

## REVIEW

## Warfarin reversal

J P Hanley

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Warfarin is the most commonly used oral anticoagulant in the UK. It is associated with few side effects apart from haemorrhage. The most appropriate way to reverse the anticoagulant effect of warfarin depends on the clinical circumstances. In serious bleeding, rapid reversal is required, whereas in minor bleeding or asymptomatic over anticoagulation, a more leisurely approach is usually appropriate. This review discusses the current approaches to warfarin reversal in clinical practice. The development of a uniform approach to warfarin reversal in the Northern Region is described.

anticoagulation.<sup>8</sup> However, it may be clinically useful to screen those individuals who exhibit warfarin sensitivity because there is some suggestion that alternative vitamin K antagonists, such as acenocoumarol, may be safer in those individuals with particular variants.<sup>9</sup> Thus, inter-individual variation in warfarin dosage requirements is the result of a complex interaction between environmental and genetic factors.<sup>10–11</sup>

These difficulties have led to the need for an entire warfarin associated industry and infrastructure devoted to the clinical use and therapeutic monitoring of this single drug. Anticoagulant services based in hospitals and the community involve doctors, nurses, pharmacists, and laboratory staff. Self testing by patients is increasingly common. Computer programs are used to calculate dose adjustments. There is even a blood test specific to warfarin monitoring—the INR (international normalised ratio: a standardised prothrombin time). Until the more widespread use and availability of novel anticoagulants (such as oral thrombin inhibitors<sup>12–13</sup>), which do not appear to require such close monitoring and are not associated with a high risk of haemorrhage, it is likely that the warfarin industry will continue to flourish!

The precise incidence of warfarin associated haemorrhage is unclear, but many studies have consistently reported the annual rate of fatal haemorrhage to approach 1%. The incidence of “major” and “minor” bleeding has varied considerably between studies.<sup>14–18</sup> There have been some difficulties in comparing studies because of the lack of a standardised approach to the classification of bleeding severity. Such a standardised classification has recently been suggested (table 1).<sup>19</sup> Even allowing for the differences in the literature, it is clear that the risk of fatal and life threatening bleeding in patients on warfarin is an important problem in contemporary clinical practice.<sup>20</sup> It is important that a clear strategy for the management of patients receiving warfarin who are either actively bleeding or potentially at risk of bleeding is available in primary and secondary care.

## OPTIONS FOR WARFARIN REVERSAL

If warfarin reversal is required, the method chosen should reflect the clinical seriousness of bleeding and balance against the thrombotic risk of a temporary suspension/reduction of anticoagulation. Factors that require consideration

There has been a dramatic increase in the number of patients receiving longterm anticoagulation with warfarin in recent years. The anticoagulant effect of warfarin results from the inhibition of the  $\gamma$  carboxylation step in the synthesis of the vitamin K dependent clotting factors II, VII, IX, and X. Multiple indications for longterm anticoagulation have become accepted, including patients with recurrent venous thrombosis, prosthetic heart valves, stroke prevention in atrial fibrillation, and anti-phospholipid syndrome.

“Interindividual variation in warfarin dosage requirements is the result of a complex interaction between environmental and genetic factors”

Warfarin treatment is problematic because of the wide interindividual and intra-individual variation in dosage requirements. There are many factors that have been reported to influence warfarin dose, including concomitant medication, diet, increasing age, liver volume, vitamin K status, and occult malignancy. More recently, it has become clear that genetic factors that lead to differences in warfarin sensitivity are also important. Apparent differences in sensitivity to warfarin between ethnic groups have been described,<sup>1</sup> and mutations in the cytochrome P450 2C9 gene that lead to decreased enzyme activity and subsequent reduced warfarin metabolism have been well characterised.<sup>2–3</sup> Warfarin sensitivity and serious bleeding in individuals with variant alleles have been reported.<sup>4–5</sup> In addition, a rare point mutation in the factor IX propeptide, leading to extremely low factor IX values during warfarin treatment and associated bleeding, has been described.<sup>6–7</sup> The prevalence of such genetic factors is not sufficiently high to warrant screening before the initiation of

Correspondence to:  
Dr J P Hanley, Department  
of Haematology, Royal  
Victoria Infirmary, Queen  
Victoria Road, Newcastle  
upon Tyne NE1 4LP, UK;  
[john.hanley@nuth.northy.nhs.uk](mailto:john.hanley@nuth.northy.nhs.uk)

