Guidelines for warfarin management in the community

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This Guideline does not address all elements of standard practice and assumes that individual clinicians have the responsibility to:

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- Advise consumers of their choice and ensure informed consent is obtained.
- Provide care within scope of practice, meet all legislative requirements and maintain standards of professional conduct.
- Apply standard precautions and additional precautions as necessary, when delivering care.
- Document all care in accordance with mandatory and local requirements.

Guidelines for Warfarin Management in the Community

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Contents

Guidelines for warfarin management in the community

Purpose

This guideline provides recommendations regarding best practice for initiation and management of warfarin for patients in the community, as well as primary and community health services (e.g. Home Based Acute Care Service or Hospital in the Home). This guideline applies to all Queensland Health patients prescribed warfarin in the community where a work unit procedure is unavailable.

Scope

This guideline provides information for all Queensland Health employees (permanent, temporary and casual) and all organisations and individuals acting as its agents (including Visiting Medical Officers, Royal Flying Doctor Service and other partners, contractors, consultants and volunteers).

Related documents

Authorising Policy and Standard/s:

- Queensland Health List of Approved Medicines

Procedures, Guidelines and Protocols:

- Queensland Health inpatient Guidelines for Anticoagulation using Warfarin – Adult (available from Medicines Regulation and Quality, Department of Health, Queensland Health, email: medicationsafety@health.qld.gov.au)

Forms and templates:

- Queensland Health Non-Inpatient Rural and Remote Warfarin Record, SW032, Material number (FAMMIS): 10202082

Other:

- Warfarin patient education booklet (e.g. medication manufacturing company, private pathology or other)

1. Guideline

1.1 General information

Warfarin 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 (see section 1.4.2) (Clarke et al. 2006). In patients at high risk of thrombosis, such as venous thromboembolism, another anticoagulant (e.g. heparin) is required to provide adequate anticoagulation cover for the first five days of warfarin initiation therapy.

Warfarin is extensively metabolised by the liver, mostly to inactive hydroxylate metabolites which are predominantly eliminated by the renal system (Micromedex 2.0 2015). For factors that may impact on the metabolism of warfarin or monitoring of the INR refer to section 1.9 Factors that Influence the INR.

The two brands of warfarin available in Australia, Marevan® and Coumadin®, are not interchangeable and swapping brands may affect INR control. Queensland Health facilities generally use the Marevan® brand.

1.2 Indications

Duration of treatment and target INR may vary depending on the indication for warfarin therapy (see Table 1 below).

Table 1 Indications for warfarin therapy with recommendations for target INR and duration

Indication	Target INR range	Minimum recommended duration
Valve repairs Bioprosthetic valve	2 – 3	6 weeks post operatively
DVT PE	2 – 3	3 months
AF* Irreversible, clinically hyper-coagulable states Mechanical AVR with no risk factors[#]	2 – 3	Life long, balanced against risks
High risk mechanical heart valves Mechanical MVR Mechanical AVR with risk factors[#]	2.5 – 3.5	Life long, balanced against risks

Source: Tran et al. 2013, Guyatt et al. 2012; Kearon et al. 2012; Cardiovascular Expert Group 2012; Ageno et al. 2012; Keeling et al. 2011
* Refer also to section 1.3.1 Risk of stroke in patients with AF
[#] Risk factors: AF, previous VTE, hypercoagulable state, left ventricular dysfunction or older generation AVR

Risk of bleeding increases if warfarin is combined with antiplatelet therapy. If considering combination with antiplatelet therapy, discuss options with a specialist. Do

not add aspirin for patients who have both AF and ischaemic heart disease. Consider addition of clopidogrel to patients with stents after discussion with a specialist (Blaauw & Crijns 2008). Literature suggests that triple therapy with warfarin, aspirin and clopidogrel is acceptable for short term treatment of up to four weeks in patients with acute coronary syndrome and AF (Camm et al. 2010).

