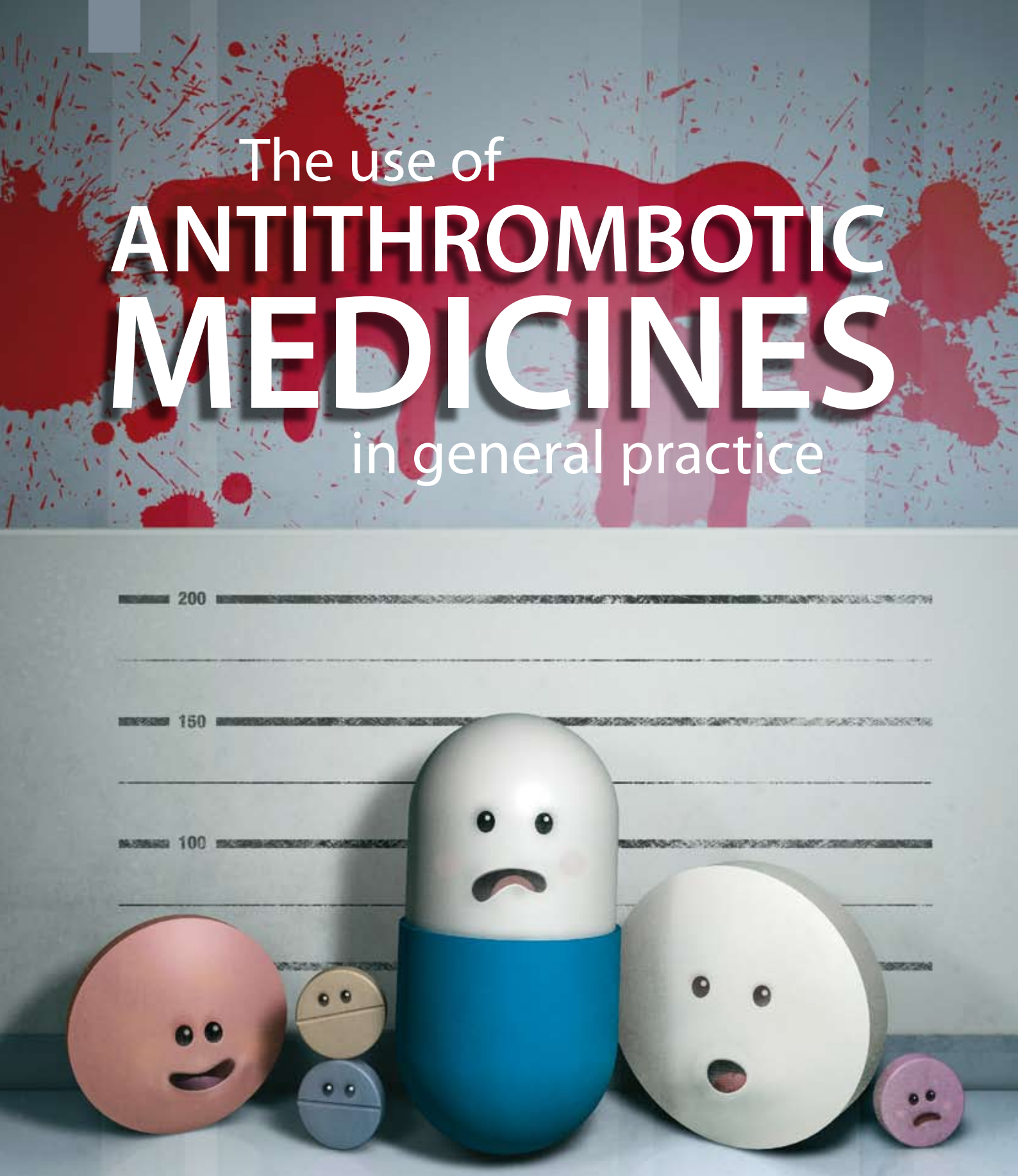
The use of ANTITHROMBOTIC MEDICINES in general practice



A CONSENSUS STATEMENT

In July 2011, a consensus forum was held in Wellington to discuss the use of antithrombotic medicines in general practice. This was attended by representatives from primary care, secondary care, bpac[nz], PHARMAC and the New Zealand Guidelines Group.

