

28. Coumadin resistance

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Q: "Is there something like Coumadin® resistance, and if so, what are the treatment alternatives? The reason I am asking is that I have seen a few members mentioning that they are on 20 mg of Coumadin, and still they cannot get their INR to go up."

A: Yes, warfarin (coumadin®) resistance exists. It is rare. Possible causes are:

- interactions with other medications (that decrease the INR);
- extreme diets with large amounts of vitamin K;
- malabsorption, leading to lack of absorption of warfarin (in patients with gastrointestinal disease);
- non-compliance with taking warfarin;
- inherited metabolic reasons

The term "Warfarin resistance" is used when patients require high doses of warfarin (such as more than 20 mg per day) to get their INR (International Normalized Ratio) into the therapeutic range. What should one do if the INR just does not increase sufficiently in spite of increasing the dose of warfarin? Just increase the warfarin dose further, until a therapeutic INR is reached. I would not have a problem recommending doses of 30 or 40 mg a day. If one still does not get a therapeutic INR, one can consider choosing a low molecular weight heparin or Fondaparinux for long-term anticoagulation.

As for the inherited reasons: Several recent reports have elucidated genetic mutations that lead to high warfarin requirements, i.e. warfarin resistance (references 1-3). These mutations are in the gene called VKORC1, which renders the enzyme "vitamin K epoxide reductase" (the therapeutic site of warfarin) resistant to warfarin.

Reference:

1. Rost S et al. Nature 2004;427:537-541.
2. Bodin L et al. J Thromb Haemost 2005;3:1533-1535.
3. Loebstein R et al. Blood 2007;109:2477-2480.