

Antithrombotic therapy in clinical practice

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Highlights - Hoogtepunte

- A condensed overview of the physiology of primary and secondary haemostasis, and thrombolysis.
- Practical prescription guidelines for the different treatment modalities.
- Anti-platelet therapy and the prevention of cardio- and cerebrovascular disease. What is the primary and secondary cardio- and cerebrovascular risk reduction and who will benefit from it more?
SA Fam Pract 2003;45(3):30-35
- 'n Bondige oorsig oor die fisiologie van primêre en sekondêre hemostase en trombolise.
- Praktiese voorskrifriglyne vir die verskillende behandelingsmoontlikhede.
- Anti-plaatjieterapie en die voorkoming van kardio- en serebrovaskulêre siekte. Wat is die primêre en sekondêre risikovermindering van kardio- en serebrovaskulêre siekte en watter pasiënte sal meer daarby baatvind?

Haemorrhage, intravascular thrombosis and embolism are common clinical manifestations of many diseases. Unregulated activation of the haemostatic system may cause thrombosis with embolism, which reduces blood flow to critical organs (eg brain, myocardium).

NORMAL HAEMOSTASIS

Primary haemostasis (Figure 1):

Sequence of events

1. Vascular injury.
2. Von Willebrand factor: It "fixes" (adheres) the platelet via its glycoprotein GpIa/IIa receptor, to adhere to the collagen fibrils exposed by the injury.
3. After "activation" of the platelet, platelets form a "plug" via GpIIb/IIIa, which links fibrinogen to platelets.

"Activated" platelets produce, among other substances, Thromboxane A₂, which contributes significantly to platelet aggregation.

Secondary haemostasis:

This is the reaction of the plasma coagulation system, which leads to fibrin formation after the initial platelet plug (See Figure 2).

Thrombolysis:

Clot lysis begins immediately after formation of the haemostatic plug (Fig. 3).

The endothelial cell secretes urokinase (UR) and tissue plasminogen activator (tPA) – they change plasminogen to plasmin. Plasmin lysis turns the fibrin clot into fibrin degradation products (FDP).

HIGH-RISK PATIENTS FOR THROMBOSIS:

1. Immobilisation: Any form of prolonged immobilisation, especially post surgery.
2. Chronic congestive heart failure.
3. Patients with atherosclerotic vascular disease, eg coronary artery disease.
4. Patients with underlying malignancy.
5. Pregnancy.

Many of these high-risk groups have inherited or acquired hypercoagulable states.

DRUG THERAPY

Anticoagulation therapy:

Heparin:

- Heparin binds to and activates

antithrombin III.

- It dramatically reduces thrombin formation and therefore fibrin formation.
- *Unfractionated, conventional heparin*, when used, should be of sufficient dose to keep the activated partial thromboplastin time (PTT) 1.5-2 times the patient's pre-heparin PTT.

A tailor-made aspirin tablet for cardiovascular protection

"When aspirin is given for primary prevention of vascular events, available data support using 75 to 81mg/day."

R.G. Hart et al. Arch. Neurol. 2000;57:326

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Figure 1: Primary haemostatis

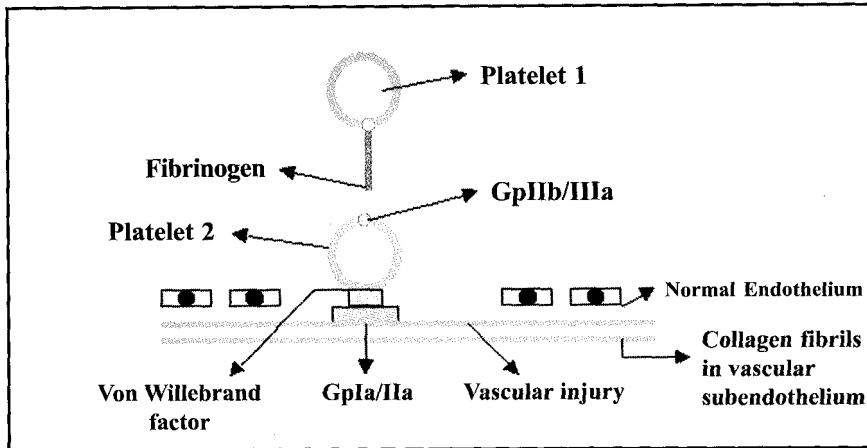


Figure 2: Diagramme of coagulation - Secondary haemostasis (Plasma coagulation)