1.3 Risk assessment

1.3.1 Risk of stroke in patients with atrial fibrillation

The CHADS2 scoring system (Gage et al. 2001) is a simple system that can be used to assess the annual risk of stroke in AF. In the CHADS2 scoring system (see Table 2) each point increases the annual risk of stroke by a factor of 1.5. Treatment with warfarin is recommended for a CHADS2 or CHA_2DS_2VASc scores of equal to or greater than 2. Whilst the CHADS2 score is simple it does not include many common stroke risk factors. The CHA_2DS_2VASc score (see Table 3) is inclusive of the most common stroke risk factors in everyday clinical practice and has been validated in multiple cohorts; the accumulated evidence shows that CHA_2DS_2VASc is better at identifying 'truly low-risk' patients with AF and is as good as, and possibly better than, scores such as CHADS2 in identifying patients who develop stroke and thromboembolism (ESC Guidelines 2012).

Table 2 $CHADS_2$ scoring system

	$CHADS_2$ 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 Attack	2
	TOTAL SCORE (max 6) =	

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

Source: Gage et al. 2001

Table 3 CHA_2DS_2VASc scoring system

	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 Attack	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%

Source: ESC Guidelines for the management of atrial fibrillation European Heart Journal (2012)

Direct comparison between the effects of Vitamin K Antagonist (VKA) and aspirin has been undertaken in nine studies, demonstrating that VKA were significantly superior, with an RR reduction of 39%.

1.3.2 Risk of bleeding

The risk of stroke should be weighed against the risk of bleeding to assess appropriateness of anticoagulant therapy. 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 (Gallus et al. 2000). The highest rate of major bleeding occurs in the first three months of treatment (Clarke et al. 2006). In comparison, aspirin causes major bleeding in 1.3 per cent of patients (van Walraven et al. 2002). Absolute risk increase for intracranial haemorrhage with warfarin compared to aspirin is only 0.2 per cent per year (Hart et al. 2007).

Risk of bleeding can be assessed using the HAS-BLED scoring system (see Table 4) where a bleeding risk score of equal to or greater than 3 indicates high risk. There are other bleeding risk assessment tools available including $HEMORR_2HAGES$ (Gage et al. 2006). Assessment may identify reversible risks that can be managed prior to initiation of warfarin. In general, clinicians should be cautious and conduct regular review of the patient if initiating warfarin (Camm et al. 2010).

Table 4 HAS-BLED scoring system

	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 International 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) =	

Source: Pisters et al. 2010

HAS-BLED scores of 0, 1 or 2 correlate to 1.13, 1.02 and 1.88 major bleeds per 100 patient-years respectively. 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 (Pisters et al. 2010).

1.3.3 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 (Smith 2011).

Absolute contraindications to warfarin therapy include:

- known large oesophageal varices
- significant thrombocytopenia (platelet count less than 50 x 10^9/L)
- within 72 hours of major surgery with risk of severe bleeding – defer and reassess post-operatively
- previously documented hypersensitivity (e.g. priapism or ischaemic necrosis)
- acute clinically significant bleed – defer and reassess stroke 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 peri-natal bleeding (Australian Drug Evaluation Committee 2015).

Relative contraindications to warfarin therapy include:

- previous history of intracranial haemorrhage – seek specialist opinion
- recent major extracranial bleed within the last six months where the cause has not been identified or treated – defer the decision for warfarin therapy
- 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 breast feeding. 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 (National Institute of Health, USA 2015; Rossi 2015).

1.4 Initiation of warfarin

When initiating warfarin, it is important to involve the patient ensuring he or she understands the benefits and potential side effects as well as the monitoring that is necessary with warfarin therapy. Obtain patient consent and document in the clinical notes.

Consideration should be given to using 1 mg tablets only, particularly for patients who have difficulty with reading or with numbers. This may assist in reducing confusion until a stable dose is achieved.

There are two methods for initiating warfarin, depending on the patient's level of risk for thrombotic events:

- low thrombotic risk patients (i.e. AF)
- high thrombotic risk patients (e.g. DVT).

Tables 5 and 6 recommend dose changes based on the assumption that the patient has taken daily doses as recommended. Adherence to therapy should be checked prior to adjusting doses in response to an INR result.

Post-operative patients can be restarted with their 'normal' pre-operative maintenance dose of warfarin without re-loading. See section 1.8 for information on stopping warfarin for procedures.