The conditions discussed were:

- Primary and secondary prevention of cardiovascular disease (including ischaemic stroke)
- Treatment after haemorrhagic stroke
- Prevention from thromboembolic events in patients with prosthetic heart valves or with haemodynamically significant valvular disease
- Venous thromboembolism (VTE) prophylaxis (post-surgery and for long haul travel) and treatment

The antithrombotic medicines associated with these conditions are: aspirin, clopidogrel, warfarin, dipyridamole and dabigatran (all fully funded with no restrictions on prescribing), enoxaparin and rivaroxaban (funded under Special Authority restriction).

This consensus statement represents the opinions of the experts involved, and although based on trial evidence, also reflects clinical practice. The advice given may therefore differ from some current guidelines.

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Primary prevention of cardiovascular disease including stroke–people without atrial fibrillation

Consensus

The role of aspirin for primary prevention of cardiovascular disease (CVD), including stroke, is controversial. Current evidence does not justify the routine use of low-dose aspirin, for the primary prevention of CVD in apparently healthy individuals, because of the potential risk of serious bleeds and the lack of beneficial effect on mortality. However, patients at high CVD risk (defined in the New Zealand Cardiovascular Guidelines as a cardiovascular risk of more than 15%) may benefit from aspirin.[1]

Primary prevention of cardiovascular disease including stroke – people without atrial fibrillation:

Medicine	Dose	Duration	Comments
Aspirin	100 mg daily	Lifelong	Cardiovascular risk > 15% only Individual assessment required

Evidence

Current evidence does not recommend the routine use of aspirin for the primary prevention of cardiovascular disease. Most guidelines continue to recommend aspirin for primary prevention in patients who are at increased CVD risk (e.g. >15%), however, individual assessment is required as recent evidence does not support routine use of aspirin in patients with risk factors such as diabetes and hypertension.

The Antithrombotic Trialist's (ATT) Collaboration was a key meta-analysis of primary prevention studies and showed a 0.06% reduction only in absolute risk with the use of aspirin.[2] There was no significant difference in cardiovascular mortality rate and the authors concluded that the benefit of using aspirin for primary prevention in low risk populations was very small. This and other similar evidence changed the way clinicians viewed the use of aspirin for primary prevention.[2, 3, 4]

This view has been reinforced in recent publications. Calculations from the ATT data have shown that the number needed to be treated (NNT) with aspirin for one year to prevent one cardiovascular event was 1666.[5] Updated meta-analyses have now included a total of nine primary prevention trials. Similar conclusions have been reached in these studies:

- Although aspirin reduced the risk of total cardiovascular events and non-fatal myocardial infarction, there was no significant reduction in the incidence of stroke, total coronary heart disease, cardiovascular mortality and all cause mortality.[6]
- If 1,000 people were treated with aspirin for five years, 2.9 major cardiovascular events would be prevented but aspirin would cause 2.8 major bleeds.[7]

The evidence of benefit of aspirin for primary prevention of stroke in people who have diabetes is also inconclusive, with several trials showing no benefit from the use of aspirin in these people.[8, 9, 10]

There is evidence that statins should be used as first-line treatment for primary prevention in people who have moderate to high CVD risk.[11] The addition of aspirin for these people appears to give no further benefit because the increased risk of bleeding offsets any improvement in cardiac morbidity.[2]

Primary prevention of stroke – people with atrial fibrillation

Consensus

Anticoagulation is recommended for the primary prevention of stroke in people with non-valvular atrial fibrillation (AF) who are at moderate or high risk of stroke. Both stroke and bleeding risk should be considered when making the decision to anticoagulate, using assessment tools such as $CHADS_2$ and HAS-BLED (see "Stroke risk assessment tools" over page).[12, 13] Co-morbidities, monitoring requirements and patient preference should also be considered when determining whether anticoagulation is suitable for a patient.

Once the decision to anticoagulate has been made, the next decision is which oral anticoagulant to use, i.e. warfarin or dabigatran.

Treatment of other modifiable risk factors such as hypertension, dyslipidaemia and smoking should also be initiated for all patients with AF.

For further information on choosing between dabigatran and warfarin, see "The use of dabigatran in general practice", BPJ 38 (Sep, 2011).