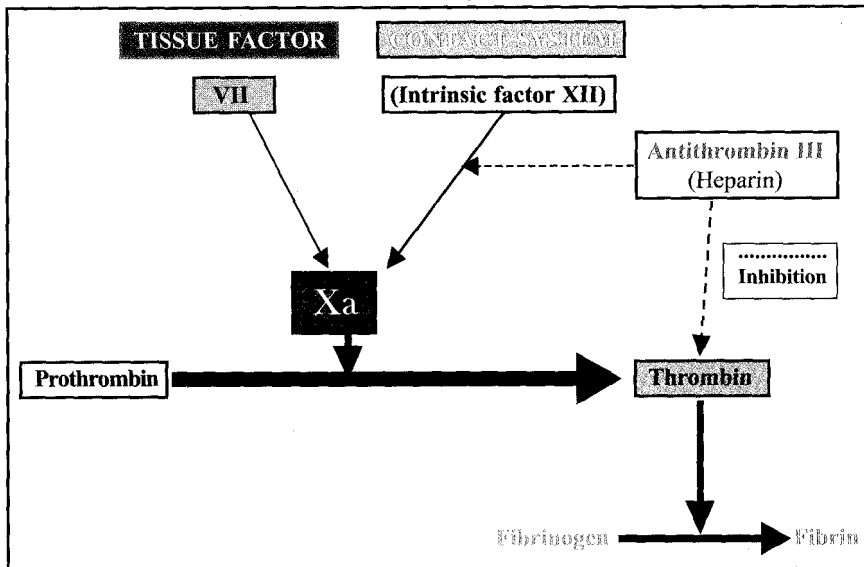
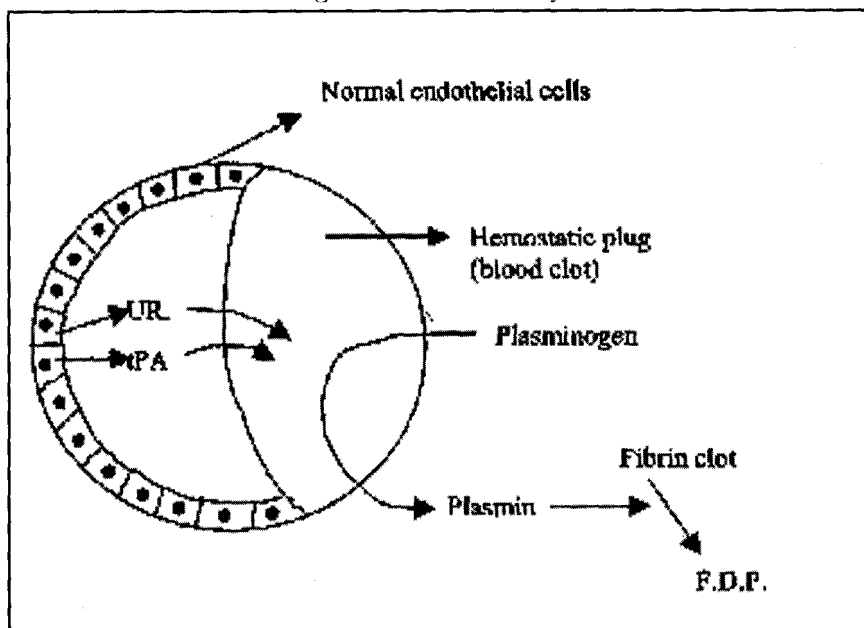


Figure 3: Thrombolysis



Complications of heparin:

The major complication is bleeding. Increased risk for bleeding:

- Advancing age.
- Any serious concurrent illness.
- Heavy alcohol intake.
- Concomitant use of aspirin.
- Renal failure.

Treatment of bleeding:

1. Stop heparin (has a short half-life).
2. Give protamine sulphate if necessary.
3. There are many other, rarer side-effects, eg thrombocytopenia.

Low-molecular-weight heparins (LMWHs) are more expensive, but:

1. They can be administered twice daily subcutaneously.
2. Their pharmacokinetics are so predictable, that PTT monitoring is not necessary.
3. They are less immunogenic, therefore less likely to cause thrombocytopenia. LMWH work by inhibiting factor Xa.
4. They have long half-lives.
5. Incidence of heparin-induced thrombocytopenia is much lower.

Enoxiparin (Clexane®)

LMWH may be superior to unfractionated heparin for the treatment of non-ST-elevated myocardial infarction [non-STEMI].

