Government of **Western Australia**
Department of **Health**

Guidelines for Anticoagulation using Warfarin

The *Guidelines for Anticoagulation Using Warfarin* may be updated at regular intervals. For the latest version of this document, please visit the WATAG website. (https://ww2.health.wa.gov.au/Articles/U_Z/Western-Australian-Therapeutics-Advisory-Group-WATAG)

For further details please contact:
Medicines and Technology Unit
Patient Safety and Clinical Quality Division
Western Australian Department of Health
189 Royal Street, East Perth Western Australia 6004
Tel: (08) 9222 4080 Fax: (08) 9222 4324
E-mail: DoH.MedicinesandTechnologyUnit@health.wa.gov.au
Web: www.safetyandquality.health.wa.gov.au

Acknowledgements

WA Department of Heath acknowledges the significant contribution of material and review from the WA Anticoagulation Steering Committee. Members of the committee are:

- Dr Dominic Pepperrell
- Dr Carolyn Grove
- Dr Tony Ryan
- Dr Mark Newman
- Dr Graham Cullingford
- Dr Justin Yeung
- Ms Michaela Walters
- Ms Barbara O'Callaghan
- Mr David Lui
- Ms Kerry Fitzsimons
- Ms Tandy-Sue Copeland
- Ms Ann Berwick
- Mr Yan Ghee Peng
- Ms Cindy Tan
- Mr David McKnight
- Mr Ping Lau

Version	Date Issued	Compiled/ Revised By	Committee/Group Consulted	Endorsed By	Revision due
1	01/2019	WA Anticoagulation Steering Committee Co-ordinated by Medicines and Technology Unit	WA Medication Safety Collaborative	WA Therapeutic Advisory Group (WATAG)	06/2020

Contents

1. Introduction

Warfarin, a vitamin K antagonist (VKA), inhibits the synthesis of vitamin K-dependent clotting factors (II, VII, IX, X) and the antithrombotic factors, protein C and protein S. The suppression of proteins C and S can create a hypercoagulable state in the first few days of warfarin treatment, especially at doses for conditions with high risk of thrombosis. In patients at high risk of thrombosis, such as venous thromboembolism, an additional anticoagulant (e.g. heparin) is required to provide adequate anticoagulation cover until the anticoagulant effect of warfarin is established (usually 5-6 days including at least 48 hours with the INR in therapeutic range).

The two brands of warfarin available in Australia, Marevan® and Coumadin®, are not interchangeable and swapping brands may affect INR control. WA Health Service Providers should use the Marevan® brand for patients initiated on warfarin. Coumadin® is for continuation only as per the WA State Medicines Formulary.

2. Indications

Warfarin is recommended for the prevention of systemic embolism, stroke associated with atrial fibrillation and venous thromboembolism. Whilst this guideline focuses on warfarin, other anticoagulants (such as Direct Oral Anticoagulants (DOACs) and heparins) are also indicated for treatment and prevention of thromboembolism. Its use is limited by several factors including a narrow therapeutic range, and drug-drug and drug-food interactions. Bleeding, particularly in the setting of over anticoagulation, is a major concern.

The effect of warfarin is measured by a blood test referred to as INR (international normalised ratio). INR is a measure of how much longer it takes the blood to clot when oral anticoagulation is used. The safety and efficacy of warfarin is critically dependent on maintaining the INR within the target range. Table 1 and 2 refer to the target INR and recommended duration of warfarin therapy based on indication.

Table 1: Target INR range based on indication[6]

Target INR, Target Range and Indication		
Target is 2.5	Range is 2 - 3	• Therapy for deep vein thrombosis (DVT) or pulmonary embolism (PE) • Preventing DVT: high risk patients e.g. hip or knee surgery • Preventing systemic embolism: atrial fibrillation (AF), valvular heart disease, post myocardial infarct (MI), and bioprosthetic heart valves (first 3 months) • Aortic bileaflet mechanical heart valve – if no other risk factors
Target is 3	Range is 2.5 - 3.5	• Starr-Edwards mechanical heart valves. • Mitral bileaflet mechanical heart valve • Aortic heart valve if risk factors for thromboembolic event including AF, previous thromboembolism, left ventricular dysfunction, hypercoagulable condition.
Other	Other	• Higher targets/ranges under Haematology consultation only

Table 2: Minimum recommended duration

Indication		
DVT/PE	Transient risk - 3 months	No identifiable or modifiable risk - Consider life long
AF	Life long, balanced against risks	
Mechanical valves, life long	Life long, balanced against risks	
Bioprosthetic valves (tissue valves)	3 months	
Irreversible, clinically hypercoagulable states	Life long, balanced against risks	

3. Risk assessment

The decision to start warfarin therapy requires an assessment of the harms and benefits for each patient. This assessment should take into account the patient's medical, social, dietary and drug history, level of education/health literacy and adherence to previous therapy. While the risk of falls plays a part in the harm-benefit assessment, published data indicate the propensity to fall is not an important factor in this decision.[1, 2]

Educating the patient is essential before they start warfarin. This includes informing them about the signs and symptoms of bleeding, the need for monitoring of the INR, the impact of diet, potential drug interactions and actions to take if a dose is missed.

3.1 Risk of stroke in patients with atrial fibrillation

The $CHADS_2$ scoring system[3] is a simple system that can be used to assess the annual risk of stroke in AF. In the $CHADS_2$ scoring system (see Table 3) each point increases the annual risk of stroke by a factor of 1.5.