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**Table 1** Classification of warfarin associated bleeding (recommended by Makris and Watson<sup>19</sup>)

Classification	Characteristics	Diagnosis
Fatal	Death caused by haemorrhage	CT or MRI Postmortem
Major	Intracranial Retroperitoneal Intraocular Muscle + compartment syndrome Invasive procedure required to stop bleeding Active bleeding from any orifice + BP <90 mmHg systolic, oliguria, or >2 g fall in Hb	Clinically obvious CT or MRI CT or MRI Not conjunctival
Minor	Any other bleeding	

BP, blood pressure; CT, computed tomography; Hb, haemoglobin; MRI, magnetic resonance imaging.

include the indication for warfarin treatment, the seriousness of bleeding (if any), and the speed and completeness of reversal required. In addition, the need for ongoing anti-coagulation in any patients who require reversal (particularly for major haemorrhage) should be reviewed.

The anticoagulant effect of warfarin may be reversed by a variety of methods. Options include simple dose omission or administration of vitamin K. For serious bleeding, the replacement of coagulation factors is required. The administration of fresh frozen plasma (FFP) has been the most widely used method for coagulation factor replacement. As a result of concern that FFP may not be the most effective way to reverse warfarin rapidly, prothrombin complex concentrates (PCCs) have been increasingly recommended. More recently, it has been suggested that recombinant activated factor VII (rFVIIa) may be effective. The evidence for the different approaches to the rapid reversal of warfarin is discussed below. Table 2 summarises the different approaches to warfarin reversal.

“For serious bleeding, the replacement of coagulation factors is required”

### CURRENT GUIDELINES FOR WARFARIN REVERSAL

Table 3 summarises the most recent UK guidelines for reversal of warfarin.<sup>21</sup> In 2001, the updated US guidelines were published.<sup>22</sup> The section on warfarin reversal was essentially unchanged compared with previous guidelines published in 1998 (table 4).

It is clear from comparing these guideline documents that there are pronounced differences in approach. Both mention a potential role for both FFP and PCCs in major haemorrhage. A variable dose of vitamin K is suggested in different clinical settings. Since the publication of these guidelines, there have been several new studies that have led to an increase in the evidence base for some of the clinical decisions in the area of warfarin reversal. It may be time to review these guidelines.

**Table 3** UK guidelines for warfarin reversal<sup>21</sup>

Clinical situation	Action
Major bleeding	Stop warfarin Vitamin K (5 mg IV or oral) PCC (50 U/kg) or FFP (15 ml/kg) Caution: FFP may not fully reverse the effect of warfarin—for example, factor IX does not rise >20% post FFP (not reflected in INR)
Non-major bleeding INR <6.0	Omit warfarin
INR >6.0 to <8.0	Omit warfarin
No/minor bleeding INR >8.0	Omit warfarin
INR >8.0 + other risk factors for bleeding	Omit warfarin + 0.5–2.5 mg vitamin K (IV or oral)

FFP, fresh frozen plasma; INR, international normalised ratio; IV, intravenous; PCC, prothrombin complex concentrate.

### MANAGEMENT OF PATIENTS WITH MAJOR HAEMORRHAGE

There is a consensus that potentially life threatening bleeding requires rapid warfarin reversal. This is based on the view that the clinical priority in the face of severe haemorrhage is to stop the bleeding as quickly as possible, regardless of the reason for anticoagulation. The debate persists as to whether FFP or a PCC should be used. The use of PCCs is based on the evidence that the traditional approach using FFP is less effective in the correction of the coagulopathy as assessed by both the INR value and assay of the individual vitamin K dependent clotting factors.<sup>23–24</sup> This is particularly in relation to the difficulty in achieving a haemostatic concentration of factor IX after FFP infusion.<sup>23</sup> In addition, several studies have shown that FFP is administered much more slowly than PCCs, and volume overload may lead to difficulties in giving an adequate dose of FFP.<sup>25–27</sup> PCCs are also subjected to virus inactivation to reduce the risk of transfusion transmitted viruses—still a potential problem with FFP (unless methylene blue or solvent detergent treated FFP is used). The

**Table 2** Options for warfarin reversal

Type of reversal	Approach
Rapid (complete; within 10–15 minutes)	PCC (immediate replacement of vitamin K dependent coagulation factors) plus IV vitamin K (switch on hepatic synthesis within a few hours)
Fast (partial)	FFP (immediate replacement of vitamin K dependent coagulation factors—but the correction of the coagulopathy is partial)
Prompt (within 4–6 hours)	IV vitamin K
Slow (within 24 hours)	Oral vitamin K
Ultraslow (over days)	Omit warfarin dose (no vitamin K)

FFP, fresh frozen plasma; IV, intravenous; PCC, prothrombin complex concentrate.