1.4.1 Patients at low risk of thrombosis (i.e. AF)

No heparin cover is required for patients at low risk of thrombosis and a low initial dose regimen starting with 3 mg warfarin is recommended. The time taken to reach a therapeutic INR is not critical; for 85 per cent of patients, this is achieved by day 29 (Clarke et al. 2006).

The regimen shown in Table 5 is based on weekly INR testing taken on day 1 (baseline), day 8 and day 15. 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 three to four days). In these instances dose adjustments should be based on clinical judgement as the recommended protocol in Table 5 would no longer apply.

Table 5 Regimen for Initiation of Warfarin in Patients at Low Risk of Thrombosis (Target range of INR 2 – 3)

Day to take INR test (Initiation = day 1)	INR	Daily Warfarin Dose (until next INR test)
Day 1	Obtain Baseline INR	3 mg (provided baseline INR is 1.4 or less)
Day 8	Less than 1.4	Increase to 6 mg Check INR again on Day 11 or 12 Refer to Section 1.13 for guidance on dosing
	1.4 – 1.5	Increase to 5 mg
	1.6 – 1.8	Increase to 4 mg
	1.9 – 2.1	Maintain 3 mg
	2.2 – 2.5	Reduce to 2.5 mg
	2.6 – 2.7	Reduce to 2 mg
	2.8 – 3	Omit one to two daily doses, then reduce to 1 mg
	Greater than 3[#]	**Stop Warfarin** Check causes and indication Repeat INR in three to five days If warfarin definitely indicated, restart at 1 mg
Day 15 and weekly thereafter	Check INR and adjust dose according to section 1.5 – Subsequent Maintenance Dosing Using Warfarin	

Source: Janes, Challis & Fisher 2004
[#]If INR is abnormally high (i.e. greater than 5), refer to section 1.7 Management of High INR.

1.4.2 Patients at high risk of thrombosis (e.g. DVT)

For patients at high risk of thrombotic events, heparin cover is required. Start warfarin on the same day as therapeutic heparin or LMWH* and overlap for a minimum of five days, until target INR has been reached for at least two consecutive days (Pisters et al. 2010; Rossi 2015). For initiation, a starting dose of 5 mg warfarin with daily INR monitoring for a minimum of five days is recommended.

Table 6 **Regimen for Initiation of Warfarin for High Risk Patients (Target range of INR 2 – 3*)**

Day to take INR test (Initiation = day 1)	INR	Daily Warfarin Dose (until next INR test)
Day 1	Less than 1.4	5 mg
Day 2	Less than 1.8	5 mg
	1.8 - 2	1 mg
	Greater than 2[#]	Nil
Day 3	Less than 2	5 mg
	2 - 2.5	4 mg
	2.6 - 2.9	3 mg
	3 – 3.2	2 mg
	3.3 – 3.5	1 mg
	Greater than 3.5[#]	Nil
Day 4	Less than 1.4	10 mg
	1.4 - 1.5	7 mg
	1.6 – 1.7	6 mg
	1.8 – 1.9	5 mg
	2 – 2.3	4 mg
	2.4 – 3	3 mg
	3.1 – 3.2	2 mg
	3.3 - 3.5	1 mg
	Greater than 3.5[#]	Nil

Source: adapted from Kovaks et al. 2003; Gedge et al. 2000
* Exercise caution in patients with impaired renal function (calculated creatinine clearance is less than 30 mL/min) where LMWH can accumulate and contribute to bleeding.
[#]If INR is abnormally high (i.e. greater than 5), refer to section 1.7 Management of High INR.
Note: Dose modification is required for patients with mechanical heart valves as the target INR range is higher (2.5 – 3.5).

After Day 4 clinicians should continue regular INR monitoring every three to four days until stabilised and if the patient is still on heparin or LMWH review the ongoing need for these additional anticoagulants. Note that a change in the INR of 0.5 over three days or 1 over seven days is considered unstable. Dose adjustments during this period will need to be based on clinical judgement; if unsure seek advice. After INR results have been stabilised, refer to subsequent maintenance dosing recommendations (Section 1.5).

1.5 Subsequent maintenance dosing using warfarin

The following regimen (see Table 7) can be used for ongoing maintenance after stabilisation. Clinicians should reflect on 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 and the patient's ability to break scored tablets when prescribing future doses.