Table 3: $CHADS_2$ scoring system[3]

	$CHADS_2$ Clinical characteristic	Add points
C	Congestive heart failure	1
H	History of hypertension	1
A	Age 75 years or older	1
D	Diabetes Mellitus	1
S_2	History of Stroke or transient ischaemic stroke (TIA)	2
	TOTAL SCORE (Max 6) =	

$CHADS_2$ score	Annual risk of stroke
0	1.9%
1	2.8%
2	4.0%
3	5.9%
4	8.5%
5	12.5%
6	18.2%

Whilst the $CHADS_2$ score is simple it does not include many common stroke risk factors. In patients with a $CHADS_2$ score of 0-1, or where a more detailed stroke risk assessment is indicated, a more comprehensive risk factor based approach is recommended.[4]

The CHA_2DS_2VASc score (see Table 4) is inclusive of the most common stroke risk factors in everyday clinical practice and has been validated in multiple cohorts. It is better at identifying 'truly low-risk' patients with AF and is as good as, and possibly better than, scores such as $CHADS_2$ in identifying patients who develop stroke and thromboembolism.[4] Treatment with an

anticoagulant (warfarin or DOAC) is recommended for a $CHADS_2$ or CHA_2DS_2VASc scores of equal to or greater than 2.[4]

Direct comparison between the effects of vitamin K antagonist (warfarin) and aspirin has been undertaken in nine studies, demonstrating that warfarin was significantly superior in preventing stroke, with a relative risk (RR) reduction of 39%.[4]

Table 4: CHA_2DS_2VASc scoring system[4]

	CHA_2DS_2VASc clinical characteristic	Add points
C	Congestive heart failure	1
H	History of hypertension	1
A	Age 75 years or older	2
D	Diabetes Mellitus	1
S_2	History of stroke or transient ischaemic stroke (TIA)	2
V	Vascular disease	1
A	Age 65 years or older	1
Sc	Sex category, female	1
	TOTAL SCORE (Max 9) =	

CHA_2DS_2VASc score	Annual risk of stroke
0	0%
1	1.3%
2	2.2%
3	3.2%
4	4.0%
5	6.7%
6	9.8%
7	9.6%
8	6.7%
9	15.2%

NB: The risk score attributable to age is either 0 (<65 years), 1 (between 65-74 years) or 2 (75 years or older).

3.2 Risk of bleeding

Bleeding is the most common complication of warfarin therapy and is related to the INR value.(5) Warfarin causes major bleeding in one to two per cent of people treated and intracranial bleeding in 0.1 to 0.5 per cent of patients each year of treatment.[6] The highest rate of major bleeding occurs in the first three months of treatment.[5,7] In comparison, aspirin causes major bleeding in 1.3 per cent of patients.[8] Absolute risk increase for intracranial haemorrhage with warfarin compared to aspirin is only 0.2 per cent per year.[9]

Risk of bleeding can be assessed using the HAS-BLED scoring system (see Table 5) where a bleeding risk score of equal to or greater than 3 indicates high risk.[4] There are other bleeding risk assessment tools available including $HEMORR_2HAGES$ (see Table 6).[3,11,12] Assessment may identify reversible risks that can be managed prior to initiation of warfarin.[10] In general, clinicians should be cautious and conduct regular review of the patient if initiating warfarin.

Table 5: HAS-BLED scoring system[4]

	HAS-BLED clinical characteristic	Add points
H	Hypertension (uncontrolled, greater than 160 mm Hg systolic)	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke (previous history, particularly lacunar)	1
B	Bleeding (history or predisposition e.g. anaemia)	1
L	Labile INRs (i.e. time in therapeutic range is less than 60 per cent)	1
E	Elderly (older than 65 years)	1
D	Drugs (e.g. non-steroidal anti-inflammatory or antiplatelet drugs, heparin or thrombolysis) OR alcohol (1 point each)	1 or 2
	TOTAL SCORE (out of maximum 9 points) =	

HAS-BLED scores of 0, 1 or 2 correlate to 1.13, 1.02 and 1.88 major bleeds per 100 patient-years respectively.[11] This risk significantly increases at higher scores with HAS-BLED scores of 3, 4 and 5 correlating to 3.74, 8.70 and 12.50 major bleeds per 100 patient-years respectively.[11]

Table 6: HEMORR$_2$HAGES scores for bleeding risk assessment in patients receiving vitamin K antagonists[3,11,12]

HEMORR$_2$HAGES clinical characteristic	Score
Hepatic or renal disease	1
Ethanol abuse	1
Malignancy	1
Older (age>75 years)	1
Reduced platelet count or function	1
Re-bleeding risk	2
Hypertension	1
Anaemia	1
Genetic factors (CYP 2C9)	1
Excessive fall risk or neuropsychiatric disease	1
Stroke	1

Patients can be categorized into low, intermediate and high bleeding risk according to scores of 0-1, 2-3 and ≥4, respectively.

The HEMORR$_2$HAGES score was studied in elderly patients with a mean age of 80 years, so it may be more suitable to assess bleeding risk in elderly patients receiving vitamin K antagonists (VKA) such as warfarin.[13]

3.3 Contraindications to warfarin therapy

In determining whether to start warfarin, there is a need to consider absolute and relative contraindications. The lists below are not exhaustive.

Table 7: Contraindications to warfarin [14,15,16]

Absolute contraindications
• known large oesophageal varices • significant thrombocytopenia (platelet count less than 50 x 10^9/L) • previously documented hypersensitivity (e.g. priapism or skin necrosis) or intolerance to warfarin • acute clinically significant bleed – defer and reassess clotting versus bleeding risk within three months • decompensated liver disease or deranged baseline clotting screen (initial INR greater than 1.5) • pregnancy and within 48 hours postpartum. (Warfarin is teratogenic and can cause foetal bleeding. It is also associated with spontaneous abortion and perinatal bleeding.[16])
Relative contraindications
• previous history of intracranial haemorrhage – seek specialist opinion • within 72 hours of major surgery with risk of severe bleeding – defer and reassess post-operatively • recent major extracranial bleed within the last six months where the cause has not been identified or treated – seek specialist advice • peptic ulcer within last three months – defer until peptic ulcer treatment completed. Ensure peptic ulcer preventative therapy is initiated whilst on anticoagulant. • recent history of recurrent falls in patient at higher risk of bleeding (i.e. HAS-BLED score greater than or equal to 3) • dementia or marked cognitive impairment with poor medicines adherence and no carer support • chronic alcohol abuse, especially if binge drinking • untreated or poorly controlled hypertension, consistently greater than 160/90 mm/Hg.

Warfarin may be used during breastfeeding. It has not been detected in breast milk at doses up to 12 mg per day. Higher doses may require periodic INR monitoring of the infant.[17]

4. Initiation of warfarin

The safety and efficacy of warfarin is critically dependent on maintaining the INR within the target range. Patients must agree to undergo regular blood tests during treatment.