Assessment of stroke risk and management using $CHADS_2$ and CHA_2DS_2-VASc

	Medicine	Dose	Duration	Comments
$CHADS_2$ score ≥2	Anticoagulant – warfarin or dabigatran	Warfarin: dose to attain INR 2–3 Dabigatran: Aged under 80 years – 150 mg, twice daily, if creatinine clearance >30 mL/min Aged over 80 years* – 110 mg, twice daily, if creatinine clearance >30 mL/min	Lifelong	Creatinine clearance must be calculated if dabigatran considered Use dabigatran with caution if < 60kg or creatinine clearance 30–50 mL/min
$CHADS_2$ score <2	**Calculate CHA_2DS_2-VASc score**			
CHA_2DS_2-VASc score ≥ 2	Anticoagulant – warfarin or dabigatran	As above	Lifelong	Creatinine clearance must be calculated if dabigatran considered Use dabigatran with caution if < 60kg or creatinine clearance 30–50 mL/min
CHA_2DS_2-VASc score 1	Anticoagulant or aspirin (with preference for anticoagulation)			
CHA_2DS_2-VASc score 0	No treatment			

* There is some suggestion that a lower dose of dabigatran is appropriate for patients aged > 75 years, but at this stage no changes have been made to dosing recommendations in the medicine datasheet.

Stroke risk assessment tools

The risk of stroke in people with AF can be evaluated using a risk stratification tool such as $CHADS_2$ or the updated version, CHA_2DS_2-VASc, preferred by many clinicians. The updated tool puts greater emphasis on increasing age (≥75 years) and also incorporates additional risk factors for stroke – female gender, age group 65 – 75 years and a history of vascular disease, e.g. myocardial infarction, peripheral arterial disease.[14] Scores for each tool are calculated as follows:

$CHADS_2$	Score
Congestive heart failure	1
Hypertension	1
Age 75 years or older	1
Diabetes mellitus	1
Previous **S**troke or TIA	2
Maximum score	**6**

CHA_2DS_2-VASc	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75 years	2
Diabetes mellitus	1
Stroke/TIA	2
Vascular disease (prior MI, peripheral vascular disease)	1
Age 65–75 years	1
Sex **c**ategory (i.e. female gender)	1
Maximum score	**9**

N.B. Maximum score is 9 as age is either allocated one or two points

If the $CHADS_2$ score is ≥ 2, the patient should be anticoagulated. If a patient has a $CHADS_2$ score of less than 2, CHA_2DS_2-VASc can be used to further evaluate risk and to guide treatment choice.

A patient with a CHA_2DS_2-VASc score of 0 is truly low risk and does not need anticoagulation and may not even need aspirin. Anticoagulation is recommended for people with a CHA_2DS_2-VASc score ≥ 1.

Aspirin may be considered as an option for patients with AF who are unsuitable for anticoagulation, e.g. patients with severe liver disease, recent history of gastrointestinal bleeding.

HAS-BLED

This tool can be used to calculate the risk of bleeding when considering anticoagulant use. A score of ≥ 3 indicates a patient who may be at high risk of bleeding complications.[13]

HAS-BLED Bleeding Risk Score[13]	Score
Hypertension (systolic blood pressure > 160 mm Hg)	1
Abnormal renal and liver function	1 point each
Stroke (past history)	1
Bleeding (previous history of bleeding or predisposition to bleeding)	1
Labile INRs (unstable, high or insufficient time within therapeutic range)	1
Elderly (> 65 years)	1
Drugs or alcohol (including concomitant use of aspirin, other antiplatelet agents and NSAIDs)	1 point each
Maximum score	**9**

For further information about HAS-BLED, see "The warfarin dilemma", BPJ 31 (Oct, 2010).

Secondary prevention of stroke* – people without atrial fibrillation

*for people where the initial event was non-haemorrhagic

Consensus

In a patient with a history of transient ischaemic attack (TIA) or stroke, who does not have AF, antiplatelet treatment for secondary prevention should be initiated (provided there are no contraindications). Although aspirin has been shown to be effective in the secondary prevention of non-embolic stroke, there is evidence that treatment with clopidogrel is slightly more effective than aspirin. The combination of aspirin and modified release dipyridamole is slightly more effective than aspirin alone and provides similar benefits to treatment with clopidogrel. However, clopidogrel monotherapy is simpler and usually better tolerated by patients.

Treatment of other modifiable risk factors such as hypertension, dyslipidaemia and smoking cessation should also be initiated for all patients.