Dose: 1 mg/kg every 12 hours.

- Essence study demonstrated a reduction of endpoint (death; MI; angina) of 16.6% vs 19.8% for I.V. unfractionated heparin.
- TIMI IIB study: Endpoint reduction 14.2% vs 16.7% for unfractionated heparin.

Dateparin (Fragmin®)

This is commercially available.

Direct thrombin inhibitors

These drugs inactivate thrombin directly, without the need for antithrombin III.

- Bivalirudin [Hirulag®]: Several short-term advantages have been shown, but more trials are still being done.

Oral anticoagulation

Warfarin (a coumarin compound) causes a state of vitamin K deficiency,

Table 1: Drug-dose schedule for Acute Coronary Syndromes (ACS)

<p>Heparin for patients who received Alteplase [STEMI] < 6h</p> <ul style="list-style-type: none"> Initial heparin bolus: 60 u/kg [maximum 4 000 u] Followed by 12 u/kg/hour infusion (maximum 1 000 u/h).
<p>Heparin for non-ST-elevated myocardial infarction [non-STEMI] (If no Alteplase is given):</p> <ul style="list-style-type: none"> Initial bolus 60-70 u/kg [maximum 5 000 u]. Followed by 12-15 u/kg/hour infusion.
<p>GOAL Heparin therapy in ACS:</p> <ul style="list-style-type: none"> PTT 50-70 seconds.

which slows *thrombin* generation by impairing the activity of prothrombin. The simplest way to introduce anti-coagulation is to administer a single dose daily and to monitor the INR (International Normalised Ratio method). In this method the patient's PT (Prothrombin time) is compared to the mean PT for a group of normal individuals.

Frequent monitoring of INR is mandatory for every patient on oral warfarin. Drug interactions may cause abrupt fluctuations of INR with thrombosis or serious bleeding as complications. (See Table 2).

Table 2: INR targets:

<p>Target INR 2.0-3.0</p> <ul style="list-style-type: none"> Prophylaxis of venous thrombosis Treatment of venous thrombosis Treatment of pulmonary embolism Prevention of systemic embolism <ul style="list-style-type: none"> Atrial fibrillation. Tissue heart valves. Valvular heart disease.
<p>Target INR 2.5-3.5</p> <ul style="list-style-type: none"> Mechanical prosthetic valves (high risk). Treatment of acute myocardial infarction.

- To reverse the anticoagulant effect of warfarin:
- Fresh-frozen plasma: works immediately but effect lasts only a few hours.
 - Vitamin K: takes 8-12 hours to become effective.

Haemorrhagic skin necrosis is a rare complication of the use of heparin.

Fibrinolytic therapy

Fibrinolytic system:

Normally, fibrinolysis (dissolving the blood clot) is initiated by the release of tPA or pro-urokinase from endothelial cells. Activators of the fibrinolytic system accelerate clot lysis when administered by activating plasminogen (See Figure 4).

Fibrinolytic agents used:

1. Streptokinase: This is isolated from haemolytic streptococci. Unfortunately, many people have anti-streptococcal antibodies in their serum, which will cause severe febrile and allergic reactions when streptokinase is given. **Maximum dose** 1.5 million units I.V. as infusion over 1 hour. Therapy can reduce mortality by 23% after one month and 9.5% mortality reduction by one year.
2. Tissue-type Plasminogen Activator (tPA): tPA is a naturally occurring molecule released from endothelial

cells. Commercially it is produced using recombinant DNA technology to produce alteplase [Actilyse®]. **Maximum dose** 100 mg over 1½ hours.

Therapy can reduce the mortality by 20% after 1 month and by 21% after 6 months.

3. Tenecteplase [Metalyse®]: Weight-adjusted dose from 30 mg (<60 kg weight) to 50 mg (≥90 kg weight).

Indications

ST-elevated myocardial infarction [STEMI] within 6 hours of onset of infarction.

