Warfarin
from rat poison to oral anticoagulant

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Warfarin is now the most widely used long term oral anticoagulant. Due to the narrow therapeutic index and the complexity associated with warfarin therapy, a sound knowledge of the drug is required. This review is aimed at providing some basic concepts on warfarin in use and takes on a UK perspective.

History
The discovery of warfarin was centred around Canada and the US in the early 20th century when sweet clover was planted to feed the cattle. However, as reported in 1921-22 by veterinary pathologist Dr Frank Schofield, improperly cured sweet clover brought a disease to cows characterised by relentless, spontaneous bleeding.¹ In 1940, Campbell and Link isolated the substance dicoumarol that was patented in 1941 for use as a rat poison. However, this was too weak a poison and continued research developed a derivative, patented as warfarin (Wisconsin Alumni Research Foundation + arin to indicate coumarin). Following an attempted suicide by a navy recruit in 1951, clinicians identified warfarin as an anticoagulant and it was clinically introduced in 1952 becoming commercially available in 1954.¹²³

Worldwide the use of warfarin is increasing due to:

(a) the increasing number of indications
(b) the increasing elderly population

Breaking this down to a more localised example in Scotland, since January 1998, the number of warfarin prescriptions dispensed has increased annually from 7 to 11% (Jan 1998 - Dec 2001).⁴ Internationally, the increase in use of warfarin and the high risk associated with use of the drug have prompted guideline development. National UK guidelines (also adopted by the BNF) have been issued by the British Society of Haematology in 1998 and SIGN 36 tackling antithrombotic therapy was published in March 1999.⁴⁵⁷

Mechanism of action
Warfarin is a Vitamin K antagonist and consequently inhibits Vitamin K-dependent clotting factors (factors II, VII, IX and X) by inhibiting the enzyme Vitamin K epoxide reductase. This is required for the conversion of clotting factor precursors into inactive clotting factors in the bloodstream. This is summarised in Figure 1.⁶

The inhibition of Vitamin K epoxide reductase by warfarin results in an accumulation of Vitamin K epoxide reducing the effective concentration of Vitamin K and shifting the equation towards the clotting factor precursors. Therefore there is a reduced amount of inactive clotting factors available in the circulation.⁹

Warfarin takes about 50 hours to start exerting its full action since Factor II has the longest half life of 50 hours. Protein C and S, which are naturally occurring anticoagulants, are also Vitamin K dependent and during initiation of treatment there is a possibility of development of a hypercoagulable state where the body’s own anticoagulants are British...
depicted and warfarin has not
yet produced a clinical response. This:
a) is a problem in patients with
hereditary or acquired deficiencies
of protein C and S and may result in
skin necrosis
b) explains why overlap treatment
with heparin is required in acute
clinical conditions such as Deep
Vein Thrombosis (DVT).6

**Monitoring**

There is no linear correlation
between the dose of warfarin and its
anticoagulant effect. Besides, various
factors may cause inter- and intra-
individual variation in response to a
warfarin dose. It is therefore
necessary to monitor the effect of
warfarin and this is done through
measurement of prothrombin time
(PT).6,9

The PT is the time taken for a
sample of platelets to clot following
addition of calcium and tissue
thromboplastin, an enzyme from
blood platelets that converts
prothrombin into thrombin. This is
usually about 12 seconds in a non-
anticoagulated individual.

Thromboplastins are not standardised
among manufacturers or between
batches. In an attempt to standardise
results, the World Health
Organisation (WHO) developed a system where
thromboplastin is compared to an
international reference
thromboplastin in order to assign an
International Sensitivity Index (ISI).

This is used to convert the PT time to
the International Normalised Ratio
(INR) for a patient and this is the
standard of practice.6,9

\[
INR = \frac{[PT \text{ patient}]}{[PT \text{ mean normal}]}
\]

Current recommendations for
intensity of the most commonly
accepted indications are summarised in
Table 1. Current guidelines recommend
that a target INR be designated for a
particular indication rather than a
range. An INR within 0.5 units of the
target would generally be satisfactory
in clinical practice.6,10 In most settings
an INR of 2.5 is the target with higher
intensity anticoagulation used in valve
replacement and conditions of
thrombotic recurrence.

