9 – Antithrombotic agents: Platelet inhibitors, acute anticoagulants, fibrinolytics, and chronic anticoagulants

KEITH A.A. FOX,
HARVEY D. WHITE,
BERNARD J. GERSH,
LIONEL H. OPIE

> *The Emperor said: "I wonder whether breathlessness results in death or life?"*
>
> *Chi'i P answered: "When there are blockages in the circulation between the viscera, then death follows."*
>
> *The Emperor said: "What can be done with regard to treatment?"*
>
> *Chi'i P replied: "The method of curing is to establish communication between the viscera and the vascular system."*
>
> *The Yellow Emperor's Classic of Internal Medicine (circa 2000 BC)*

Mechanisms of thrombosis

The proaggregatory and antiaggregatory factors of the hemostatic system are normally finely balanced, opposing mechanisms. To protect against vascular damage and the risk of bleeding too strong, the proaggregatory system is poised to rapidly form a thrombus to limit any potential hemorrhage. As coronary endothelial damage is a prominent feature of ischemic heart disease, there is a constant risk that antiaggregatory forces will be overcome by the proaggregatory forces, with the risk of further vascular damage and, potentially, thrombosis.

The three main types of agent discussed in this chapter act at different stages of the thrombotic process. First, *platelet inhibitors* act on arterial thrombogenesis and help prevent consequences such as myocardial infarction (MI) and transient ischemic attacks (TIAs). Second, *anticoagulants* given acutely (e.g., heparin) limit the further formation of thrombus, and, when given chronically (e.g., warfarin), help prevent thromboembolism from a dilated left atrium or from the venous system. Both antiplatelet and antithrombotic agents are required to inhibit thrombotic complications of percutaneous coronary intervention (PCI) with revascularization. Third, *fibrinolytic agents* are most useful in the setting of acute arterial thrombosis and occlusion, such as ST-elevation myocardial infarction (STEMI) and peripheral arterial thrombosis, especially when prompt mechanical revascularization (primary PCI) is not feasible. The different sites of action of these three types of agent mean that combination therapy can be beneficial. For example, fibrinolytic agents are used together with antiplatelet agents and anticoagulants in the management of acute myocardial infarction (AMI), but the greater efficacy of combinations is offset by the increased incidence of bleeding.

The *formation of thrombus* (clot in Fig. 9-1) occurs in four steps according to the cell-based concept that stresses the initial role of tissue factor:[1-3] (1) *Subendothelial tissue factor is exposed* to circulating blood as when vascular endothelium is damaged as by atherosclerotic plaque rupture. (2) *Coagulation factors are rapidly activated* by tissue factor to generate thrombin, thus converting fibrinogen into fibrin, which is an essential step to thrombus –formation. (3) *Platelet adhesion, activation, and aggregation* occur almost simultaneously as thrombin acts on the platelets already adhering to the site of injury (Fig. 9-1). During platelet activation there are shape and conformational changes. Activated platelet receptors promote aggregation by cross-links that result in the formation of the *primary platelet plug.* Thrombin, generated both by coagulation factors and platelets (next section), is a very powerful stimulator of platelet adhesion and aggregation. Thrombin forms fibrin, which stabilizes the inherently weak primary platelet plug. Thus platelet

adhesion, activation, and aggregation are overlapping processes, with the platelets releasing substances that further promote aggregation and cause vasoconstriction. (4) *Thrombus forms* as fibrin forms polymer cross-links and aggregated platelets tightly combine. The thrombus is not free floating, but adheres to the damaged vessel wall by platelet adhesion.[4] However, fragments of thrombus and platelet aggregates may embolize, stimulating changes in vascular tone and potentially causing microinfarcts in the distal territory. The typical arterial thrombus at the site of a coronary stenosis has a white head caused by platelet aggregation, and a red friable clot forming distally in continuity to the thrombus, caused by stasis beyond the lesion.