The management of TIA and a minor stroke are largely the same and both should be regarded as a medical emergency. The highest risk of a stroke is within the first week (particularly in the first 48 hours) after a TIA. If a patient presents with signs and symptoms of a stroke which are still present after one hour, then this event should be regarded as a stoke as the majority of "true" TIAs resolve within one hour. The main difference in management is that all patients with stroke should be referred immediately to hospital for investigation prior to commencing antithrombotic treatment due to the possibility of intracerebral haemorrhage (ICH). Antiplatelet treatment should be initiated immediately (after resolution of symptoms) for patients with TIA to avoid delay prior to assessment as the risk of ICH is extremely low.

For further information see "Transient ischaemic attack" (Page 30)

Secondary prevention of stroke – people without atrial fibrillation

Medicine	Dose	Duration	Comments
First-line: Clopidogrel	Loading dose of 300 mg followed by 75 mg daily	Lifelong	Although evidence and consensus opinion favours clopidogrel monotherapy first line, combination treatment with aspirin and dipyridamole or aspirin monotherapy remain alternative first-line choices
Second-line: Aspirin + dipyridamole	Aspirin 100 mg and dipyridamole 150 mg* twice daily	Lifelong	Consider for patients who cannot tolerate clopidogrel
Third-line: Aspirin alone	Aspirin 100 mg	Lifelong	Consider for patients who cannot tolerate clopidogrel or dipyridamole

*The funded strength of dipyridamole in New Zealand is the 150 mg long-acting tablet, however, in the majority of clinical trials the dose used was 200 mg extended release capsules, twice daily.

Evidence

The Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial found that clopidogrel significantly reduced the risk of the combined outcomes of ischaemic stroke, myocardial infarction or death in people with atherosclerotic cardiovascular disease.[15, 16] There was an approximately 9% reduction in relative risk of these events (N.B. figures for absolute risk were not reported). However, among the subgroup of people who had previous stroke, there was no significant difference in outcomes between aspirin or clopidogrel monotherapy (p value 0.26). The combination of aspirin and clopidogrel has not been shown to provide any greater benefit in preventing stroke and dual antiplatelet treatment significantly increases the risk of bleeding. This combination is, however, effective in acute coronary syndromes.[17, 18]

The Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial looked at the combination of modified-release dipyridamole with aspirin compared to clopidogrel. The results showed similar risks and benefits with each antiplatelet regimen.[19]

Evidence from the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) found treatment with aspirin and dipyridamole, compared with aspirin monotherapy, resulted in a reduction in absolute risk of 1.0% per year.[20]

Secondary prevention of stroke* – people with atrial fibrillation

*For people where the initial event was non-haemorrhagic

Consensus

Oral anticoagulants have been shown in a number of randomised controlled trials to be effective in reducing stroke in people with AF. Individualised bleeding risk should be considered prior to anticoagulation.

In addition to oral anticoagulation treatment, a patient with a TIA or stroke, who has AF, should also be started on a statin and an antihypertensive (usually an ACE inhibitor) unless there are contraindications. Aspirin should only be used in the immediate post-stroke period before the establishment of effective anticoagulation or in patients who are unable to tolerate ongoing oral anticoagulation.

Secondary prevention of stroke – people with atrial fibrillation

Medicine	Dose	Duration	Comments
Anticoagulant – warfarin or dabigatran	Warfarin: dose to attain INR 2–3 Dabigatran: Aged under 80 years – 150 mg, twice daily, if creatinine clearance > 30 mL/min Aged over 80 years – 110 mg, twice daily, if creatinine clearance > 30 mL/min	Lifelong	Stop aspirin and clopidogrel Creatinine clearance must be calculated if dabigatran considered Use dabigatran with caution if weight < 60kg or creatinine clearance 30–50 mL/min

Evidence

There is evidence that oral anticoagulation with warfarin reduces stroke risk more effectively than aspirin in people with AF.[21, 22] If oral anticoagulation is contraindicated, not indicated or is declined by the patient, aspirin should be prescribed, as it reduces the risk of stroke compared to placebo.

Evidence for the effectiveness of dabigatran in the secondary prevention of stroke in patients with non-valvular AF comes from the RE-LY trial.[23]

See "The use of dabigatran in general practice", BPJ 38 (Sep, 2011), for further discussion of the RE-LY trial.