**Management of warfarin dosing**

Prior to initiation of warfarin
therapy, essential baseline
investigations include a full blood
count including platelets, urea and
electrolytes, PT and liver function
tests.6,7 Various protocols are available
for the induction of warfarin
anticoagulation. The most commonly
used method is the Fennerty induction
dosing which employs initial doses of
10mg with consequent dosing
adjustments depending on the patient’s
INR.6,9,10 Such a regimen is suitable for
the induction of in-patients where rapid
anticoagulation is required and where
daily INR monitoring is feasible. It
provides a predicted maintenance dose
on day 4.10 However, efforts have been
made to establish less intense regimens
for starting off warfarin which may be
especially useful in less acute
indications such as anticoagulation due
to chronic atrial fibrillation. These may
be a safer alternative in elderly
patients where a Fennerty regimen may
be too severe or where initial daily
monitoring is not appropriate. The Tait
method employs a 5mg dose from day 1
to day 4 and INR monitoring and dose
adjustments on day 5 and day 8. Dose
at day 8 predicts the actual
maintenance dose.11 An alternative
regimen, established by Oates et al
starts the patient at 2mg daily with an
INR check on day 8. The dose is
adjusted accordingly and the patient
returns weekly until the INR is stable
(usually defined as the first of two INR
results at least 7 days apart which are
within target with no dose alteration).
This method allows prediction of
warfarin dose after two weeks of
treatment.12 Overall, both methods
have been shown to result in fewer
INRs >4.0. There are few protocols that
provide guidance for dosing
adjustments during the maintenance
phase. The more useful regimens
recommend dose adjustments as a
percentage change in dose.13 Dose
adjustments should take into
consideration individual patient factors
such as age, nutritional status,
comorbid conditions and any change in
drug treatment. Various computer
assisted aids have been devised to take
variables into consideration to aid in
dosing adjustment. A Cochrane review
has concluded that computerised
prescribing of dosage improved
prescribing. This included shorter times
to achieve therapeutic control, a
reduction in toxic drug levels and
incidence of adverse drug reactions and
a reduction in the length of hospital
stay.14 Guidance on recall periods
during maintenance therapy recommend
a maximum recall time of 12 weeks
once INR is stable and provided no new
factor has arisen (apart from patients
with prosthetic valves where a
maximum recall of 6 weeks is
recommended).5,11 In a document on
anti-coagulation monitoring, the

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**Figure 1: Schematic representation of the action of warfarin**

Vitamin K

\[\text{Vitamin K epoxide reductase} \quad \xrightarrow{\text{Vitamin K epoxide}} \quad \text{Warfarin} \quad \xrightarrow{\text{Carboxylation}} \quad \text{Inactive clotting factors}\]

Oxidation of Vitamin K to Vitamin K epoxide is coupled to the carboxylation of clotting factor precursors to inactive clotting factors. The regeneration of Vitamin K is accomplished by the action of vitamin K epoxide reductase on Vitamin K epoxide. The inhibition of Vitamin K epoxide reductase by warfarin results in reduced concentrations of Vitamin K, and a consequent reduction in the carboxylation of clotting factor precursors to inactive clotting factors.
Medical Association has produced evidence-based criteria for the frequency of monitoring that may be adopted in clinical practice. This review presents an overview of the development, mechanism of action and clinical use of warfarin. Such a basic knowledge is essential to ensure safe and effective use of the drug. Due to the complexity associated with warfarin therapy, safe use requires an understanding of factors affecting response to warfarin including drug interactions and comorbid states. The latter will be the focus of a second review article.