The dose modifications in Table 7 below are based on the total weekly dose of warfarin. The weekly dose can be prescribed using a range of dosing regimens (e.g. alternate day dosing or dose regimens with different doses for weekdays compared to the weekend). Dose modifications based on the total weekly dose also enable dose adjustments for low dose regimens whereas a change would not be recommended if calculations were based on the daily dose.

Table 7 Regimen for Subsequent Maintenance Dosing Using Warfarin (Target range of INR 2 – 3*)

INR	Dosage adjustment
Less than 1.5	Increase weekly dose by 20%
1.5 – 1.9	No change – recheck in one week If persistent, increase weekly dose by 10%
2 – 3	No change
3.1 – 3.9	No change – recheck in one week If persistent, decrease weekly dose by 10%–20%
4 – 4.9	Omit one dose Decrease weekly dose by 10%–20% Re-check INR in two to five days
Greater than or equal to 5	See section 1.7 – Management of High INR

Source: adapted from Guidelines & Protocols Advisory Committee 2010
* Note: Dose modification is required for patients with mechanical heart valves as the target INR range is higher (2.5 – 3.5).

Worked examples of dose modifications:

1. Current dose regimen of 1 mg daily (equates to 7 mg weekly). If INR result is 1.6:

Recommended dose adjustment is an increase of 7 mg x 10% = 0.7 mg.

Example of new dose regimen:

	Mon	Tue	Wed	Thur	Fri	Sat	Sun	Total weekly dose
Current dose	1mg	1mg	1mg	1mg	1mg	1mg	1mg	7mg
Suggested new dose (1)	1mg	1mg	1mg	1mg	1mg	1mg	2mg	8mg
Suggested new dose (2)	1mg	1mg	1.5mg	1mg	1mg	1.5mg	1mg	8mg

2. Current dose regimen of 4 mg on Monday, Wednesday and Friday, 3 mg every other day (equates to 24 mg weekly). If INR result is 4.2:

Recommended dose adjustment is a dose omission then a reduction of 24 mg x 10%-20% = 2.4-4.8 mg over the week.

Example of new dose regimen: omit one dose; then change dose to 3 mg daily.

3. Current dose regimen of 5 mg daily (equates to 35 mg weekly). If INR result is 4.8:

Recommended dose adjustment is a dose omission then a reduction of 35 mg x 10%–20% = 3.5–7 mg over the week.

Example of new dose regimen: omit one dose; then change dose to 4 mg daily.

1.6 Frequency of INR monitoring

There are two regimens for monitoring INR, depending on the patient's level of risk for thrombotic events:

- low thrombotic risk patients (i.e. AF) - see Table 8
- high thrombotic risk patients (e.g. DVT) - see Table 9.

Note that if the INR falls out of range (e.g. due to illness or initiation of an interacting medication), then it may be necessary to step back to daily monitoring.

1.6.1 Patients at low risk of thrombosis (i.e. AF)

Table 8 Monitoring of INR with patients at low risk of thrombotic events

Frequency of monitoring based on INR	Duration until change of test frequency
Initially: • when INR less than or equal to 4, weekly • when INR more than 4, every two to three days	Until the INR is in target range for at least **two** consecutive test results
Then, fortnightly	Until the INR is in target range for **two to three** consecutive test results
Thereafter	Test every four to six weeks for most patients. For patients who are very stable, it may be reasonable to extend monitoring frequency to eight weeks.

Source: adapted from Clarke et al. 2006

1.6.2 Patients at high risk of thrombosis (e.g. DVT)

Table 9 Monitoring of INR with patients at high risk of thrombotic events

Frequency of monitoring based on INR	Duration until change of test frequency
Initially, daily for at least five days	Until the INR is in target range for **at least two** consecutive test results
Then, every three to five days	Until the INR is in target range for **at least two** consecutive test results
Then, weekly	Until the INR is in target range for **two to three** consecutive test results
Then, fortnightly	Until the INR is in target range for **two to three** consecutive test results
Thereafter	Test every four to six weeks for most patients. For patients who are very stable, it may be reasonable to extend monitoring frequency to eight weeks.

