

# Providing accurate information to patients who develop deep vein thrombosis

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**ABSTRACT – Venous thromboembolism is an increasingly recognised complication in the community and in hospital inpatients. Nowadays, most physicians are familiar with the algorithmic approach to the management of suspected deep vein thrombosis. However, a lack of understanding remains with regard to certain aspects of the diagnostic and treatment pathways, which has resulted in the wrong information being imparted to patients. Some of these issues are discussed in this paper, with considerations for changes in management.**

**KEY WORDS:** Anticoagulation, heparin, thrombosis, warfarin

## Introduction

In recent years, there has been better awareness of the heightened risks associated with venous thromboembolic disease (VTE). This has translated to better recognition of thromboembolic problems and reduced morbidity or mortality from the appropriate use of anticoagulation for these cases. Most physicians are now familiar with the diagnostic algorithms for VTE and also the initiation of anticoagulant therapy with low molecular weight heparin and warfarin. Despite this, some of the information passed on to the patients suffering from VTE is not accurate and requires clarity and explanation.

## Anticoagulation treatment will dissolve the blood clots

Currently available anticoagulant options such as heparins and warfarins do not have the ability to dissolve thrombi that have already formed. The primary role of these agents is to prevent thrombus progression and the development of new clots. For this reason, telling patients that these agents are meant to dissolve their blood clots is incorrect.

The fate of the primary thrombus is decided by the clot-breakdown (fibrinolytic) capacity of each patient. As the fibrinolytic potential may vary between individuals, clot resolution can remain incomplete in many patients.<sup>1</sup> In most of these cases, residual original thrombus is present in the same anatomical area. This was confirmed in studies by Hull *et al*, who demonstrated that at least 80% of patients who received anticoagulation treatment had a residual clot after 3 months.<sup>2</sup>

Another study that looked at 1-year follow-up scans in patients with deep vein thrombosis (DVT) showed that residual thrombus is present in about 50% of cases.<sup>3</sup> This fact may complicate the management of patients who develop symptoms on discontinuing anticoagulation after the planned period of 3–6 months. After a first episode of DVT, about half of patients will develop complaints suggestive of recurrent DVT. Of these patients, only about 20% do have a recurrent episode.<sup>4</sup> Unless a repeat Doppler scan confirms the presence of a new clot, residual thrombus should not be considered on its own as qualifying for prolonged anticoagulation.<sup>5</sup>

It therefore is crucial not to tell the patient that the anticoagulation treatment will dissolve their initial clot. It is also correct to explain in cases of suspected recurrence that the thrombus discovered on repeat Doppler scan is often an old clot that does not require higher intensity anticoagulation in patients who are already receiving warfarin.

## A simple blood test called D-dimer can rule out deep vein thrombosis

The validity of D-dimer in the exclusion of venous thromboembolism (VTE) has been shown repeatedly in several studies and it is now considered to be an integral part of the initial work up for suspected VTE. However, over-reliance on D-dimer to minimise costs from further radiological investigations and repeat hospital visits has led to the notion that a negative D-dimer test practically rules out the possibility of DVT, but this statement is not true.<sup>6</sup>

D-dimer is the product of fibrinolytic breakdown of the blood clots. As mentioned before, the capacity for fibrinolytic breakdown varies between individuals and increased levels of D-dimer need not accompany the symptoms of VTE in those with hypo-fibrinolytic tendencies.<sup>7</sup> In addition, if a patient has had treatment for DVT in the community, prior to presenting to hospital, the D-dimer test can be negative. Even a short period of 24 hours has been shown to affect D-dimer results in people who receive anticoagulation.<sup>8</sup> Another, probably more common, reason for a negative result is the delay in presentation with symptoms of a DVT due to patients initially attributing pain and tenderness in the calf (common symptoms of DVT) to other physical injuries, including muscle strain. If there is a delay in presentation, the generation of D-dimer by fibrinolysis would have ceased, giving a normal D-dimer result but with definite presence of VTE.<sup>7</sup> Lastly, many different types of D-dimer assays are available and, depending on the reliability of the chosen assay and the cut-off thresholds used for exclusion of DVT, it is possible that a normal D-dimer test has not excluded a DVT.<sup>9,10</sup>

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Both the British Committee of Standards in Haematology and the British Thoracic Society give clear guidance for the use of D-dimer in the diagnostic pathway for venous thromboembolism.<sup>11,12</sup> D-dimer should be used only in cases of low clinical probability according to a clinical prediction score like the Well's score, in which case a low pretest probability and negative D-dimer test can be used to exclude DVT without the need for diagnostic imaging. The reliability of negative D-dimer test results in patients with moderate pre-test probability is dependent on the sensitivity of the test used, while D-dimers should not be used in isolation to exclude DVT in cases with high pre-test probability.

