Oral anticoagulants, especially warfarin, are one of the most frequently prescribed drugs worldwide. Several guidelines and expert recommendations have been published to guide the practising physicians in appropriate prescription of these agents. Despite being one of the most effective medications, several misconceptions exist about their use which has no evidence basis. This article aims to dispel five such myths.

Warfarin causes bleeding

Bleeding is one of the commonest adverse effects observed in patients who are prescribed warfarin. However, haemorrhagic complications do not develop in majority of patients on warfarin, despite prolonged usage. The contribution from any anticoagulant drug to ‘bleeding’ is the ‘prolongation’ of bleeding, being inhibitors of coagulation factors, rather than ‘causation’ of bleeding. For example, an international normalized ratio (INR) of 3 to 4 means that an individual is likely to bleed 3 to 4 times more than someone who is not on warfarin, but only after bleeding has commenced due to a different cause. For the same reason, when an individual who is on any anticoagulant medication including warfarin develops bleeding, it is imperative that a cause of bleeding is identified (arrange gastrointestinal endoscopy, cystoscopy, etc.).\(^1\) In this context, anticoagulant-related bleeding or warfarin-related bleeding maybe a better terminology for general use to avoid this commonly held misconception.

The role of anti-platelet agents, non-steroidal anti-inflammatory drugs and cyclo-oxygenase-2 inhibitors in worsening warfarin-related bleeding needs emphasis. It is preferable to avoid the latter two in patients who are on anticoagulant therapy since the risk of gastrointestinal haemorrhage, especially in older individuals, is very much increased (odds ratio \(\sim 2.0\)).\(^2\) With respect to anti-platelet therapy, there are situations where the combination of a platelet-inhibitory drug in combination with warfarin can be beneficial. This includes patients with mechanical heart valves and those undergoing percutaneous coronary intervention for acute coronary syndrome.\(^3,4\) Patients with stable coronary artery disease do not require addition of aspirin to their existing anticoagulation for atrial fibrillation, since the risk of bleeding with combination therapy outweighs the benefits.\(^5\)

In a patient on warfarin, a high INR is always due to warfarin (see Figure 1)

It is assumed in patients on warfarin, who is identified to have a high INR, that the abnormal laboratory values are always due to the anticoagulant. INR, being a derived form of the coagulation test, prothrombin time, is also prolonged if a patient develops vitamin K deficiency or disseminated intravascular coagulation. Three hypothetical clinical scenarios exemplify these situations:

(i) A patient waiting for abdominal surgery has abnormally high INR despite discontinuation of warfarin 5–6 days prior to the planned surgery. Perioperative anticoagulation guidelines recommend withholding warfarin for a similar time period as being adequate for normalizing the coagulation parameters and proceeding with the surgery.\(^6\) However, low vitamin K due to poor oral intake (secondary to the abdominal...
pathology), rather than warfarin, is the likely cause of the abnormal INR in this setting and is easily correctable with parenteral vitamin K administration.

(ii) Another patient on warfarin admitted with pancreatitis secondary to ethanol excess has high INR despite vitamin K replacement and withholding warfarin. Clearly liver impairment and the decreased synthesis of coagulation factors is the cause of high INR and not warfarin. It is worth bearing in mind that vitamin K does not correct the abnormal INR if it is due to impaired hepatic synthesis rather than cholestatic liver disease. Measurement of coagulation factor V can help in difficult cases to confirm liver disease-related coagulation impairment, as this factor is not vitamin K dependent.

(iii) A third patient is admitted with pneumonia and has been on warfarin for atrial fibrillation for a number of years with steady INR. The admission INR was 5.0 and has not improved despite withholding warfarin for over 4 days and vitamin K being administered. In this case, sepsis-related disseminated intravascular coagulation is a possible cause for the high INR. Full coagulation screen, platelet count and D-dimer values can aid in the diagnosis of this condition and warfarin should be exempted from the blame for causing the high INR.

Warfarin-related bleeding is always secondary to a high INR

Although many cases of warfarin-related bleeding occur at supra-therapeutic INR, the most feared complication of intracranial haemorrhage can occur even at normal-range INR, especially in older individuals. A case-control study looking at the risk for intracranial haemorrhage in patients on warfarin identified equal number of cases of bleeding in those whose INR was <2.0 compared with INRs between 2.0 and 3.0. Another study of the effect of warfarin and intensity of anticoagulation on the outcome of intra-cerebral haemorrhage noted 68% of all warfarin-related haemorrhages occurred at an INR of 3.0 or less.

It is also important that if a patient presents with bleeding while on warfarin and has a normal-range INR, alternative aetiologies are investigated. Activated partial thromboplastin time (APTT) is a part of the routine coagulation tests, which is often overlooked in a patient with warfarin. A prolonged APTT can be due to disseminated intravascular coagulation or the under-recognized condition, acquired haemophilia. The latter is secondary to the development of antibodies to coagulation factor VIII, which usually occurs in older people, who are the very likely candidates for warfarin. The clinical presentation is usually with soft tissue bleeds and urgent treatment is necessary to prevent morbidity and mortality.

Patients on warfarin in therapeutic range INR do not develop thrombosis

If a patient is adequately anticoagulated, it is very unlikely that a further thrombus develops as the coagulation factors necessary for the clot formation is lacking. However, patients who have antiphospholipid syndrome, disseminated malignancies and vascular abnormalities can have alternative reasons like platelet activation, cancer procoagulant and endothelial dysfunction respectively, which can promote thrombosis and are not altered by warfarin. Such patients need referral to physicians with experience in complex coagulation disorders for considering warfarin at higher intensity INRs, addition of anti-platelet agents or switching to a different form of anticoagulation.

Patients who require high doses of warfarin are warfarin resistant

Warfarin resistance has been defined as the inability to bring the INR to the adequate levels of anticoagulation when administered at a dose near or equivalent to the normally recommended doses. The commonest cause for the resistance is non-compliance although drug interactions, hyperlipidaemia and altered pharmacokinetics are the other contributing factors. However in all these cases, the dose of warfarin can be increased to achieve the desired INR and overcome the ‘resistance’. True hereditary warfarin resistance, where there is no effect of this drug, is extremely rare and has been reported in only two kindreds.
worldwide.\textsuperscript{11,12} It is thus preferable to give higher doses of warfarin (in addition, a personal drug information card to document the high doses to avoid physician scares at a different hospital) rather than switching to a different agent like low molecular weight heparin (requiring injections) with less patient compliance, or phenindione or acenocoumarol (less physician experience and rare hypersensitivity reactions).

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References


