

- 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>

### OMIM

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

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