Source: adapted from Clarke et al. 2006

1.7 Management of high INR

An INR greater than or equal to 5 significantly increases the risk of bleeding. Refer to Table 10 for recommended actions for high INR results. Consider whether or not a patient with a high INR result requires admission to hospital for access to specialised treatment (e.g. blood products) and monitoring.

Table 10 **Recommendations for reversal of warfarin -** Seek early advice if any bleeding occurs

Clinical setting		Recommendation
No bleeding	INR greater than therapeutic range but less than 4.5 and **NO** bleeding	• Reduce or withhold next dose of warfarin based on sensitivity risk factors (see section 1.3.2). • Resume lower dose of warfarin once INR approaches therapeutic range. If INR is only minimally above therapeutic range (i.e. by 10%) dose reduction is generally not necessary.
	INR 4.5–10 and **NO** bleeding	• Cease warfarin. Consider reasons for elevated INR and patient specific factors. Vitamin K is usually not required. If bleeding risk high* give vitamin K[#] 1-2 mg orally or 0.5–1 mg IV. • Check INR within 24 hours. Resume lower dose of warfarin once INR approaches therapeutic range.
	INR greater than 10 and **NO** bleeding	• Cease warfarin. Give vitamin K[#] 3-5 mg orally (the higher dose may lead to difficult re-warfarinisation) or 0.5-1 mg IV. If bleeding risk is high*, consider Prothrombinex^{TM}-VF 15-30 units/kg. • Check INR in 12 to 24 hours and continue to monitor every one to two days over the following week. • Resume lower dose of warfarin once INR approaches therapeutic range.
Bleeding SEEK SENIOR ADVICE	INR greater than or equal to 1.5 with life-threatening (critical organ) bleeding	• Cease warfarin. Give vitamin K[#] 5-10 mg IV, Prothrombinex^{TM}-VF 50 units/kg and FFP 150-300 mL. If Prothrombinex^{TM}-VF is unavailable, increase FFP dose to 15 mL/kg. • Assess INR frequently until clinically stable.
	INR greater than or equal to 2 with clinically significant bleeding (not life-threatening)	• Cease warfarin. Give vitamin K[#] 5-10 mg IV and Prothrombinex^{TM}-VF 35-50 units/kg. If Prothrombinex^{TM}-VF is unavailable, give FFP 15 mL/kg. • Assess INR frequently until clinically stable.
	Any INR with minor bleeding	• Omit warfarin. Repeat INR the following day and adjust warfarin dose to maintain INR in target therapeutic range. If bleeding risk is high* or INR greater than 4.5, consider vitamin K[#] 1-2 mg orally or 0.5-1 mg IV.

Source: adapted from Tran et al. 2013
[#] Not for intramuscular injection; Konakion MM®, the intravenous preparation of vitamin K (phytomenadione), may be given orally.
* Major bleed in previous four weeks, major surgery in previous two weeks, thrombocytopaenia with platelets less than 50 x 10^9/L, known liver disease or concurrent antiplatelet therapy.
Note: For patients that have been treated for warfarin reversal, reassess the patient for suitability of warfarin therapy.

1.8 Perioperative thromboembolism risk stratification

Table 11 Level of thrombosis risk dependent on indication for warfarin therapy

Thrombosis risk	Indication for Warfarin Therapy		
	Mechanical valve	Atrial fibrillation	Venous thromboembolism
Low Bridging unlikely to be required	Present – discuss with cardiologist	• AF and no history of cardiac embolism • CHA_2DS_2-VASc score of 0-4	• One DVT or PE more than three months ago • Prior VTE and low risk thrombophilia (heterozygous Factor V Leiden or prothrombin gene mutation)
Moderate to High Consider bridging	Present – discuss with cardiologist	• Rheumatic AF (mitral valve disease stenosis / regurgitation) • AF with history of cardiac embolism or mechanical heart valve in any position • CHA_2DS_2-VASc score 5-9	• VTE within the past three months or very strong family history • High risk thrombophilia: Deficiency of protein C, protein S or antithrombin III; homozygous Factor V Leiden mutation; antiphospholipid antibody syndrome; more than one laboratory thrombophilic defect (compound heterozygotes) • Two or more arterial or idiopathic venous thromboembolic events

Source: adapted from Tran et al. 2013
*There is uncertainty with CHA_2DS_2-VASc scores 4-6 and an individual approach may be required.