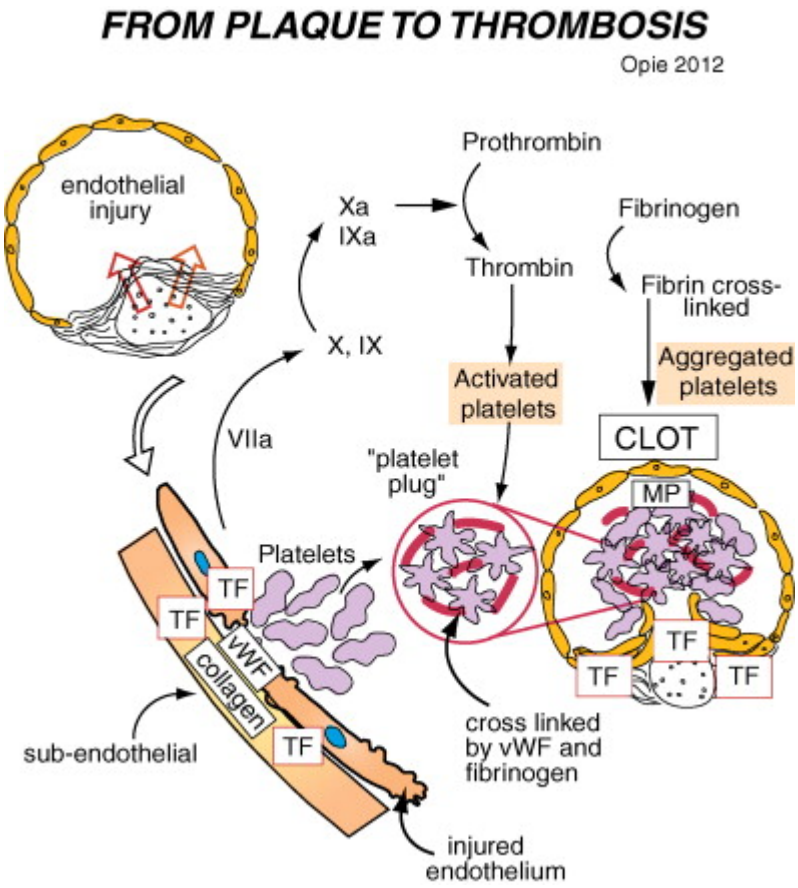

Figure 9-1 From unstable plaque to thrombus. As the plaque becomes unstable with endothelial damage, platelets become exposed to tissue factor (TF) found in either the damaged dysfunctional endothelium or in the subendothelial tissue. TF, acting via factor VIIa (and IXa), activates factor X to Xa, which then converts prothrombin to thrombin. Thrombin converts fibrinogen to fibrin and activates platelets. Platelets then change shape and readily aggregate under the influence of fibrin and other cross-linking molecules (see Fig. 9-2) that bind the platelets together to form the stable fibrin-linked clot (thrombus). Further activation of the coagulation system occurs via TF conveyed in microparticles (MP) to the developing thrombus (TF in lumen of the artery, *bottom left*). There are several paths for rapid self-amplification of these complex platelet changes, including those shown in Figure 9-2. *vWF,* von Willebrand factor.
(Figure © L.H. Opie, J.J.S Opie, 2012.)

Tissue factor and thrombin.

Tissue factor and thrombin warrant more detailed consideration. Tissue factor is a cell surface glycoprotein (Gp) abundantly expressed in damaged endothelial and exposed subendothelial cells, and in the atherosclerotic plaque (Fig. 9-2). Tissue factor is also derived from circulating *microparticles* released during plaque rupture.[3] Tissue factor forms a complex with and activates coagulation factor VII. Factor VIIa activates factor X to Xa (first step of the final common coagulation pathway), both directly and indirectly by also activating factor IX (part of the intrinsic pathway, next section). Factor Xa converts prothrombin to thrombin. Although thrombin is the end-product of the coagulation process, it also activates two platelet receptors (protease-activated receptors [PARs], Table 9-1).[5] Signals from both receptors lead by different

routes to rapid platelet activation (Figs. 9-3, 9-4).[6] Thrombin also positively feeds back on the coagulation pathway activating factors including V, VIII, XI, and XIII (these are shown in Fig. 9-5). XIIIa is necessary for full stabilization of the fibrin clot. *Thrombin is thus the lynchpin of the coagulation process.*