- A patient's response to warfarin is driven primarily through genetic variance in the hepatic clearance, and vitamin K handling.
- Diet, age, and dose also influence the anticoagulant effect. Assessing the response to changes in the warfarin dose is complicated by a delay of 2-3 days (time taken for INR to change following a dose change).

When commencing warfarin it is important to measure the baseline INR. If the baseline INR is 1.4 or above without warfarin, then liver function and nutrition status should be assessed and specialist advice sought regarding the patient's suitability for anticoagulation with warfarin.

Warfarin is usually started with loading doses. When possible, a single strength warfarin tablet should preferably be prescribed so that doses are multiples of one tablet. Patients should take their warfarin once a day at the same time, preferably in the evening, so that when an INR level is taken in the morning the results can be reviewed in the afternoon prior and the patient advised of a dosage change if required. Refer to Table 8 for warfarin dosing nomogram below.

Before initiating warfarin therapy
Consider if the benefits of anticoagulation outweigh the risks for each patient e.g. bleeding (section 3).
Ensure coagulant screen, **INR,** platelet and liver functions tests are normal. If not seek senior/specialist advice.
Dosing principles [18, 19, 20]
Warfarin should be **prescribed** in the **designated** area of the WA anticoagulant chart.
The initiating team must document **target INR, indication, initial dose** and consider **duration** of therapy.
Suggested initial dosing of 5mg daily for first 2 days, modify dosing for day 3 based on day 3 INR.
For younger patients (<60 years) consider 7-10mg on day 1 and day 2.
Consider smaller starting doses when the patient is elderly, has low body weight or abnormal liver function, is at high bleeding risk or has severe chronic renal impairment.
When recommencing warfarin post-surgery/intervention, patient's regular dose should be prescribed.
Consider dose modification in the presence of interacting drugs.
Therapeutic management of venous thromboembolism (VTE) (i.e. PE or DVT) with parenteral heparin anticoagulation should be overlapped with warfarin until the anticoagulant effect of warfarin is established (usually 5-6 days including at least 48 hours with the INR in the therapeutic range). Refer to section 4.3 regarding appropriate settings for bridging of anticoagulants.
Check that the patient has received **education** and **warfarin booklet/leaflets** before discharge. Ask your pharmacist to assist.

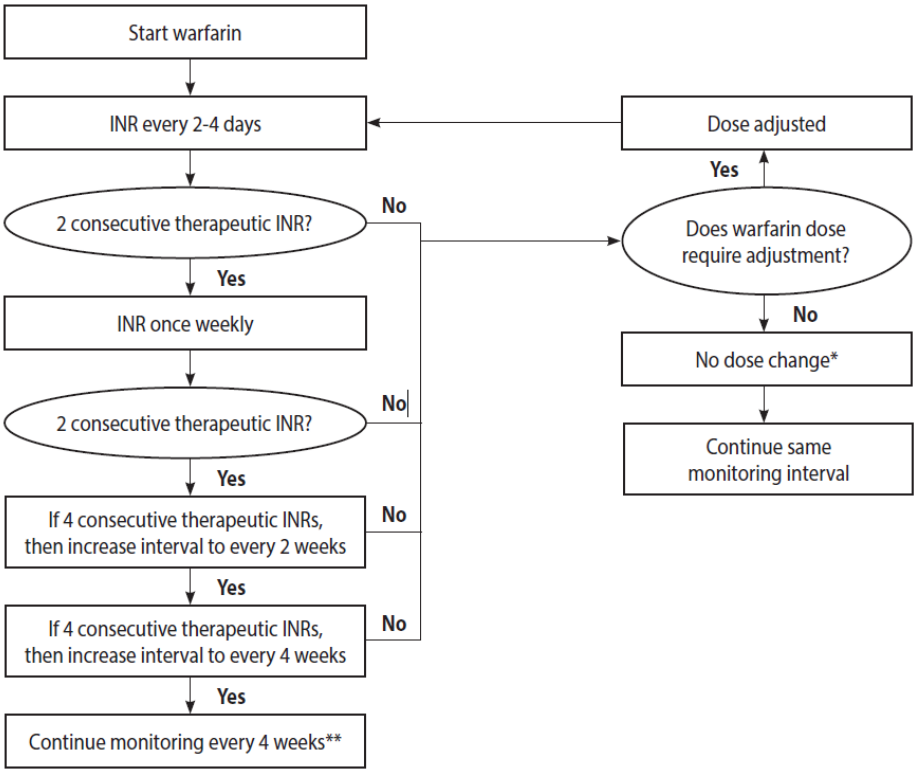
Table 7: Warfarin dosing nomogram [18, 19, 20]

Day	INR	Suggested dose
1	1-1.4	5 mg
2	No INR	5mg
3	<1.8 ≥1.8	5mg 1mg
4 & 5	<1.5 1.5-1.9 2.0-2.5 2.6-3.5 3.6-4.0 4.1-4.5 >4.5	7mg 5mg 4mg 3mg 2mg 1mg See treatment reversal
6 onwards	Measure on alternate days until stable (daily if drug interaction or high bleeding risk)	As for day 4 & 5, or per clinical judgement

4.1 Recommended frequency of INR monitoring

During the induction or initiation phase, it is recommended that INR be monitored every 2–4 days (initially daily if on therapeutic heparin) until the INR is in the patient's target range for two consecutive values. Once the INR is stabilised within the patient's target range, it can be monitored weekly. The interval can be gradually increased up to every 4 weeks if the INR remains stable and within the therapeutic range.[11,15] For more information about INR monitoring, refer to Figure 1 below.

Figure 1: Recommended frequency of INR monitoring[15]



Footnotes: Increase frequency of INR (every 2 - 4 days) if any of the following happens: non-therapeutic INR, intercurrent illness, any medication change (including herbal), significant diet change.
* Some reasons for **not** changing the dose when the INR is not therapeutic: 1) Patient noncompliant (forgot doses or took too many doses); 2) Inadequate number of days before previous dose change to take full effect; 3) Binge alcohol use (will transiently elevate INR).
**In a small group of very stable patients (stable INRs and no dosage change for 3 months), INR values can be monitored every 12 weeks.