In the Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA), which included people with AF aged over 75 years, the risk of a primary endpoint (stroke, intracranial haemorrhage or arterial embolism) was significantly lower with warfarin (1.8%) compared with aspirin (3.8%), and there was no evidence that warfarin caused more bleeding complications than aspirin.[24]

Secondary prevention after haemorrhagic stroke

Consensus

Patients with a suspected haemorrhagic stroke should be referred immediately to hospital (do not give aspirin) and decisions on treatment will be made in hospital after appropriate imaging has been completed.

In a general practice setting, decisions on treatment for patients who have a history of intracranial haemorrhage (ICH) may be difficult. Treatment choices are not straightforward, e.g., in a patient who has a history of ICH, who subsequently develops AF. The decision regarding medicines in these patients will depend on the individual patient circumstances, the site of the ICH, the underlying pathology, and co-morbidities. The care of these patients requires discussion with, and usually referral to, secondary care. Accurate documentation of the history of ICH must be available to guide treatment decisions.

Patients who do not have a documented history of ICH, but who may recall a problem or have information in their patient notes that may raise suspicion of a past ICH need to have this history clarified – this role will generally fall to the primary care team.

Secondary prevention of acute coronary syndrome*

*Acute coronary syndrome includes ST and non-ST elevation mycoardial infarction and unstable angina

Consensus

Early combination treatment with dual antiplatelet medicines is highly effective in patients with acute coronary syndromes. Treatment choice depends on the type and outcome of the event, the time since it occurred and the stability of the patient.

Evidence

In patients with acute coronary syndrome without ST-segment elevation, combined treatment with clopidogrel and aspirin gave a 20% reduction in relative risk of MI, stroke and cardiovascular death.[25]

Clopidogrel and aspirin should be used in combination for patients who have had angioplasty, insertion of a bare metal or a drug-eluting stent. The duration of treatment is usually 12 months except if a bare metal stent is used, where treatment is required for a minimum of six months, as outlined in the table over the page.

If aspirin is not tolerated, clopidogrel can be used as monotherapy.[25] Allergy or intolerance to both aspirin and clopidogrel is rarely seen, however, aspirin desensitisation therapy is available in some clinics around the country.

Secondary prevention of acute coronary syndrome

Scenario	Medicine	Dose	Duration	Comments
After acute event: no stent	Aspirin and clopidogrel	Aspirin 100 mg daily and clopidogrel 300 mg loading dose followed by 75 mg daily	12 months	After 12 months stop clopidogrel
After acute event: bare metal stent	Aspirin and clopidogrel	Aspirin 100 mg daily and clopidogrel 300 mg loading dose followed by 75 mg daily	12 months (do not stop treatment in first 6 months)	After 12 months stop clopidogrel
After acute event: drug eluting stent	Aspirin and clopidogrel	Aspirin 100 mg daily and clopidogrel 300 mg loading dose followed by 75 mg daily	12 months (do not stop treatment in this period)	After 12 months stop clopidogrel
After acute cardiac event: patients with indications for anticoagulation, e.g. AF	Aspirin and warfarin	Aspirin 100 mg daily and warfarin – dose to attain INR 2-3	Lifelong anticoagulation Aspirin for 6-12 months or lifelong if high CVD risk and lower bleeding risk	Warfarin is the preferred anticoagulant for these patients* Clopidogrel may also be given for 6–12 weeks although there is an increased risk of bleeding
After acute cardiac event: patients with a mechanical heart valve	Warfarin and aspirin	Warfarin – dose to attain INR 2.5-3.0 for aortic valve prosthesis, 3.0–3.5 for mitral valve prosthesis Aspirin 100 mg daily and in selected patients, clopidogrel 300 mg loading dose followed by 75 mg daily	Lifelong anticoagulation Aspirin for 6-12 months or lifelong if high CVD risk and lower bleeding risk Clopidogrel for 2–12 weeks depending on the use of stents and bleeding risk	Warfarin is the preferred anticoagulant for these patients* The risk of bleeding is substantially increased in patients taking warfarin, aspirin and clopidogrel and this combination should be used in consultation with a cardiologist
High risk patients: multiple events in more than one vascular territory, e.g. MI and stroke	Aspirin and clopidogrel	Aspirin 100 mg daily and clopidogrel 300 mg loading dose followed by 75 mg daily	Lifelong	Treatment for these high risk patients often requires secondary care input
Stable patients: no acute cardiac event in past 12 months†	Aspirin	If the event was cardiac: aspirin 100 mg daily	Lifelong	

N.B. Table excludes the immediate use of 300 mg aspirin used in the acute treatment of ACS

* Warfarin is preferred to dabigatran in these patients because:

- There is a possible increase in the risk of MI with dabigatran use
- Dabigatran is not currently indicated for use in patients with prosthetic valves or haemodynamically significant valvular disease

† In all stable patients >12 months post ACS, the combination of aspirin and anticoagulation is not usually required, but may be appropriate in selected high risk patients. Consultation with a cardiologist is recommended.