**Table 4** US guidelines for warfarin reversal<sup>22</sup>

INR	Clinical situation	Action
Above therapeutic but <5	No bleeding	Lower dose or omit warfarin
>5 but <9	No bleeding	Omit warfarin Monitor more frequently
	High risk of bleeding	Vitamin K (1–2.5 mg orally; 2–4 mg orally if more urgent reduction needed)
>9	No bleeding	Omit warfarin Vitamin K (3–5 mg orally)
>20	Serious bleeding	Vitamin K (10 mg IV) FFP or PCC
Any INR	Life threatening bleeding	Vitamin K (10 mg IV) PCC

FFP, fresh frozen plasma; INR, international normalised ratio; IV, intravenous; PCC, prothrombin complex concentrate.

drawbacks with PCCs are in relation to cost, thrombogenicity, and the residual concern that pooled plasma products may transmit prions or unknown pathogens.

“There is a consensus that potentially life threatening bleeding requires rapid warfarin reversal”

It is essential that intravenous (IV) vitamin K is given at the same time as a PCC or FFP to switch on endogenous synthesis of vitamin K dependent clotting factors.<sup>23</sup> It is now clear that oral vitamin K has no therapeutic usefulness in clinical settings that require rapid warfarin reversal because it works too slowly.<sup>28</sup>

### PCCS FOR WARFARIN REVERSAL IN LIFE THREATENING HAEMORRHAGE

PCCs are intermediate purity pooled plasma products (table 5), previously widely used in the treatment of patients with haemophilia B before the availability of high purity plasma derived and recombinant factor IX concentrates. Currently, although in widespread clinical use, of the available PCCs, only HTDEFIX is licensed in the UK for warfarin reversal. This is in contrast to many European countries where some PCCs are licensed for warfarin reversal and a variety of other clinical indications.

There appear to be wide variations in the use of PCCs for warfarin reversal between different countries and between hospitals. In the USA, PCCs are used infrequently and in the UK many hospitals do not keep stocks of these drugs so that their use is limited by lack of ready availability.

There are differences between PCCs, with some containing therapeutic amounts of factors II, VII, IX, and X (“four factor concentrates”), whereas others contain II, IX, and X but low

amounts of VII (“three factor concentrates”). In addition, there are differences in the amounts of protein C and S between concentrates. Because there are no comparative studies it is unclear whether these differences are clinically important.

### PCC dose

The optimum dose of PCCs for warfarin reversal has not been established. Some have recommended dose adjustment according to INR<sup>23–29</sup>—for example, INR 2–3.9, 25 U/kg; INR 4–5.9, 35 U/kg; and INR > 6, 50 U/kg. Using this approach, complete reversal was reported in 30 of 36 patients.<sup>29</sup> More recently, successful rapid reversal has been achieved by using a standard dose of 30 U/kg, regardless of INR.<sup>30</sup> A smaller dose of 500 U has been reported to be sufficient in elderly patients.<sup>31</sup>

### Lingering doubts about PCCs

There is a legitimate criticism that despite the relative rapidity of action of PCCs, no studies have shown an advantage in terms of outcome. If complete correction of warfarin associated coagulopathy is so important in major bleeding, then the demonstration of an improvement in outcome should be possible. A recent Swedish retrospective study of warfarin associated intracranial haemorrhage showed no difference in outcome (assessed by 30 day mortality) between patients who received FFP compared with those who received a PCC.<sup>32</sup> A randomised prospective study comparing PCCs with FFP would be required to answer this question. It would be challenging to undertake a study with sufficient power to provide a conclusive answer.