Reproduced with permission

4.2 Subsequent maintenance dosing using warfarin

- Patients being re-initiated on warfarin post-surgery/intervention should be prescribed the dose taken prior to intervention post-operatively and check INR day 3
- In acutely ill patients with ongoing warfarin therapy, daily monitoring of INR may be appropriate
- Monitor INR more frequently when any change in treatment involves medications known to interact with warfarin
- Clinicians should consider whether the patient has had INR variations in the past to guide future adjustments in maintenance doses. Changes are recommended based on confirmation that regular daily doses have been taken as prescribed and the patient has had a consistent diet.
- Clinicians should consider available tablet strengths when prescribing future doses (especially for those patients that will be managing their warfarin management independently upon discharge).

4.3 Pre- and post-operative management of warfarin

Interruption of warfarin therapy temporarily increases thromboembolic risk, and continuing anticoagulation increases the risk of bleeding associated with invasive procedures. Management of warfarin therapy perioperatively should take into account these risks, as well as determining the time of anticoagulation interruption and whether bridging anticoagulation is required.[21,22]

Due to the risk of bleeding, warfarin may need to be withheld prior to surgery. Simple dental or dermatological procedures may not require cessation of warfarin therapy. However clinicians should be aware of potential drug interactions if antibiotic cover is required.

The major factors that increase thromboembolic risk post-operatively are AF, prosthetic heart valves and recent (within the preceding three months) venous or arterial thromboembolism.[21] Refer to Table 10 for estimating thromboembolic risk.

Appropriate settings for bridging of anticoagulants [21,22,23,24]

Bridging of anticoagulants involves the practice of prescribing heparin (low molecular weight heparin or intravenous unfractionated heparin infusion) concurrently with warfarin to cover the pro-coagulant phase of warfarin therapy and is usually continued for 48 hours once a therapeutic INR is reached, at which point the heparin is ceased. The intent of bridging is to minimise the time the patient is not anticoagulated, thereby minimising the risk of thromboembolism. However, this needs to be balanced with the importance of mitigating the risk of bleeding.

Table 9: When to consider bridging with treatment dose heparin in patients who are initiating warfarin or who have stopped warfarin pre-intervention if thrombotic risk is especially high.[22]

Consider bridging with treatment dose heparin in:	
Venous Thromboembolism (VTE)	Patients with a VTE within previous 3 months
	Very high risk patients such as patients with a previous VTE whilst on therapeutic anticoagulation who now have a target INR of 3.5
Atrial Fibrillation (AF)	Patients with a previous stroke/TIA in last 3 months
	Patients with a previous stroke/TIA and three or more of the following risk factors: • Congestive cardiac failure • Hypertension (>140/90 mmHg or on medication) • Age >75 years • Diabetes mellitus
	Patients with AF who have $CHADS_2$ score of 4 or less and who have not had a stroke or TIA in the last three months should not receive bridging. [23]
Mechanical Heart Valve (MHV)	MHV patients other than those with a bileaflet aortic valve and no other risk factors

Patients at low risk of thrombosis[22]

No heparin cover is required for patients at low risk of thrombosis. The time taken to reach a therapeutic INR is not critical; most patients will reach therapeutic INR by day 9 ± 3.5 days.[7] Stabilisation of warfarin needs to take into account factors that influence the INR or affect the risk of bleeding. Note that older people tend to respond more slowly with changes to the INR. However, rarely, there may also be patients who are more sensitive to the effects of warfarin. If there are clinical concerns regarding response to warfarin, INR monitoring should be conducted more frequently (e.g. every 3-4 days). In these instances dose adjustments should be based on clinical judgement.

Patients at high risk of thrombosis (e.g. DVT/PE/mechanical valve)

For patients at high risk of thrombotic events, heparin cover is required. Start warfarin on the same day as therapeutic heparin or LMWH and cover until target INR has been reached for at least 48 hours.[11]

Table 10: Estimating thromboembolic risk[21, 24, 25]

	High Risk	Intermediate risk	Low risk
AF	– $CHADS_2$* score of 5 or 6 – Recent (less than 3 months) stroke or transient ischaemic attack – Rheumatic valvular heart disease		– $CHADS_2$* score of 0-4 [22]
Mechanical heart valves	– Any mitral valve prosthesis – Older (caged-ball) aortic valve prosthesis – Recent (less than 6 months) stroke or transient ischaemic attack	– Bileaflet aortic valve prosthesis and one of the following: • atrial fibrillation, • prior stroke or transient ischaemic attack, • hypertension, • diabetes, • congestive heart failure, • age >75 years	– Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke
DVT and thromboembolism	– Recent (less than 3 months) venous thromboembolism (VTE) – Active cancer – Severe thrombophilia (e.g. deficiency of protein C, protein S, antithrombin, antiphospholipid antibodies, multiple abnormalities)	– VTE 3-12 months prior – Non-severe thrombophillic conditions (e.g. heterozygous factor V leiden mutation, prothrombin gene mutation) – Recurrent VTE (treated within 6 months or palliative)	– Single VTE occurred >12 months ago and no other risk factors

Estimating procedural bleeding risk is based on type of surgery/intervention as well as patient comorbidities and medications that affect haemostasis.[22] Refer to Table 11 for bleeding risk determination. Table 12 refers to the peri-operative management of warfarin.

Table 11: Bleeding risk determination[21,25]

Low bleeding risk (consider continuing anticoagulant)	Intermediate bleeding risk	High bleeding risk
Some dental interventions	Endoscopy with biopsy	Complex left-side ablation
Ophthalmology-cataract, glaucoma	Prostate/bladder biopsy	Spinal or epidural anaesthesia
Endoscopy without surgery	Electrophysiological/ radiofrequency catheter ablation	Thoracic, abdominal or major orthopaedic surgery
Superficial interventions	Angiography or pacemaker/ICD implantation	Liver or kidney biopsy

Table 12: Peri-operative management of warfarin[21,25,26]

Assess bleeding risk of surgery

Low bleeding risk

Continue warfarin if INR is in range. Consider a lower peri-operative INR goal of 2.