Side-effects

All agents cause haemorrhage, therefore major contraindications to their use are bleeding risks – such as recent surgery,

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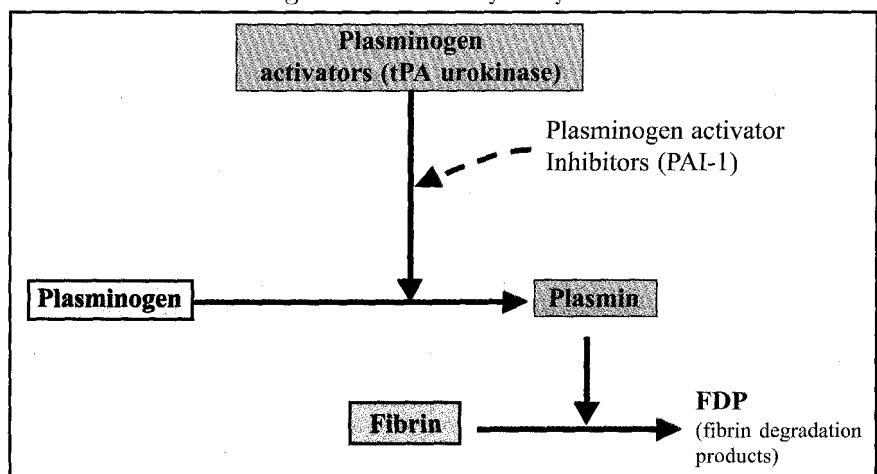


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Figure 4: Fibrinolytic system



severe hypertension, neurological lesions (CVA, head injuries and intracranial aneurysms) or gastrointestinal bleeding.

Timing of administration

The ideal time to administer fibrinolytic therapy is within 6 hours after onset of acute chest pain. This time to fibrinolytic therapy can be extended to 12 hours but after that there is very little, if any, benefit.

Antiplatelet Drug Therapy

Aspirin:

A single dose of aspirin inhibits thromboxane A_2 and the platelet then remains inactive for the rest of its lifespan (7-10 days).

Indications

- Primary prevention:** Taking the trials into account, the use of aspirin leads to 32% reduction in non-fatal MI and 13% reduction in any vascular event with a trend towards increased risk of haemorrhagic stroke. The benefit has only been shown for people at least 45-50 years old. (See Table 3).
- Acute coronary syndrome:** In unstable angina and non-STEMI [non-ST elevation] MI aspirin causes a 50% reduction in death or MI. The beneficial effect of aspirin in acute myocardial infarction has been demonstrated with a 23% reduction in vascular mortality by aspirin (vs 25% reduction in death with streptokinase). But if both aspirin and streptokinase are used simultaneously the mortality reduction is 42%.
- Secondary prevention:** Aspirin reduces the incidence of second infarctions by 25%.
- TIA/stroke:** Aspirin reduce the frequency of transient ischaemic attacks (TIAs). Aspirin also reduces the risk of second stroke by 25%.

Aspirin dosage:

- In acute events:**
160 mg/day-320 mg/day.
- Long-term therapy:**
75-100 mg (this dose is effective with least GI bleeding). Enteric-coated aspirin application aims to reduce gastrointestinal side-effects.

Outcomes at 3.8-6.8 years	Event rates			
	Aspirin	Placebo	RRR (95%)	NNT (95% CI)
Myocardial Infarction	1.7%	2.4%	30% [20 to 38]	150 [113 to 224]
All cardiovascular events	4.5%	5.2%	13% [6 to 19]	149 [97 to 317]
All cause mortality	3.2%	3.4%	6% [3 to 14]	N.S.
Bleeding complications	1.0%	0.7%	Relative risk increase 63% [34-99]	NN to harm 375 [251-739]
Final analysis: Aspirin for primary prevention:				
<ul style="list-style-type: none"> In persons at high risk for C.V.D., aspirin reduces the incidence of coronary artery disease. Aspirin does not reduce all-cause mortality. Reduction of C.A.D. is associated with an increase of bleeding complications. 				

Outcome event	Aspirin	Clopidogrel	RRR [95% CI]
Ischemic stroke			
M.I.	5.83%	5.32%	8.7% [0.3 to 16.5]
Vascular death			
Death from any cause	3.11%	3.05%	2.2% [-9.9 to 12.9]

Gp IIb/IIIa inhibitors (antagonists)

Final platelet aggregation is mediated through the Gp IIb/IIIa receptors on platelets binding to one another via fibrinogen. This is the rationale for these agents. They do *not* block Thromboxane A_2 , therefore if used with aspirin (which does block Thromboxane A_2) they have an enhanced action.

Three drugs are currently used for acute coronary syndrome treatment or in coronary intervention:

1. Abciximab [ReoPro®]
2. Eptifibatide [Integrilin®]
3. Tirofiban [Aggrastat®]

These agents are administered intravenously in the abovementioned very specialised situations and in the treatment of acute coronary syndrome they reduce composite end points in patients who are treated medically or with a percutaneous coronary intervention.