1.9 Stopping warfarin for procedures

Due to the risk of bleeding, warfarin may need to be withheld prior to surgery (see Table 12). Simple dental or dermatological procedures may not require cessation of warfarin therapy. However, clinicians should be aware of potential drug interactions (see Section 1.9) if antibiotic cover is required.

Table 12 Warfarin management before and after procedures

Thrombosis risk	Before surgery	After surgery
Low (e.g. AF and no history of cardiac embolism)	• Withhold warfarin for five days before surgery • Night before surgery: If INR greater than 2, give 3 mg vitamin K[#] IV or oral • Day of surgery: – If INR less than or equal to 1.5, surgery can proceed – If INR greater than 1.5, defer surgery or, if urgent give Prothrombinex™-VF 15–30 units/kg depending of initial and target INR or, if Prothrombinex™-VF not available, give FFP 10–15 mL/kg – Employ pre-operative thromboprophylaxis as per hospital policy.	• Start warfarin on the day of surgery at the **previous** '**normal**' maintenance dose as long as there is no evidence of bleeding • Employ thromboprophylaxis as per hospital policy.
Moderate to High (e.g. VTE within past three months)	**Option 1: Planned surgery** • Withhold warfarin for five days before surgery • Two to three days before surgery: When INR is less than 2 commence treatment dose of LMWH* subcutaneously or unfractionated heparin (UFH) IV: – If using LMWH*, last dose should be given at least 24 hours before surgery – If using UFH IV, cease infusion 4 to 6 hours before surgery **Option 2: Planned surgery with stable INR in preceding weeks** • Night before surgery: If INR is stable at 2-3 in the two to four weeks preceding surgery, give 3 mg vitamin K IV or oral • Day of surgery: – If INR less than or equal to 1.5, surgery can proceed – If INR greater than 1.5, defer surgery or, if urgent give Prothrombinex™-VF 15-30 units/kg depending on initial and target INR or, if Prothrombinex™-VF not available, give FFP 10-15 mL/kg **Option 3: Urgent surgery** • For urgent surgery, check INR before surgery and give Prothrombinex™-VF 15-30 units/kg depending on initial and target INR • For procedures with low risk of bleeding, warfarin may not need to be ceased.	• Recommence warfarin as soon as possible at the **previous 'normal'** maintenance dose as long as there is no evidence of bleeding — DO NOT RE-LOAD. • Consider bleeding risk against thrombosis • Start LMWH or UFH 12 to 24 hours postoperatively: • If using LMWH begin with prophylactic dose • If using UFH IV, avoid bolus and aim to prolong APTT as recommended by your site • Consider delaying resumption of therapeutic LMWH for 48 to 72 hours after major surgery • Continue LMWH or UFH for minimum of five days and cease 48 hours after target INR is reached • In surgery with high risk of bleeding, consider using prophylactic dose LMWH or UFH IV only and cease 48 hours after target INR is reached.

Source: adapted from Tran et al. 2013
*Exercise caution in patients with impaired renal function (calculated creatinine clearance is less than 30 mL/min) where LMWH can accumulate and contribute to bleeding.

[#]Not for intramuscular injection; Konakion MM®, the intravenous preparation of vitamin K (phytomenadione), may be given orally.

1.10 Factors that influence the INR

- **Drug interactions** with warfarin therapy are a common and significant cause of morbidity and mortality and should be considered whenever **starting** or **stopping** a drug (particularly **antibiotics**). With expert advice it may be possible to predict a dose effect. In general, dose adjustments should only be made after checking the INR at 48-72 hours after initiating an interacting medication. The INR should continue to be monitored every 48-72 hours for the course of interacting medication therapy or until INR is again confirmed stable. If dose adjustments are required refer to recommendations in Tables 7, 8 or 9, and 10 (sections 1.5 – 1.7). Monitor the INR again after ceasing the interacting medication until the INR is stable (refer to Tables 8 and 9).
- In assessing potential drug interactions, consider **all concomitant therapy** including **herbal/complementary** and **over-the-counter** medications.
- Dramatic changes in **diet** can affect the INR due to varying vitamin K levels within different foods (e.g. green leafy vegetables are high in vitamin K).
- Altered health status (e.g. acute illness or worsening chronic renal or hepatic impairment) may alter response to warfarin due to effects on the synthesis of clotting factors or changed metabolism of warfarin.