Intermediate to high bleeding risk

Low thrombotic risk

- Stop warfarin 4-5 days before surgery if ordered
- No bridging anticoagulation
- No bridging anticoagulation if AF is the indication for warfarin unless patient has $CHADS_2$ score of 5 or 6
- Restart warfarin on evening of day of surgery if appropriate

Intermediate thrombotic risk

- Stop warfarin 4-5 days before surgery if ordered
- Bridging anticoagulation to be considered if the thromboembolic risk clearly outweighs the increased bleeding risk from bridging
- Consider more conservative bridging strategies such as prophylactic dose of Low Molecular Weight Heparin (LMWH) 2-3 days before surgery
- Last prophylactic LMWH dose 12 hours before surgery if renal function is normal
- Restart warfarin on evening of day of surgery if appropriate
- Restart therapeutic bridging anticoagulation once haemostasis is adequate

High thrombotic risk

- Stop warfarin 4-5 days before surgery if ordered. It is important to consider an adequate period to withhold warfarin as the requirement to reverse with vitamin K prior to surgery will delay re-warfarinisation post-surgery (especially for patients with metallic heart valves).
- Consult haematology/cardiology to discuss bridging options. For example, patients with mechanical heart valves may require bridging with intravenous heparin infusion.
- If therapeutic dose of LMWH is ordered, start 2-3 days before surgery
- Commence when INR is subtherapeutic
- Last dose is 24 hours before procedure is commenced if renal function is normal
- Consider switching to intravenous heparin if patient very high thrombotic risk – stop 4 hours prior to commencement of surgery
- Restart warfarin on evening of day of surgery if appropriate
- Restart bridging anticoagulation when haemostasis is adequate, for patients with high bleeding risk consider restarting LMWH at prophylactic dose or IV heparin without a bolus dose.

5. Management of high INR and warfarin reversal

An INR greater than or equal to 5 significantly increases the risk of bleeding. Refer to Table 13 for recommended actions for high INR results.

There are 3 options available to reduce a patient's INR. This may be a desired action if the INR is well above the therapeutic range or in the presence of bleeding and/or bruising. The appropriate option is dependent upon the urgency of INR reduction/normalisation or the patient's risk of bleeding and/or bruising.

5.1 Withholding of warfarin doses

In the setting of an elevated INR in a patient who is not unwell and has no bleeding or bruising, withholding warfarin will allow the INR to slowly drift into the target range. This option is desirable when maintenance of the patient's anticoagulation is desirable and reversal of treatment is not clinically required.

5.2 Vitamin K (Phytomenadione)

Vitamin K reverses the effects of warfarin. Route of administration for vitamin K varies with indication; careful evaluation of route of administration is important. The oral route is preferred in the treatment of **nonbleeding** patients with warfarin-associated coagulopathy and can be administered orally for doses less than 10mg. The IV route may be used in select **nonbleeding** patients and should be used in patients with **major bleeding** due to warfarin-associated coagulopathy. In patient who require semi urgent surgery (e.g. fractured neck of femur), vitamin K should be given as early as possible, to minimise the need for additional reversal agents, such as prothrombin complex concentrate, which have additional potential risks.

Administering vitamin K orally has an onset of action of 6 to 10 hours compared to the IV route with an onset of action of 1 to 2 hours. [27]

In the presence of high INR results without bleeding, vitamin K can be administered orally or intravenously. The dose can range from 0.5-10mg depending on the patient's INR range and whether there is any significant bleeding.[27] The half-life of vitamin K is shorter than that of warfarin, so the INR may rise again after the administered vitamin K wears off. Daily INR monitoring is recommended.

5.3 Prothrombin Complex Concentrate (PCC) or Fresh Frozen Plasma (FFP)

The dose to be administered and the indications for prothrombin concentrates are clinically driven and should be directed by a clinical haematologist. For patients with either an elevated INR or an INR within their therapeutic range, but with concomitant bleeding, Prothrombin complex concentrate (Prothrombinex® -VF or PCC) or FFP can be administered to immediately reverse warfarin's effect. Refer to Table 13 below for Prothrombinex®-VF recommended dosage guide based on weight.

Only add Fresh Frozen Plasma (FFP) if critical organ bleeding (150-300mL) and/or if Prothrombinex®-VF is unavailable (FFP 15mL/kg). If required, seek consultation with a haematologist/specialist.

Administration of pro-coagulant proteins such as PCC can carry a risk especially for patients with thromboembolic risk factors. Monitor closely for signs or symptoms of intravascular coagulation or thrombosis; risk is higher in patients with congenital or acquired coagulation disorders, and with repeated dosing or high doses. Use with caution when administering to patients with liver disease, history of coronary artery disease, pre- or post-operatively, neonates, or patients at risk of thromboembolic phenomena, disseminated intravascular coagulation or patients with signs of fibrinolysis due to the potential risk of thromboembolic complications. Discontinue infusion immediately if signs or symptoms of thrombosis or embolism occur.[28]

Table 13: Reversing warfarin over-treatment[6]

Table below is an excerpt from the 2018 WA Anticoagulation Medication Chart.

REVERSING WARFARIN OVER-TREATMENT (bleeding risk increases exponentially from INR 5 to 9. Monitor closely INR ≥ 6)					
Clinical Setting		Management			
INR	Bleeding	Warfarin	Vitamin K	Prothrombinex VF	Comments
Greater than therapeutic range but <4.5	Absent	Reduce dose or omit next dose			Resume warfarin at reduced dose when INR approaches therapeutic range. If INR <10% above therapeutic level, dose reduction may not be necessary.
4.5 – 10	Absent (Low risk)	Stop			Measure INR in 24 hours. Resume warfarin at reduced dose when INR approaches the therapeutic range.
	Absent (High Risk)*	Stop	Consider 1–2 mg (oral)[1] Or 0.5–1mg IV[2]		Measure INR within 24 hours. Resume warfarin at reduced dose when INR approaches the therapeutic range.
>10	Absent (Low risk)	Stop	3–5mg (oral)[1] Or IV[2]		Measure INR in 12-24 hours. Resume warfarin at reduced dose when INR approaches the therapeutic range.
	Absent (High Risk)*	Stop	3–5mg IV[2]	Consider 15-30 Units/kg[3,4] See weight based nomogram	Measure INR in 12-24 hours. Resume warfarin at reduced dose when INR approaches the therapeutic range. Close monitoring over the following week.
Clinically significant bleeding where warfarin is a contributing factor. e.g. Intracranial or massive haemorrhage		Stop	5–10 mg (IV)[2]	25–50 Units/kg[3,4] doses may be appropriate as per warfarin reversal guidelines, See weight based nomogram	*Only add Fresh Frozen Plasma (FFP) if critical organ bleeding (150-300mL) or if Prothrombinex VF is unavailable (FFP 15mL/kg).* *If required seek consultation with a haematologist / specialist.*
Notes		[1] *undiluted paediatric IV formulation* [2] *undiluted as slow IV bolus over at least 30 seconds* [3] *at a rate of 3mL/min. 500 Units of factor IX in 1 vial of Prothrombinex VF* [4] *available from transfusion service* ***For reversal prior to a procedure – Refer to hospital guidelines or seek specialist advice.*** ***Seek advice with Vitamin K in cardiac valve replacement.***			
*High Bleeding Risk One or more ⇨		• Recent surgery / trauma / bleed • Advanced age	• Renal Failure • Hypertension	• Alcohol abuse • Active GI bleed	• Antiplatelet therapy • Other relevant co-morbidity