The different attitudes to PCCs are probably the result of concerns that the products have considerable side effects, including thrombogenicity, exacerbation of disseminated intravascular coagulation, and virus transmission. The last

**Table 5** Prothrombin complex concentrates available in the UK

Product	Manufacturer	Virus inactivation	Coagulation factor composition* (IU)				Protein C (IU)
			II	VII	IX	X	
HTDEFIX	SNBTS, Edinburgh, UK	80°C for 72 hours	>200	0	>300	>200	Not stated
Prothromplex T	Baxter, Vienna, Austria	Terminal dry heat 60°C for 10 hours and 80°C for 1 hour	600	500	600	600	>400
Beriplex P	Aventis, ZLB Behring, Marburg, Germany	60°C for 10 hours and vapour heating	400–960	200–500	400–620	440–1200	300–900
Octaplex	Octapharma, Vienna, Austria	nanofiltration solvent detergent and nanofiltration	220–760	180–480	500	360–600	140–620

\*Coagulation factor and protein C composition in a single vial (information from product data sheets produced by manufacturers). BPL, Bioproducts Ltd; SNBTS, Scottish National Blood Transfusion Service.

factor is clearly historical because all PCCs are subject to virus inactivation methods and have a good safety track record. Thrombogenicity and disseminated intravascular coagulation are almost certainly dose related problems,<sup>33</sup> and the incidence of such events in the context of warfarin reversal appears to be low.

Cost is an issue with PCCs. The current cost in the UK is around 25 pence/unit (total cost for a single treatment for a 70 kg individual would be between £437 and £875, depending on the dose used). This is significantly more expensive than the current cost of FFP. (A standard 250–300 ml unit of FFP produced from UK plasma currently costs about £30. FFP that is methylene blue treated or produced from non-UK plasma is more expensive.) However, the expense of using PCCs should be seen in the context of the efficacy and safety issues discussed above.

### INTRACRANIAL HAEMORRHAGE IN PATIENTS RECEIVING WARFARIN

Intracranial haemorrhage (ICH) is probably the most dreaded scenario in warfarinised patients and is worthy of specific consideration. It has been recognised for some time that the incidence of ICH can be as high as 1% in patients on warfarin. There is a tenfold increased risk of ICH in patients over 50 years of age compared with non-anticoagulated patients.<sup>34</sup> Patients receiving warfarin have been reported to make up 14% of all those presenting to neurosurgical units with ICH.<sup>35</sup>

Risk factors for ICH in patients on warfarin include older age (greater than 65 years), cerebrovascular disease, recent initiation of anticoagulation, and hypertension.<sup>36–37</sup> A raised INR is also associated with an increased risk of ICH; however, it is important to remember that ICH may also occur with an INR within the therapeutic range.<sup>36–38</sup> Coadministration of aspirin with warfarin has been reported to increase the risk of ICH,<sup>39</sup> although this has not been confirmed by others.<sup>37</sup>

“The incidence of intracranial haemorrhage can be as high as 1% in patients on warfarin”

Some studies have found a relation between changes present on computed tomography scan and an increased risk of ICH. White matter changes on computed tomography scan (termed “leukoaraiosis”), thought to represent small vessel vasculopathy, were over-represented in patients with transient cerebral ischaemia who developed ICH on warfarin.<sup>40</sup> This observation has recently been confirmed in a prospective case control study.<sup>41</sup> In addition, cerebral amyloid angiopathy, associated with particular apolipoprotein E genotypes, has been reported to be common in warfarin associated ICH.<sup>38</sup> Possibly as a result of the vascular changes that occur with increasing age, it has been suggested that usually asymptomatic, self limiting intracranial “microbleeds” are common in the elderly.<sup>42</sup> Warfarin treatment may compromise the ability to stop such microbleeds, leading to the development of symptomatic ICH. In the future, more sophisticated imaging techniques may be able to identify individuals at high risk of warfarin associated ICH. Perhaps where there is a borderline risk–benefit ratio it might be reasonable to reduce the intensity of anticoagulation in those considered at high risk of ICH.

Early studies suggested that there was not a major difference in overall mortality after ICH in anticoagulated compared with non-anticoagulated patients.<sup>34</sup> Subsequently, however, numerous studies have shown that the outcome after ICH in patients receiving warfarin is much worse than in non-anticoagulated individuals (30 day mortality of approximately 40%, which increases to 60% in those on warfarin after correction for all other factors).<sup>43</sup> ICH after

trauma is also associated with a poorer outcome in anti-coagulated patients.<sup>44</sup>

The reasons for this increase in mortality are poorly understood, although several recent studies have identified factors that might be important. In a retrospective multi-centre study of 151 patients on warfarin presenting with ICH, both the initial ICH volume and haematoma enlargement within the first 24–48 hours of admission to hospital were associated with poor outcome.<sup>32</sup> Haematoma enlargement within 24 hours of admission is associated with incomplete warfarin reversal.<sup>45</sup> Apart from mortality studies, morbidity is also related to initial haematoma size—those with larger haematomas on initial computed tomography have a poorer functional outcome.<sup>46</sup>

In other words patients on warfarin, perhaps not surprisingly, have both an increased risk of initial bleeding, which only stops after a prolonged period when compared with non-anticoagulated patients (leading to a greater initial volume), and there is a greater chance of haematoma expansion as a result of re-bleeding.