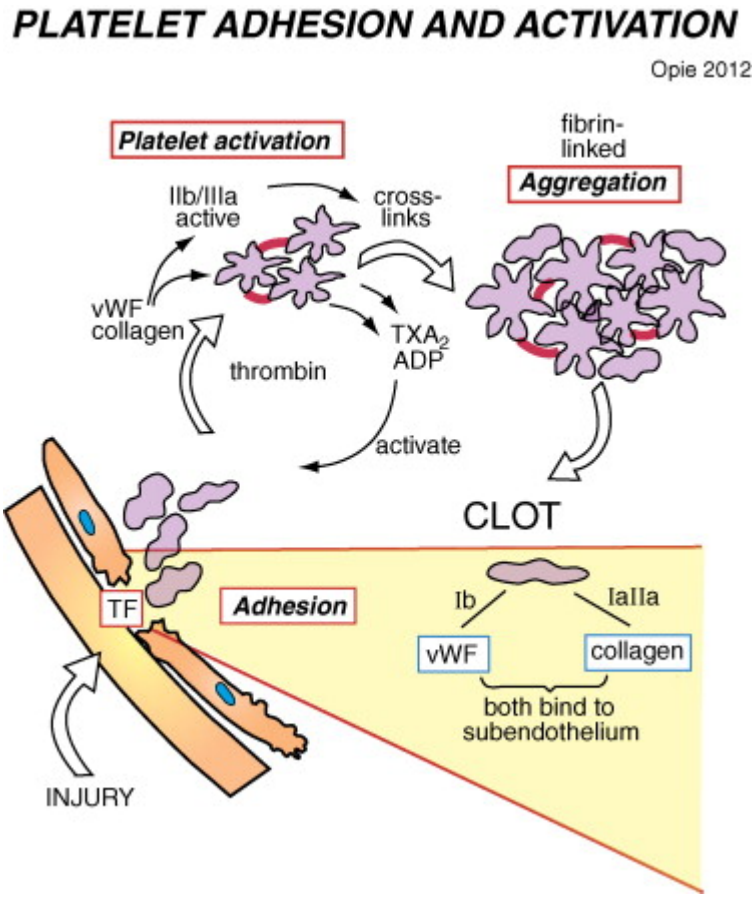

Figure 9-2 Platelet adhesion and activation. Injury to the endothelium exposes the subendothelial receptors for von Willebrand Factor (vWF) and collagen that promotes adhesion of platelets at the site of injury. Platelet activation then occurs under the influence of thrombin, rapidly formed by the effects of subendothelial tissue factor (TF), also exposed by the injury. Thus the glycoprotein IIb/IIIa receptor is now activated, allowing the vWF and fibrinogen to form strong cross-links between them. Platelet activation also liberates thromboxane A2 (TXA2) and adenosine diphosphate (ADP), which further promotes platelet activation (self-amplification; see Fig. 9-3). The overlapping third stage of aggregation occurs as fibrin, also rapidly formed by the activation of the extrinsic and intrinsic pathways, binds the platelets even more tightly together. The result is the formation of the thrombus (clot).
(Figure © L.H. Opie, J.J.S Opie, 2012.)

Table 9-1 -- Platelet Receptors and Their Function

Receptor	Alternate or Related Name	Function	Therapeutic Inhibitor	Reference
GpIb-IX-V (receptor complex)	GpIbα	Adhesion receptor; tethers platelets to tissue-bound vWF	None	9
GPVI/FcR-γ	GpIa	Binds collagen to platelets; generates inside-out integrin activation	None	4,8
αIibβ3	GpIIbIIIa (integrin)	Binds fibrinogen and vWF to form platelet crosslinks and platelet plug	AbciximabTirofiban Eptifibatide	4
α2β1	GpIaIIa (integrin)	Collagen receptor	None	4.8

Receptor	Alternate or Related Name	Function	Therapeutic Inhibitor	Reference
$P2Y_1P2Y_{12}$	ADP receptors (G-protein linked)	Platelet activation; Ca ↑ by IP_3 ↑ ($P2Y_1$) or cAMP ↓ (Y_{12})	$P2Y_{12}$ receptor:Clopidogrel Ticlopidine Prasugrel AZD6140 Cangrelor	5,10
PAR	Thrombin, TXA_2 (G-protein linked receptors)	Respond to thrombin and TXA_2 to activate platelets	Aspirin, indirectly (blocks TXA_2 synthesis)	5

ADP, Adenosine diphosphate; *Ca,* calcium; *cAMP,* cyclic adenosine monophosphate; *PAR,* protease activated receptors; *TXA_2*, thromboxane A_2; *vWF,* von Willebrand factor.