Vitamin K (phytomenadione) can be administered orally for doses less than 10mg. For IV doses less than or equal to 1mg, it is recommended that the contents of the 10mg ampoule be diluted with 20mL of Glucose 5% and the appropriate dose measured from this volume (i.e. 0.5mg in 1mL or 1mg in 2mL).

Table 14: Recommended dosage chart for Prothrombinex®-VF based on weight[28]

Prothrombinex®-VF recommended dosage chart (1 vial per 20kg rounded to nearest vial)			
Patient weight	60kg	70-80kg	100kg
Dose at 25units/kg	1500units	2000units	2500units
Number of vials at 25 IU/kg	3 vials	4 vials	5 vials
Total volume	60mL	80mL	100mL

6. Factors that influence the INR

Warfarin management is complex and affected by numerous factors including:

- Age > 75 years;
- History of bleeding;
- Baseline INR > 1.4;
- Concomitant drugs affecting warfarin metabolism (see “Warfarin Drug Interactions” below);
- Co-morbid diseases i.e. hypertension, cerebrovascular disease, ischaemic stroke, heart disease, renal insufficiency, hepatic impairment or low platelets;
- Presence of malignancy;
- History of falls;
- Major surgery in the last 10 to 14 days.

Warfarin management should be performed by a clinician experienced in warfarin dosing.

6.1 Warfarin drug interactions

- Drug interactions are a common and significant cause of morbidity and mortality
- Whenever starting or stopping a drug, particularly antibiotics, the INR must be re-checked 48-72 hours after a change in therapy
- Do not pre-empt a change. Make dose adjustments only after checking INR at 48 to 72 hours.
- Consider all concomitant therapy including herbal/complementary and over the counter medications (OTCs)
- Some potential drug interactions with warfarin are outlined in Tables 15, 16 and 17.

Note: these lists are not comprehensive or exhaustive. Contact your pharmacist or haematologist for further information. Note that a change in risk of bleeding may not be reflected in the INR (e.g. aspirin increases the risk of bleeding however does not affect the INR).

Table 15: Medications which can increase the risk of bleeding[26,29]

Medication Class	Example drug(s)
Anticoagulants	apixaban, dabigatran, rivaroxaban, heparin, LMWH
Antiplatelet agents	aspirin, clopidogrel, dipyridamole, prasugrel, ticagrelor, ticlopidine
Antithrombotic agents	alteplase, tenecteplase
Non-Steroidal Anti-inflammatory Drugs (NSAIDs)	ibuprofen, ketoprofen, naproxen
Complementary medicines/foods with antiplatelet effects	cranberry, fish oil, garlic, ginger, ginkgo, papaya extract
Serotonin Re-uptake Inhibitors (SSRIs)	Fluoxetine, paroxetine, sertraline, fluvoxamine

Table 16: Potential drug interactions[(29,30)]

✓ Refers to a review article that states the interaction is not likely to be clinically significant, or less than two cases reports with no clinically significant outcomes (i.e. bleeding, bruising, haematoma, death).

✓✓ Refers to a review article containing no information regarding clinical significance or a single case study with a clinically significant outcome

✓✓✓ Refers to a review article which states that the interaction is clinically significant

Interacting medication (drug or class)	↑ risk of bleeding	↓ risk of bleeding
Aminoglutethimide		✓✓
Amiodarone	✓✓✓	
Amoxicillin	✓✓	
Anabolic steroids/androgens e.g. nandrolone, oxandralone	✓✓✓	
Anticoagulants e.g. low molecular weight heparin **Antiplatelet agents** e.g. clopidogrel, aspirin, prasugrel **Antithrombotic agents** e.g. tenecteplase	✓✓✓	
Antithyroid agents e.g. carbimazole, propylthiouracil		✓✓
Aprepitant		✓✓✓
Azathioprine/mercaptopurine		✓✓
Capecitabine	✓✓	
Carbamazepine		✓

Interacting medication (drug or class)	↑ risk of bleeding	↓ risk of bleeding
Cefalosporin e.g. cefazolin	✓	
Cholestyramine		✓✓
Ciprofloxacin	✓✓✓	
Ciclosporin		✓
Danazol	✓✓	
Dicloxacillin		✓✓
Disulfiram	✓✓	
Fibrates e.g. gemfibrozil, fenofibrate	✓✓✓	
5-Flurouracil	✓✓	
Gatifloxacin	✓✓	
Griseofulvin		✓
Imidazole antifungals e.g. ketoconazole, miconazole	✓✓	
Isoniazid	✓	
Leflunomide	✓✓	
Macrolides e.g. azithromycin, clarithromycin, erythromycin, roxithromycin	✓✓✓	
Metronidazole and tinidazole	✓✓✓	
Moxifloxacin	✓✓	
Norfloxacin	✓✓✓	
NSAIDs/COX-2 inhibitors e.g. naproxen, celecoxib	✓✓✓	
Paracetamol *(if taking > 3.5-7g/week)*	✓✓✓	
Phenobarbitone		✓✓✓
Phenytoin	✓✓✓ (initially)	✓ (long-term)
Proton pump inhibitors e.g. omeperazole, esomeprazole, pantoprazole	✓✓	
Quetiapine	✓✓	
Quinidine	✓✓	
Quinine	✓✓	
Ranitidine	✓	
Rifabutin		✓✓✓
Rifampicin		✓✓✓
Salicylates *(topical)* e.g. methyl salicylate	✓✓	
Statins e.g. fluvastatin, simvastatin	✓	
SSRIs e.g. fluoxetine, sertraline, paroxetine	✓✓	
Sucralfate		✓
Sulfamethoxazole *(in co-trimoxazole)*	✓✓✓	
Tamoxifen	✓✓✓	
Tricylic antidepressants (TCAs) e.g. amitriptyline	✓✓	
Tetracyclines e.g. doxycycline	✓	
Thyroxine	✓	
Tramadol	✓✓	
Triazole antifungals e.g. fluconazole, itraconazole, voriconazole	✓✓	
Vancomycin	✓	