Overall it appears that, in patients with ICH, there is a relatively short window of opportunity for warfarin reversal first to avoid haematoma enlargement and second to facilitate appropriate neurosurgical intervention. For rapid reversal in this setting, PCCs are more effective in terms of speed of administration and correction of coagulopathy.<sup>25–27</sup>

The decision to restart warfarin after ICH is difficult. In an attempt to overcome the lack of helpful literature in this area, a recent study reported the use of a decision analysis model to aid clinical management. This model suggests that re-anticoagulation after lobar ICH is contraindicated, whereas the risk–benefit ratio of re-anticoagulation in deep hemispheric haemorrhage is more finely balanced.<sup>47</sup>

The management of patients on warfarin for mechanical heart valves who develop ICH is a particularly difficult and controversial area.<sup>48</sup> There is often a reluctance to discontinue or reverse warfarin because of concern related to possible valve thrombosis. However, the available literature supports warfarin reversal in this setting because the need to prevent ICH expansion overrides all other considerations. A retrospective study of 39 patients on warfarin with mechanical heart valves revealed that 13 died within 48 hours (as a result of ICH); the remaining 26 survived after reversal of warfarin. Warfarin was discontinued for a median period of eight days (range, two days to three months), with no evidence of valve thrombosis or embolic events, and all survivors were subsequently re-anticoagulated.<sup>49</sup> Similar results have been reported in other studies, suggesting that in the ICH setting, the risk of valve thrombosis after the short term interruption of therapeutic anticoagulation and the risk of recurrent haemorrhage after the reintroduction of warfarin are both low.<sup>50–51</sup>

### IS THERE A ROLE FOR rFVIIa IN RAPID WARFARIN REVERSAL?

rFVIIa (Novoseven; Novo Nordisk, Copenhagen, Denmark) is used to control haemorrhage in congenital haemophilia complicated by inhibitors and acquired haemophilia. More recently, rFVIIa has been advocated in the management of bleeding in a wide range of clinical settings, including warfarin reversal.

rFVIIa has been studied in a small number of studies of warfarin reversal. It has been reported that rFVIIa normalises the INR in anticoagulated volunteers.<sup>52</sup> In 13 warfarinised patients requiring urgent reversal, INR normalisation was achieved using rFVIIa (dose range, 15–90 µg/kg).<sup>53</sup> Small numbers of patients with ICH successfully treated with rFVIIa have been reported recently.<sup>54–56</sup>

On the basis of this limited data, the role of rFVIIa in warfarin reversal remains unclear. Further studies are required to establish the optimum dose and confirm safety. It has been pointed out that although rFVIIa does reverse the INR, it does not lead to complete reversal of all aspects of warfarin associated coagulopathy.<sup>57</sup>

### MANAGEMENT OF PATIENTS WITH MINOR BLEEDING OR ASYMPTOMATIC HIGH INR

In contrast to the management of warfarinised patients with major haemorrhage, where rapid and complete, or near complete, reversal is indicated, those with a raised INR who are asymptomatic (or with minor bleeding such as bruising or intermittent epistaxis, etc) require a more gentle approach. In the asymptomatic high INR scenario, the aim of management is to restore the INR to the target range as quickly as possible, without leading to subtherapeutic anticoagulation, which may be associated with a risk of thrombosis. It is universally agreed that coagulation factor replacement is not appropriate in the management of such patients. Equally, there is consensus that omission of warfarin is essential to allow the INR to drift back towards the target range. The debate persists, however, concerning whether simple dose omission is sufficient or vitamin K should be administered to accelerate INR correction. There is concern that over enthusiastic vitamin K administration may lead to both subtherapeutic anticoagulation and resistance to subsequent re-introduction of warfarin, with an associated risk of thrombosis. There is also debate about whether it is possible to identify individuals who may be at increased risk of bleeding when over anticoagulated, who may require more rapid reversal. The current UK guidelines recommend intervention with vitamin K when INR is greater than 8 in the presence of risk factors for bleeding.<sup>21</sup>