(Queensland Health Statewide Anticoagulant Working Party 2015)

Some potential drug interactions with warfarin are outlined in Tables 13, 14 and 15. 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 13 Medications which can increase the risk of bleeding

Medication Class	Example drug(s)
Anticoagulants	apixaban, dabigatran, rivaroxiban, heparin, LMWH
Antiplatelets	aspirin, clopidogrel, dipyridamole, prasugrel, ticagrelor, ticlopidine
Antithrombotics 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

Source: Micromedex 2.0 2015

Table 14 Potential drug interactions

KEY
Severity of Interaction

Red: ++ The interaction may be life-threatening and/or require medical intervention to minimise or prevent serious adverse effects; or the drugs are contraindicated for concurrent use.

Black: + The interaction may result in an exacerbation of the patient's condition and/or require an alteration in therapy.

Level of evidence

A Controlled studies have clearly established the existence of the interaction.

B Documentation strongly suggests the interaction exists, but well-controlled studies are lacking

C Available documentation is poor, but pharmacological considerations lead clinicians to suspect the interaction exists; or documentation is good for a pharmacologically similar drug

Interacting Medication (Drug or Class)	Increased risk of bleeding	Decreased risk of bleeding	Level of evidence
Allopurinol	+		B
Amiodarone	++		A
Antibiotics			
• cephalosporins, penicillins (except dicloxacillin), metronidazole	++		B/C
• dicloxacillin		++	A
• doxycycline	++		C
• isoniazid, vancomycin	+		B
• macrolides, quinolones	++		A/B
• sulfamethoxazole i.e. in co-trimoxazole	++		A
• rifabutin, rifampicin		+	B
Antifungals			
• azoles e.g. fluconazole, voriconazole	++		A/B
• griseofulvin		+	B
Antithyroid agents e.g. carbimazole, propylthiouracil		+	B
Aprepitant		++	B
Azathioprine / Mercaptopurine		++	B
Carbamazepine		+	B
Cholestyramine		+	B
COX-2 inhibitors e.g. celecoxib	++		B
Cyclosporin		+	B

Interacting Medication (Drug or Class)	Increased risk of bleeding	Decreased risk of bleeding	Level of evidence
Fibrates • **fenofibrate** • gemfibrozil	 **++** +		 **C** B
H2-Antagonists e.g. cimetidine, ranitidine	+		B
Imatinib	**++**		**B**
Infliximab		**++**	**C**
Influenza vaccine	**++**		**B**
Leflunomide	**++**		**B**
Methotrexate	**++**		**B**
Nandrolone	**++**		**C**
Paracetamol (within one to two weeks at 2-4 g/day)	+		A
Phenytoin (initially increase risk; long-term decrease risk	+	+	C
Proton Pump Inhibitors e.g. omeprazole	+		B
Quetiapine	+		B
Ropinirole	**++**		**B**
Salicylates (topical) e.g. methyl salicylate	**++**		**B**
Sodium valproate i.e. valproic acid	**++**		**B**
Statins • **simvastatin** • fluvastatin, rosuvastatin	 **++** +		 **A** B
SSRIs e.g. citalopram, fluoxetine, sertraline	**++**		**B**
SNRIs e.g. desvenlafaxine, venlafaxine	**++**		**B**
Sulfasalazine	+		B
Tamoxifen	**++**		**B**
TCAs e.g. amitriptyline, doxepin	+		B
Testosterone	**++**		**B**
Thyroxine	+		B
Tramadol	+		B

Source: Micromedex 2.0 2015

Table 15 Potential interactions with complementary medicines

KEY

Severity of Interaction

Red: ++ The interaction may be life-threatening and/or require medical intervention to minimise or prevent serious adverse effects; or the drugs are contraindicated for concurrent use.

Black: + The interaction may result in an exacerbation of the patient's condition and/or require an alteration in therapy.