### You are likely to bleed with heparin or warfarin

Although any anticoagulant can affect the coagulation system, spontaneous bleeding does not usually occur with any of these agents.<sup>13</sup> It is very important to stress this fact, as a message like 'increased risk of bleeding' from a healthcare professional does have a significant psychological impact on patients' lifestyle and well-being. In such cases, it is more correct to say that 'these medications thin your blood and can make you bleed more if you have a cut or an injury'.

An offshoot of this fact is the need to investigate patients who present with bleeding while receiving anticoagulant therapy.<sup>14</sup> Even in the presence of a high international normalised ratio (INR), warfarin would usually cause bleeding if an underlying precipitating factor for haemorrhage, such as gastric ulcer, exists. In older adults, who may present with spontaneous intracranial bleeds, it is possible that a high INR translates into prolonged bleeding from what otherwise would have been a non-significant bleed – a hypothesis that would be difficult to validate.

It is therefore important that patients are better educated about the risks and benefits of anticoagulant therapy, so that they are not frightened into taking warfarin or remain nonchalant about the risks of bleeding. At the same time, in a person presenting with bleeding related to an anticoagulant, an earnest search for a cause for bleeding should be explored in addition to reversing the anticoagulant effects.

### You should not have vitamin K-rich foods and you should avoid cranberry juice while on warfarin

Although warfarin's mechanism of action interferes with the metabolism of vitamin K, it is highly unlikely that any foodstuffs, including those that contain high amounts of vitamin K,

will have a significant impact on the INR unless consumed in excess amounts.

In a nested case-control study, Rombouts *et al* examined patients on warfarin for an association between intake of vitamin K and INR.<sup>15</sup> Compared to patients with normal intake of vitamin K, those with a high intake of vitamin K had a lower risk of subtherapeutic INR, while patients with a low intake of vitamin K had an increased risk. In this context, unstable anticoagulation control is related to low and erratic intake of vitamin K.<sup>16</sup> This can be a particular problem in older adults, who may have little home support and are less likely to be receiving balanced nutrition. In support of this concept, concomitant supplementation of vitamin K has been shown to improve anticoagulation control significantly in patients with unexplained instability of response to warfarin by reducing variability in dietary intake of vitamin K.<sup>17</sup>

Cranberry juice has been listed as a drink to be avoided completely in those on warfarin, which is once again a myth. Zikria *et al* examined this in detail by analysing 15 case reports and seven clinical trials and found only two cases suggesting a 'probable' interaction, but a definite drug interaction was questionable even in these two patients.<sup>18</sup> Interestingly, a study involving 10 volunteers who drank 240 ml of cranberry juice twice daily for 1 week did not identify an effect on the pharmacodynamics of warfarin, while a recent case report described a case in which INR increased to 4.6 in a woman who drank about 1,420 ml of cranberry juice cocktail daily for 2 days.<sup>19,20</sup>

In summary, any foodstuff in reasonable amounts is unlikely to cause fluctuations in INR in those receiving warfarin.

### You cannot get blood clots while taking warfarin or receiving heparin

The most common cause of recurrent thrombosis while receiving anticoagulation is under-anticoagulation.<sup>21</sup> In the case of warfarin, although the INR may be within range on the day of presentation, it is important to bear in mind that it is the INR values in the preceding weeks that are indicative of under-anticoagulation rather than the value at presentation.<sup>22</sup>

In the case of heparin, the rare heparin-induced thrombocytopenia, which leads to simultaneous development of low platelet count and thrombosis, is a possible cause of thrombosis in the first 2 weeks after starting treatment, in addition to subtherapeutic levels.<sup>23</sup> Even if the therapeutic range for anticoagulant medications is satisfied, conditions such as cancer and antiphospholipid syndrome can lead to clots, because thrombosis is initiated in these cases by mechanisms other than those that affect the coagulation system, such as activated platelets and vascular endothelium.<sup>24,25</sup>

In summary, although thrombosis is rare in those who are receiving adequate doses of warfarin or heparin, it is not impossible. Select individuals may therefore need investigations for a predisposing cause such as malignancy.

#### Box 1. Key points.

- Anticoagulation treatment will not lyse deep vein thrombus
- D-dimer cannot always exclude deep vein thrombosis
- Patients on warfarin or heparin will not have spontaneous haemorrhages
- Patients on warfarin do not need to avoid vitamin-K rich foods or cranberry juice in normal quantities
- Venous thrombosis can develop while receiving adequate anticoagulation

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