Table 16: Potential complementary medication interactions[26]

Interacting complementary medication	↑ risk of bleeding	↓ risk of bleeding
Cranberry	✓✓	
Dong Quai *Angelica sinensis*	✓✓	
Garlic *Allium sativum*	✓✓	
Ginkgo	✓✓	
Ginseng *Panax ginseng*		✓
Glucosamine ± Chondroitin	✓	
Papaya extract (containing papain) *Carica papaya*	✓	
St John's Wort *Hypericum perforatum*		✓✓✓
Tan-Shen *(also known as danshen)*	✓✓	
Vitamin E	✓✓	

7. Patient counselling

It is important to provide patients with the WA Therapeutic Advisory Group (WATAG) warfarin patient education booklet which includes a table for recording INRs and dosages.

Clinicians should provide patients with advice which includes the following[30]:

- Always take the same brand of warfarin tablets
- Take warfarin tablets at the same time every day preferably in the evening
- Inform a doctor if a painful, purplish, bruise-like rash develops
- Use a calendar or the tables in the back of a warfarin patient education booklet to keep a record of INRs and doses. Additionally, clinicians could suggest patients tick the date immediately after taking a dose so that any missed doses can easily be identified.
- Eat a normal, balanced diet without dramatic changes, to keep intake of vitamin K stable. Note that warfarin is affected by vitamin K which is found in certain foods (e.g. green leafy vegetables).
- Avoid excessive alcohol consumption (generally one to two standard drinks per day are considered a safe limit)
- Avoid drinking large amounts of cranberry juice as this may increase the effects of warfarin
- Seek advice from a doctor or pharmacist before starting or stopping any other medication or taking vitamin supplements, herbal or over-the-counter products (e.g. St John's Wort or fish oil)
- Inform any health care professional including dentists that they are taking warfarin
- Arrange appointments for regular blood tests in case the dose of warfarin needs adjusting and ensure they have been advised of the next dose to take when the test result is known
- Inform a doctor if experiencing symptoms of any other illness (including diarrhoea, vomiting, infection or fever) as extra blood tests may be needed
- Seek medical advice immediately if experiencing any unexplained bruising; bleeding, pink red or dark brown urine; or red or black faeces; prolonged bleeding from gums or nose; dizziness, trouble breathing or chest pain; severe headache; unusual pain, swelling or bruising; unusual weakness; dark purplish or mottled fingers or toes; vomiting or coughing up blood; excessive menstrual bleeding or if patient experiences a fall and has a head injury.

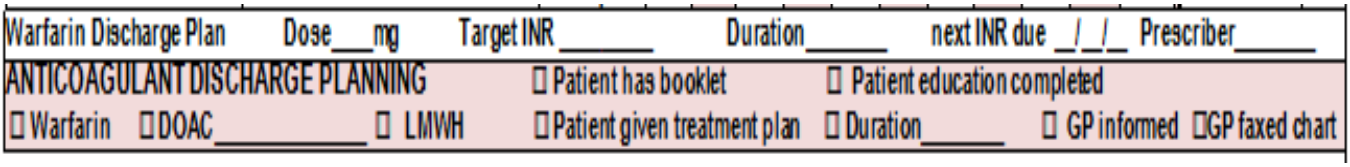
The ‘Living with Warfarin’ Booklet is a patient information booklet originally developed by the WA Medication Safety Group (WAMSG). A print-ready electronic version of this publication is available on the WATAG website for health services to print.

8. Follow up post-discharge

The transition from inpatient to outpatient care, if poorly managed, may adversely affect health outcomes.[31] Follow up immediately after discharge is particularly important for patients on warfarin because of the high risk nature of warfarin and the high risk setting upon transition to community. Ensure patient is aware of warfarin doses required until GP appointment is available. If the hospital has a dedicated anticoagulation service, refer patient prior to discharge.

A discharge summary to the clinician who is assuming post-discharge care including information on any arrangement of post-discharge services, follow up appointments and coagulation testing should be provided. The WA Anticoagulant chart has a section for discharge that should be used for discharge planning (see Figure 2 below). It is recommended that this following section is completed at discharge and scanned/faxed to the clinician that is assuming post-discharge care.

Figure 2: Warfarin discharge plan section from the WA Anticoagulant Chart



Key components of the hospital discharge process[29] are listed below:

- Educate the patient about diagnosis during hospitalisation
- Make appointments for clinician's follow up and post-discharge testing; identify and resolve barriers to follow up care
- Talk to the patient about testing done in the hospital and who will follow up on results
- Organise post-discharge services; identify and resolve barriers to receiving services
- Medication reconciliation; counsel the patient about medications and identify barriers to adherence and compliance
- Educate the patient on dietary recommendations such as being consistent with vitamin K intake
- Reconcile the discharge plan with evidence-based guidelines
- Educate the patient on problem-solving strategies, including contacting the primary care physician
- Expedite transmission of the discharge summary to clinicians and services that will be involved post-discharge care
- Assess the patient's understanding of the discharge plan; ask patients to explain in their own words; identify and resolve barriers to understanding
- Provide patient with a written summary detailing clinical course, follow-up, medication instructions and doctor's contact information.