### Dose, formulation, and route of administration of vitamin K

Simple warfarin dose omission results in slow reversal of the effect of warfarin over several days.<sup>58</sup> It has been known for many years that vitamin K administration is an effective method of warfarin reversal.<sup>59</sup> Vitamin K is available in several formulations that can be administered by a variety of routes (oral, subcutaneous, intramuscular, or IV). It is now clear that there is considerable variation between different IV and oral vitamin K preparations. The administration of IV vitamin K leads to INR reversal within four to six hours, except for those patients who are massively over anticoagulated, whereas oral vitamin K works more slowly. The differences between vitamin K preparations and routes of administration were emphasised in a recent comparative study.<sup>28</sup> The INR at four and 24 hours after vitamin K administration was measured. There were pronounced differences at both time points, depending on vitamin K formulation and route of administration. This study showed that the most reliable (in terms of successful reversal into the target INR range in most patients) oral vitamin K preparation is IV vitamin K (Konaktion) administered orally. Using 2 mg Konaktion (IV preparation given orally), 75% of INRs were < 4 by 24 hours. This approach was not associated with either thrombotic problems or subsequent warfarin resistance.

*“It has been known for many years that vitamin K administration is an effective method of warfarin reversal”*

Other studies have shown that 1–2.5 mg of oral vitamin K is also safe and effective. A randomised, double blind, placebo controlled trial of vitamin K in asymptomatic patients with INR values 4.5–10 found 1 mg oral vitamin K to be superior to placebo both in terms of speed of reversal

and restarting warfarin.<sup>60</sup> Another randomised study confirmed that oral vitamin K (2.5 mg) hastened INR reduction compared with placebo, with overcorrection more common in the vitamin K group.<sup>61</sup> Oral vitamin K (1 mg) administered to 30 over anticoagulated patients (INR > 8) led to an INR < 7 in 29 of 30 at 24 hours, with 10 achieving an INR 2–4.5 and only two an INR < 2.<sup>62</sup> Similarly, in a study of the effect of oral vitamin K (2.5 mg) in 81 patients with an INR > 5, 90% achieved an INR < 5 at 24 hours. Only patients with an initial INR of greater than 10 failed to correct to < 5.<sup>63</sup> Oral vitamin K (2 mg) has also been shown to be effective in reducing raised INRs without omission of warfarin.<sup>64 65</sup>

IV vitamin K has also been shown to be a safe and effective method of warfarin reversal. A dose finding study recommended 1 mg IV vitamin K for patients with an INR > 10.<sup>66</sup> Others have reported that 1 mg IV vitamin K is associated with a high risk of subtherapeutic anticoagulation at 24 hours after administration, whereas 0.5 mg is safe and effective.<sup>67</sup> In addition, in severely over anticoagulated patients several doses of IV vitamin K may be required to achieve successful reversal.<sup>68</sup>

### Risk factors for serious bleeding during asymptomatic over anticoagulation

Recently, a model has been described that attempts to base the decision to use vitamin K on the relative risk of haemorrhage as a result of over anticoagulation with the potential risk of thrombosis as a result of overcorrection with oral vitamin K.<sup>19</sup> This model estimates that the risk of bleeding is greater than the risk of thrombosis for INR > 7 (regardless of indication for warfarin). The authors recommend vitamin K for all patients with INR values > 7. This approach is supported by studies that show a pronounced increase in risk of bleeding once INR is > 7. For lesser degrees of over anticoagulation (INR, 4.5–6.9), vitamin K is only recommended for those perceived to be at high risk of bleeding.<sup>18</sup>