Prevention of thromboembolic events: post elective surgery

Consensus

Prophylaxis for the prevention of thromboembolic events post elective surgery is the responsibility of the surgeon, however, General Practitioners should be aware of the requirements and of the length of the post-operative course so that medicines are not continued (or discontinued) in error.

Prevention of thromboembolic events: post elective surgery

Medicine	Dose	Duration	Comments
Dabigatran*	220 mg (as 2 x 110 mg), once daily, if creatinine clearance > 50 mL/min 150 mg (as 2 x 75 mg), once daily, if creatinine clearance between 30-50 mL/min	Hip replacement: up to 35 days post- op Knee replacement: 10 days post-op	
Enoxaparin	40 mg sub cut, once daily	7-10 days	Dose reduced to 20 mg once daily in severe renal impairment (Creatinine clearance <30 mL/min)
Rivaroxaban*	10 mg tablet, once daily	Hip replacement: up to 5 weeks post- op Knee replacement: up to 2 weeks post-op	Special authority criteria apply Contraindicated in hepatic disease

*indicated for use after elective orthopaedic surgery

Prevention of thromboembolic events: prosthetic valves or haemodynamically significant valvular disease

Consensus

Warfarin is currently the only anticoagulant recommended for people with prosthetic heart valves or haemodynamically significant valvular disease (usually mitral valve stenosis). Dabigatran is currently not recommended for this indication. Anticoagulation treatment for these people will usually be initiated in secondary care. Aspirin is generally not effective for the prevention of thromboembolic events in these people although the risk of events is higher with no treatment.

Some patients may require combination treatment with warfarin and aspirin but guidelines differ in their recommendations regarding this.

Evidence

Patients with haemodynamically significant valvular heart disease or prosthetic valves were excluded from the RE-LY trial.[23] Patients with these conditions who are currently on warfarin must not be switched to dabigatran.

N.B. Patients who have valvular disease (excluding patients with severe mitral stenosis or prosthetic valves) but are in sinus rhythm do not usually require anticoagulation.

Prevention of thromboembolic events: prosthetic valves or haemodynamically significant valvular disease

Medicine	Dose	Duration	Comments
Warfarin	Warfarin – to attain INR of 2.5-3.5*	Lifelong	Dabigatran not indicated If high risk, aspirin may also be added

*The recommended INR range may vary depending on the type and location of the prosthetic valve

Prevention of thromboembolic events from long haul travel

Consensus

There is a risk of venous thromboembolism (VTE) during travel, particularly with longer flights (> four hours).

People at high risk of VTE include those with pro-thrombotic states (e.g. deficiencies of antithrombin III, protein C, protein S), a history of previous VTE, recent surgery or a significant medical illness. In these people consideration should be given to the use of: [26]

- Correctly fitted compression stockings which reduce the incidence of VTE by approximately 18 times in high risk people
- Prophylactic low molecular weight heparin (one injection on the day of travel). There is evidence to support the use of enoxaparin, although this medicine is not funded for this indication.

There is currently no evidence to support the use of dabigatran or rivaroxaban for VTE prophylaxis during travel. Aspirin is not adequate for prophylaxis and the risks of adverse effects (e.g. bleeding) outweigh the benefits of treatment. Routine use of prophylactic medicines for long haul travel is not necessary for people with no risk factors for VTE.

The following advice should be given to all people who are travelling long distances:[27]

- Sitting in an aisle seat provides more opportunity for movement. Also consider exercising leg muscles while seated and walking whenever possible.
- Ensure adequate hydration and avoid alcohol, particularly if combined with sedative medicines

Treatment of VTE

Treatment for VTE is increasingly initiated in the community with the availability of low molecular weight heparin (LMWH). LMWH is used until an INR level of 2–3 is attained for two consecutive days. Warfarin is used simultaneously, with the duration of treatment varying with individual circumstances.

Dabigatran is not currently indicated for use in the treatment of VTE.

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