9. References

1. Man-Song-Hing M, Nichol G, Lau A, Laupacis A. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. Arch Intern Med. 1999;159:677-85.
2. Donze J, Clair C, Hug B, Rodondi N, Waeber G, Cornuz J, et al. Risk of falls and major bleeds in patients on oral anticoagulation therapy. Am J Med. 2012;125(8):773-8.
3. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001;285(22):2864-70.
4. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace: European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2010;12(10):1360-420.
5. Tran HA, Chunilal SD, Harper PL, Tran H, Wood EM, Gallus AS. An update of consensus guidelines for warfarin reversal. The Medical journal of Australia. 2013;198(4):198-9.
6. Gallus AS, Baker RI, Chong BH and Ockelford PA. Consensus guidelines for warfarin therapy. Recommendations from the Australasian Society of Thrombosis and Haemostasis. MJA. 2000;172(12):600-5.
7. Pushpinderdeep Kahlon,1 Shahzaib Nabi,1,* Adeel Arshad,2 Absia Jabbar,3 and Ali Haythem[4] Warfarin Dosing and Time Required to Reach Therapeutic International Normalized Ratio in Patients with Hypercoagulable Conditions. Turk J Haematol. 2016 Dec; 33(4): 299–303. Published online 2016 Dec 1. doi: 10.4274/tjh.2015.0271. Accessed 1 May 2018 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5204184/
8. van Walreven C, Hart R, Singer D, Laupacis A, Connolly S, Petersen P. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: An individual patient meta-analysis. The Journal of the American Medical Association. 2002;277(19):2441-8.
9. Hart R, Pearce L, Aguilar M. Meta-Analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Annals of Internal Medicine. 2007;146:857-67.
10. Tideman PA, Tirimacco R, St John A, Roberts GW. How to manage warfarin therapy. Australian Prescriber. 2015;38(2):44-8.
11. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010;138(5):1093-100.
12. Gage BF, Yan Y, Milligan PE, et al Clinical classification schemes for predicting haemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). American Heart Journal, 2006;151(3):714-19.
13. Hanon O, Assayag P, Belmin J, Collet JP, Emeriau JP, Fauchier L, et al. Expert consensus of the French Society of Geriatrics and Gerontology and the French Society of Cardiology on the management of atrial fibrillation in elderly people. Archives of Cardiovascular Diseases. 2013;106(5):303-23.
14. Smith M. Contraindications to the initiation of oral anticoagulants and anti-platelet agents in patients with atrial fibrillation in primary care. Surrey, UK: National Health Service; 2011.
15. Medical Services Commission of British Columbia, Guidelines and Protocols Advisory Committee Warfarin Therapy Management. 2015. [cited 2018 March 15]. Available from http://www.bcguidelines.ca/. Reproduced with permission.
16. Prescribing medicines in pregnancy [Internet]. Therapeutic Goods Administration. [cited 28th August 2017]. Available from: http://www.tga.gov.au/prescribing-medicines-pregnancy-database#searchname.

17. LACTMED [Internet]. US National Library of Medicine. [cited 28th August 2017]. Available from: https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~VpvO7k:1.
18. Heneghan, C., Tyndel, S., Bankhead, C., et al. Optimal loading dose for the initiation of warfarin: a systematic review. BMC Cardiovascular Disorders, 2010;10(18). from URL: http://www.biomedcentral.com/1471-2261/10/18 (Accessed 2012 June 5)
19. Keeling D, Baglin T, Cambell T et al Br J Haem. Guidelines on oral anticoagulation with warfarin – 4th Edition 2011 from URL: www.bcshguidelines.com/documents/warfarin_4th_ed.pdf
20. Gedge J. Orme S. Hampton K. Channer K. Hendra T. A comparison of a low-dose warfarin induction regimen with the modified Fennerty regimen in elderly inpatients. Age & Ageing. 2000. 29(1):31-4
21. Up To Date: Perioperative management of patients receiving anticoagulants, Up to date – Mar 23 2018, Sourced 4/2/2018 https://www-uptodate-com.smhslibresources.health.wa.gov.au/contents/perioperative-management-of-patients-receiving-anticoagulants?search=warfarin%20bridging&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H2126501
22. Keeling D, Tait C et al. Peri-operative Management of anticoagulation and antiplatelet therapy. British Journal of Haematology, 2016, 175, 602–613.
23. Douketis JD, Spyropoulos AC et al Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation NEJM, 2015;373:823-33.
24. Rechemacher SJ, Fang JC. Bridging Anticoagulation. Journal of the American College of Cardiology. 2015;66(12).
25. Allman K, Wilson I. Haematology Disorders. 2011. In: Oxford Handbook of Anaesthesia [Internet]. Oxford University Press. 3rd edition. Available from: http://oxfordmedicine.com.smhslibresources.health.wa.gov.au/view/10.1093/med/9780199584048.001.0001/med-9780199584048-chapter-010#med-9780199584048-div1-511.
26. Department of Health Queensland. Guidelines for Warfarin Management in the Community. State of Queensland (Queensland Health) and the Royal Flying Doctor Service Queensland Section; 2016.
27. Up-To-Date: Vitamin K (phytomenadione): Drug Information. Accessed 12/6/2018 https://www-uptodate-com.smhslibresources.health.wa.gov.au/contents/vitamin-k-phytonadione-drug-information?search=vitamin%20k&source=search_result&selectedTitle=1~148&usage_type=default&display_rank=1
28. Up-To-Date: Prothrombin complex concentrate, 3-factor, unactivated, from human plasma: Drug Information. Accessed 12/6/2018 https://www-uptodate-com.smhslibresources.health.wa.gov.au/contents/prothrombin-complex-concentrate-3-factor-unactivated-from-human-plasma-drug-information?search=prothrombinex&source=search_result&selectedTitle=1~28&usage_type=default&display_rank=1
29. Drug Interactions [Internet]. MIMS Australia. 2017 [cited 22nd August 2017]. Available from: https://www-mimsonline-com-au.nmahslibresources.health.wa.gov.au/Search/Search.aspx.
30. Toleman J. Guidelines for Anticoagulation using Warfarin. In: Queensland Health Medication Safety Implementation Group and Safe Medication Practice Unit Board, editor. Version 5 ed: The State of Queensland (Queensland Health); 2006.
31. Michota F. Transitions of care in anticoagulated patients. Journal of Multidisciplinary Healthcare. 2013;6:215-28.

This document can be made available in alternative formats on request for a person with a disability.