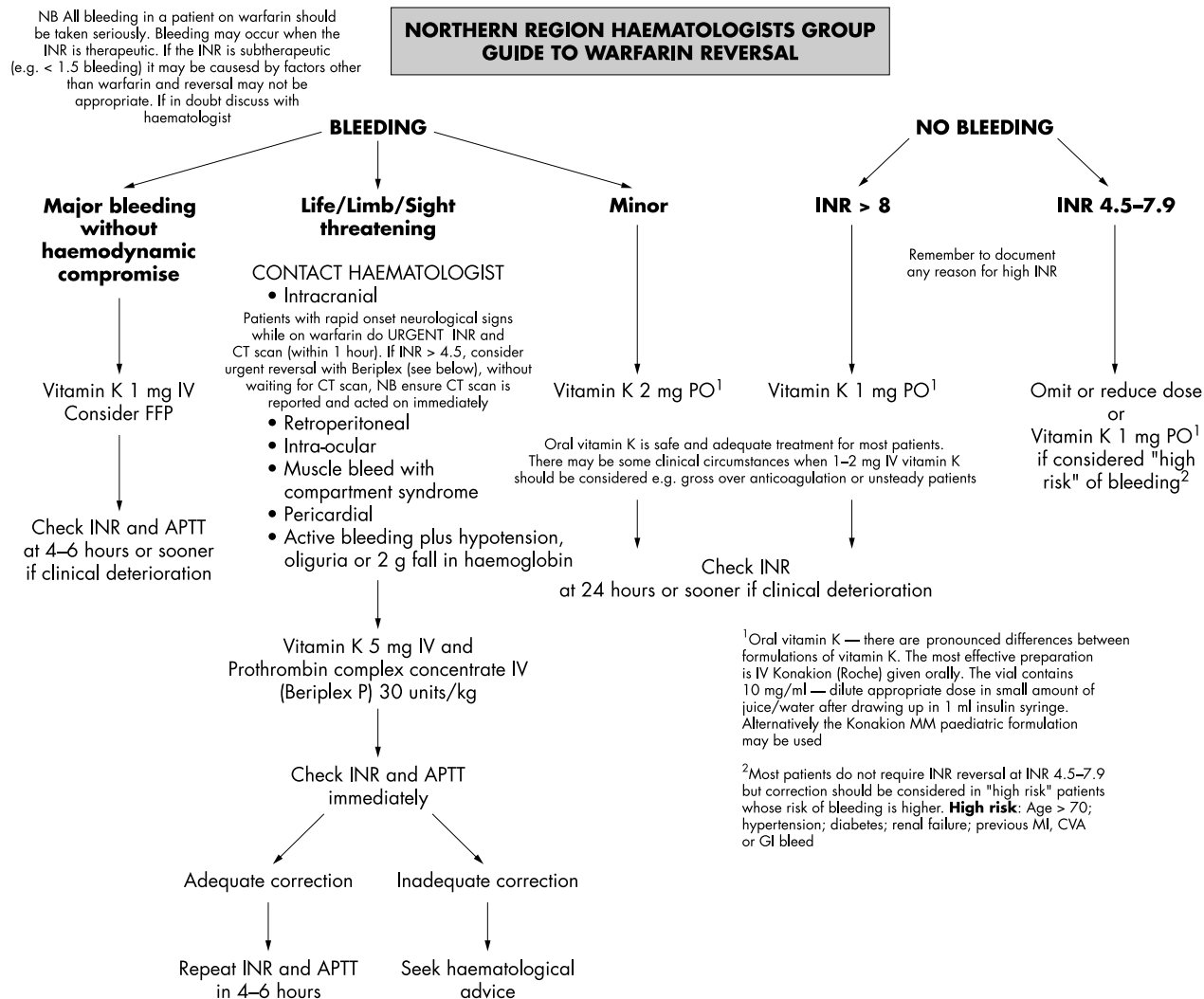
It is important to stress that the role of vitamin K in the reversal of warfarin cannot be extrapolated to other vitamin K antagonists (such as acenocoumarol or phenprocoumon). A recent randomised study comparing dose omission with low dose vitamin K in asymptomatic over anticoagulated patients receiving acenocoumarol found no more effective reversal in the vitamin K group, with a significant risk of a subtherapeutic INR at 24 hours.<sup>69</sup>

### REVERSAL OF WARFARIN IN CHILDREN

There are few data available to guide the optimum approach to reversal of warfarin in children. It seems reasonable to apply a similar approach to adults in relation to major haemorrhage. An extremely small dose of IV vitamin K (30 µg/kg) has been reported to be effective in reversing asymptomatic high INR in clinically well children. Children who are unwell may require a higher dose of vitamin K.<sup>70</sup>

### DEVELOPMENT OF A WARFARIN REVERSAL PROTOCOL FOR USE IN THE NORTHERN REGION

After discussion within the Northern Region Haematologists' Group (NRHG) it emerged that the approach to warfarin reversal varied considerably between haematologists in the region. In addition, there were differences in approach between hospital doctors and general practitioners. Poor compliance with published guidelines for warfarin reversal has been reported previously.<sup>71 72</sup> The NRHG initiated a discussion that led to the development of a protocol for use throughout the region to cover all aspects of warfarin reversal. The protocol was produced after a detailed literature review and review of protocols already in use in the UK. There was widespread consultation before finalising the