Dipyridamole

The precise antiplatelet action is unknown. This drug is weak on its own,

but enhances the beneficial effect of aspirin to prevent progression of peripheral occlusive arterial disease or for the secondary prevention of ischaemic stroke.

New oral antiplatelet agents

These are thienopyridine derivatives. They inhibit ADP-dependent pathways of platelet activation. They have a slow onset of action.

- **Ticlopidine [Ticlid®]:** Severe neutropenia has been noted up to 1% of patients. A rare, fatal side-effect is TTP (thrombotic thrombocytopenic purpura).
- **Clopidogrel [Plavix®]:** Severe neutropenia occurs much less than with Ticlid. The CAPRIE-study demonstrated that Plavix® significantly reduces events in high-risk patients. (See Table 4).

In patients similar to the CAPRIE study, aspirin would be expected to prevent 19 major events versus 24 for Plavix® for each 1 000 patients treated for one year.

Clopidogrel (Plavix®) for patients undergoing PCI (percutaneous coronary intervention)

- This is the PCI Core Trial: Plavix® vs Placebo.
- **Primary endpoint:** (CV death; MI; urgent revascularisation):
 - 45% reached endpoint on Plavix®.
 - 6.4% reached endpoint on Placebo.

RR:
0.70 [95% CI: 0.50-0.97](p=0.03)

RR reduction:
30% [95% CI: 3-50%]

CONCLUSION

This short summary should be adequate for practitioners as a core knowledge from which they can employ anti-thrombotic treatment modalities. □

Please refer to CPD Questionnaire on page 55.

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Advertorial

American Heart Association rapid access journal report: Clopidogrel reduces death, stroke, heart attack now and later

DALLAS, Feb. 18 – The blood thinner clopidogrel, when used with aspirin, reduced the risk of subsequent heart attack, stroke and death in people who came to the emergency department with new or increasing chest pain or a heart attack, according to a report in today's rapid access issue of *Circulation: Journal of the American Heart Association*.

Researchers also found that the drug's benefits emerged within hours of administration and continued for up to a year when patients took it daily after hospital discharge.

Researchers in this study looked at whether adding clopidogrel to aspirin therapy would further benefit these high-risk patients.

Previous studies on clopidogrel have shown benefit in these patients, but the drug's effects over this length of time have never been reported on such a large population, says study co-author Shamir R. Mehta, M.D., assistant professor of medicine at McMaster University in Hamilton in Ontario, Canada.

Emergency department physicians in 28 countries participated in the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial, which involved 12,562 patients with unstable angina or non-ST segment elevation heart attack. Patients had an average age of 64 and 38 percent were women.

Patients in the study received either clopidogrel or placebo. All were treated with aspirin. Patients in the clopidogrel group received an immediate loading dose of 300 milligrams (mg) of the medication, followed by 75 mg each day for up to one year.

Researchers found that clopidogrel had a beneficial effect within hours of the first dose. Within the first 30 days, 5.4 percent of patients in the placebo group and

4.3 percent of patients in the active group had a heart attack, stroke or death. This meant that clopidogrel users had a 21 percent reduction in major events. After 30 days, 6.3 percent of those in the placebo group suffered a major event versus 5.2 percent in the clopidogrel group – an 18 percent difference.

"It is important to note the apparent universality of these results," Mehta says. "The benefit of combined aspirin and clopidogrel therapy was observed against a broad range of clinical practices in multiple countries."

Patients on clopidogrel had no significant excess in life-threatening bleeds; however, there was an excess of non-life-threatening bleeds, according to the study. The researchers write that benefits of the drug far outweighed the risk of bleeding.

Mehta says that the study's results can change the practice of medicine in important ways. "Clopidogrel gives cardiologists a new alternative for use in this group of patients to improve outcomes."

Mehta's results support the American Heart Association/American College of Cardiology guidelines for managing acute coronary syndromes, which recommend the short-term use of clopidogrel, and suggest that longer-term use may be beneficial.

"Both aspirin and clopidogrel should be initiated early and continued long-term, with other medications as appropriate," Mehta says. "The combined use of these treatments will lead to the greatest benefits in the largest number of patients."

Co-authors are: Salim Yusuf, MBBS; Feng Zhao, MSc; Bernard Gersh, MBChB; Patrick Commerford, MBChB; Mel Blumenthal, MD; Andrzej Budaj, MD; Thomas Wittlinger, Dr Med; and Keith A.A. Fox, MBChB.