Table 1: Most common indications for warfarin use. All recommendations are related to warfarin use in adult males and adult non-pregnant females.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Target INR</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Venous Thromboembolism</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated DVT - calf vein with no risk factors in nonsurgical patients</td>
<td>2.5</td>
<td>3 months</td>
</tr>
<tr>
<td>First event PE/proximal vein thrombosis with no risk factors</td>
<td>2.5</td>
<td>6 months</td>
</tr>
<tr>
<td>Recurrence of PE OFF warfarin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Two episodes of idiopathic DVT</td>
<td>2.5</td>
<td>Long term</td>
</tr>
<tr>
<td>b) Repeated provoked DVT</td>
<td>2.5</td>
<td>6 months or until risk factors resolve</td>
</tr>
<tr>
<td>Recurrence of PE ON warfarin</td>
<td>2.5</td>
<td>Long term or until risk factors resolve</td>
</tr>
<tr>
<td>Post-op calf vein thrombosis without persistent risk factors</td>
<td>2.5</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Post-op calf vein thrombosis with persistent risk factors</td>
<td>2.5</td>
<td>Long term or until risk factors resolve</td>
</tr>
<tr>
<td>Recurrence of DVT OFF warfarin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Two episodes of idiopathic DVT</td>
<td>2.5</td>
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</tr>
<tr>
<td>b) Repeated provoked DVT</td>
<td>2.5</td>
<td>6 months</td>
</tr>
<tr>
<td>Recurrence of DVT ON warfarin</td>
<td>3.5</td>
<td>Long term or until risk factors resolve</td>
</tr>
<tr>
<td><strong>Nonvalvular (Non-rheumatic AF)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous or paroxysmal AF with at least one risk factor to develop thromboembolism</td>
<td>2.5</td>
<td>Long term</td>
</tr>
<tr>
<td>AF associated with</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) clinical thyrotoxicosis</td>
<td>2.5</td>
<td>a) Till controlled</td>
</tr>
<tr>
<td>b) intracardiac thrombus</td>
<td></td>
<td>b) As recommended by cardiologist</td>
</tr>
<tr>
<td>c) non-cerebral thromboembolism</td>
<td></td>
<td>c) Long term</td>
</tr>
<tr>
<td>d) congenital heart disease</td>
<td></td>
<td>d) Long term</td>
</tr>
<tr>
<td>Elective cardioversion</td>
<td>2.5</td>
<td>3 weeks before 4 weeks after</td>
</tr>
<tr>
<td><strong>AF associated with valvular disease (Rheumatic)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatic mitral valve disease ± atrial fibrillation</td>
<td>2.5</td>
<td>Long term</td>
</tr>
<tr>
<td><strong>Heart Valve Disease</strong></td>
<td></td>
<td></td>
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<tr>
<td>Mitral valve prolapse, mitral annular calcification, aortic valve disease + previous systemic embolism or AF</td>
<td>2.5</td>
<td>Long term</td>
</tr>
<tr>
<td><strong>Heart Valve Prostheses</strong></td>
<td></td>
<td></td>
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<tr>
<td>Mechanical heart valves</td>
<td>3.5</td>
<td>Long term</td>
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<tr>
<td>Bioprosthetic heart valves</td>
<td></td>
<td></td>
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<tr>
<td>After implant surgery</td>
<td>2.5</td>
<td>3 months or as per guidance from cardiac unit</td>
</tr>
<tr>
<td>+ associated risk factors</td>
<td>2.5</td>
<td>Long term</td>
</tr>
</tbody>
</table>

a) Cancer, thrombophilia, (antithrombin III deficiency, Protein C and S deficiency, antiphospholipid syndrome, chronic infection, inflammatory bowel disease, nephrotic syndrome, pulmonary hypertension  
b) Other risk factors: Advancing age (>65 years), history of hypertension, diabetes, heart failure, left ventricular dysfunction, previous ischaemic stroke or TIA, history of thromboembolism. The risk/benefit of warfarin needs to be determined for every individual patient above 75 years of age and needs to be reassessed annually particularly in this age group  
c) Risk factors: atrial fibrillation, history of systemic embolism, evidence of left atrial thrombus at surgery, persistent left atrial enlargement, or persistent heart failure
References