**Figure 1** Northern Region Haematologists' Group guide to warfarin reversal. APTT, activated partial thromboplastin time; CT, computed tomography; CVA, cardiovascular accident; FFP, fresh frozen plasma; GI, gastrointestinal; INR, international normalised ratio; IV, intravenous; MI, myocardial infarction; PO, oral.

protocol. An attempt was made to produce a consensus protocol that would be useful and useable in day to day practice. Prospective audit of the protocol has been undertaken.<sup>73</sup> Figure 1 shows the current version of the NRHG guide to warfarin reversal.

### Life/limb/sight threatening bleeding

Overall, there are haemostatic and practical advantages of PCCs over FFP. On the basis of the current evidence, a PCC plus IV vitamin K is the treatment of choice for patients with major haemorrhage. The definition of major haemorrhage is restricted to genuine life, limb, or sight threatening bleeding to ensure that PCCs are not used inappropriately. In many hospitals, there may be problems associated with obtaining urgent imaging in patients with suspected ICH. In the face of therapeutic or excessive anticoagulation in patients with progressive neurological signs, urgent reversal is recommended even before imaging.

*"On the basis of the current evidence, a prothrombin complex concentrate plus intravenous vitamin K is the treatment of choice for patients with major haemorrhage"*

To overcome the problems with ready availability of PCCs, a system for coordinated supply and audit was established.

The regional supply is ordered via a central pharmacy. A small stock is distributed to each hospital blood bank in the region. Following use, the stock is replenished. Stock rotation is undertaken to avoid unnecessary wastage as a result of product expiry. Beriplex was selected because this is the PCC with most information in the published literature. A dose of 30 U/kg (regardless of INR) was chosen because this is simple and has been reported to be effective.

### Major bleeding that is not life threatening

The management of patients with major bleeding that is not life threatening is a grey area that is fairly common in clinical practice—for example, gastrointestinal bleeding without haemodynamic compromise or brisk epistaxis requiring a nasal pack. Many physicians would feel reluctant to use a PCC in such circumstances. Oral vitamin K would probably work too slowly, but IV vitamin K is usually adequate. Some would like to have the option of using FFP in such circumstances, although this is not strongly supported in the literature.

### Minor bleeding and asymptomatic high INR

After review of the literature it is difficult to make a strongly evidence based recommendation concerning the optimum

## Take home messages

- Regardless of the reason for anticoagulation, major haemorrhage in a patient on the anticoagulant warfarin is best managed by rapid and complete reversal with a prothrombin complex concentrate and intravenous (IV) vitamin K
- This approach ensures that the acute effect of haemorrhage is minimised
- Minor bleeding or an asymptomatic high international normalised ratio (INR) can be safely treated by warfarin omission or oral vitamin K (or IV vitamin K in selected cases), which results in partial reversal, with the aim of restoring the INR to the target value for the individual

dose and route of administration of vitamin K. It is clear that many patients with an asymptomatic INR can be safely managed by simple warfarin dose omission. The protocol recommends oral vitamin K (using IV Konaktion preparation) for moderately severe over anticoagulation (INR > 8). It was felt that using a lower INR threshold would result in an increase in the use of vitamin K, which would be unacceptable to many. The formal identification of individuals at high risk of bleeding, although widely recommended in the literature, is seldom used in practice. Again, strict adherence to the list of high risk factors (elderly, hypertension, previous gastrointestinal bleeding, cerebrovascular disease, etc) would lead to an increase in the use of vitamin K.

The literature suggests that the most reliable form of oral vitamin K is IV Konaktion preparation administered orally. To avoid inappropriate hospital attendance or admission it is important that this is readily available for use in the community. In practice, there may be some patients (for example, the massively over anticoagulated or the physically unsteady) in whom the use of IV rather than oral vitamin K would be preferable for more speedy reversal.

## CONCLUSION

Major haemorrhage in a patient on warfarin is most appropriately managed by rapid and complete reversal with a PCC and IV vitamin K, regardless of the reason for anticoagulation. This approach ensures that the acute effect of haemorrhage is minimised. Minor bleeding or asymptomatic high INR can be safely treated by dose omission or oral vitamin K (or IV vitamin K in selected cases), which results in partial reversal, with the aim of restoring the INR to the target value for the individual.

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## Warfarin reversal

J P Hanley

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