Level of evidence

A Controlled studies have clearly established the existence of the interaction.

B Documentation strongly suggests the interaction exists but well-controlled studies are lacking

C Available documentation is poor, but pharmacological considerations lead clinicians to suspect the interaction exists; or documentation is good for a pharmacologically similar drug

Interacting Complementary Medication	Increased risk of bleeding	Decreased risk of bleeding	Level of evidence
Black Tea / Green Tea		+	A/B
Co Enzyme Q10		+	B
Dan shen / Tan shen *Salvia miltiorrrhiza*	**++**		**B**
Dong Quai *Angelica sinensis*	+		B
Ginseng		+	B
Glucosamine +/- Chondroitin	+		B
St John's Wort *Hypericum perforatum*		**++**	**B**
Vitamin A, Vitamin E	+		B
Vitamin K		**++**	**A**

Source: Micromedex 2.0 2015

1.11 Patient counselling

It is important to provide patients with a warfarin patient education booklet which includes a table for recording INRs and dosages. These can be obtained by contacting the medication's manufacturing company.

Clinicians should provide patients with advice which includes the following:

- Always take the same brand of warfarin tablets.
- Take warfarin tablets at about 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 also 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.
- Ensure they have 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.

(Rossi 2015)

- Inform a doctor 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 (Clarke et al. 2006; Rossi 2015).

1.12 Auditing management of warfarin

Periodic auditing of INR test results is recommended, with a target of 60 per cent time in therapeutic range (Gallus et al. 2000; Baglin, Keeling & Watson 2005).

1.13 Guide for patients non-responsive to warfarin therapy

For patients at low risk of thrombosis whose INR result at day 8 is less than 1.4, the regimen in Table 16 can be used. Review adherence to therapy prior to considering the 6 mg daily dose recommendation.

Table 16 Guide for patients on 6mg on days 8 to day 14

Day to take INR test (Initiation = day 1)	INR	Daily Warfarin Dose (until next INR test)
Day 15	Less than 1.4 Unusual	Check medication adherence, drug interactions, etc. Increase to 10 mg if appropriate
	1.4 – 1.6	Increase to 8 mg
	1.7 – 1.8	Increase to 7 mg
	1.9 – 2.4	Maintain 6 mg
	2.5 – 2.9	Reduce to 5 mg
	3 – 4	Consider omitting one to two daily doses Reduce to 4 mg
	4.1 – 5	Omit two daily doses Check doses taken by patient Reduce to 4 mg
	More than 5	See Section 1.7 on *Management of High INR* Check dose taken by patient

Source: Janes, Challis & Fisher 2004

2. Review

This Guideline is due for review on: February 2018

Date of Last Review: 18/12/2015

Supersedes: Guidelines for warfarin management in the community v1_0

3. Business Area Contact

Medicines Regulation and Quality

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Phone: 07 3328 9818

4. Glossary of terms used in the policy and supporting documents

Term	Definition / Explanation / Details	Source
AF	Atrial fibrillation	
APTT	Activated partial thromboplastin time	
AVR	Aortic valve replacement	
$CHADS_2$	scoring system for risk of stroke in patients with atrial fibrillation	Gage et al. 2001
CHA_2DS_2-VASc	scoring system for risk of stroke in patients with atrial fibrillation	European Heart Journal (2012)
DVT	Deep vein thrombosis	
FFP	Fresh frozen plasma	
HAS-BLED	scoring system for risk of major bleeding	Pisters et al. 2010
$HEMORR_2HAGES$	scoring system for risk of major bleeding	Gage et al. 2006
INR	International Normalised Ratio	
IV	Intravenous	
LMWH	Low molecular weight heparin	
MVR	Mitral valve replacement	
PE	Pulmonary embolism	
VTE	Venous thromboembolism	

5. Approval and Implementation

Policy Custodian:

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Approving Officer:

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Approval date: 18/4/2016

Effective from: 18/5/2016

6. Version Control

Version	Date	Prepared by	Comments
1.0	10/09/2012	S Mathers	Based on initial draft by P Modlmayr, RFDS
2.0	18/04/2016	S Mathers/J Quin	Update due to new consensus guidelines

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