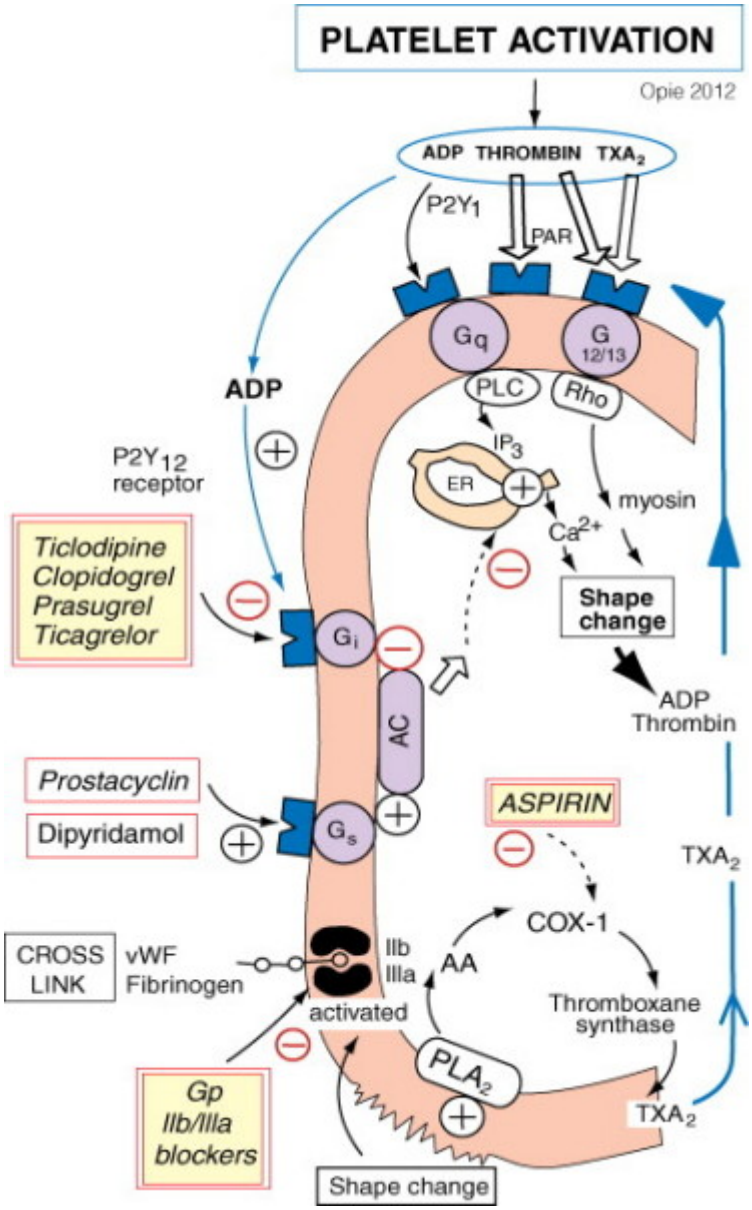

Figure 9-3 Platelet activation and receptors involved. Different platelet inhibitors act at different sites and on different mechanisms, ultimately to inhibit the calcium-dependent pathways of platelet activation. Note the self-amplification platelet activation cycle on the *right side* of the figure, initiated by platelet membrane damage that "exposes" and alters membrane configuration, and activates crucial receptors (thrombin, thromboxane A2 [TXA2], glycoprotein (Gp) IIb/IIIa, and others). *AC,* Adenyl cyclase; *ADP,* adenosine diphosphate; *Ca2+*, calcium; *ER,* endoplasmic reticulum; *Gi*, G protein, inhibitory form; *Gs*, G protein, stimulatory form; *PAR,* protease-activated receptors; *PLC,* phospholipase c; *Rho,* Rho kinase; *vWF,* von Willebrand factor.
(Figure © L.H. Opie, J.J.S Opie, 2012.)

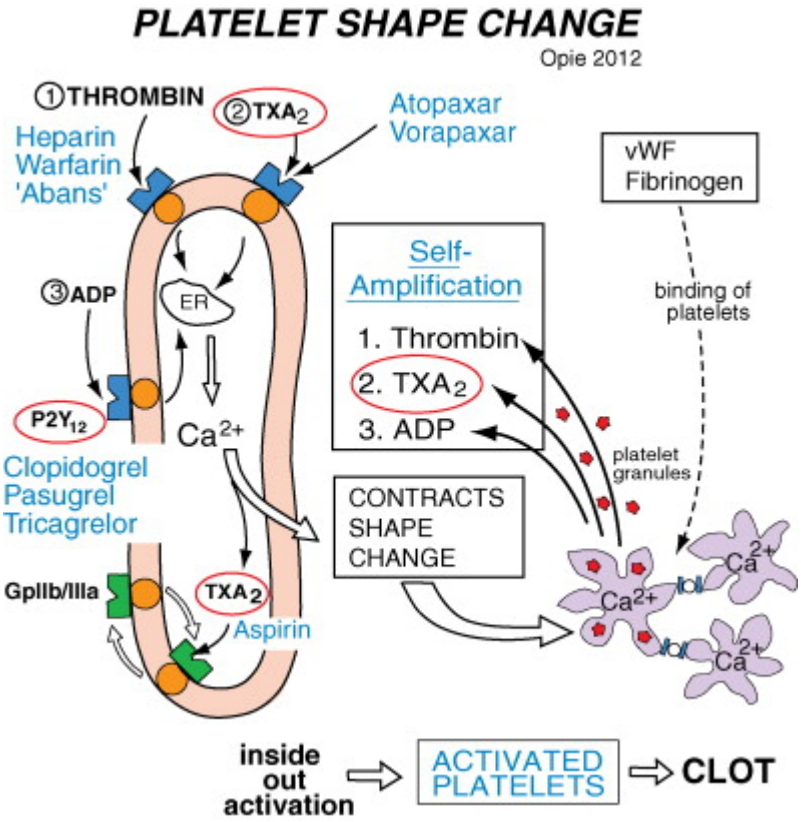

Figure 9-4 Platelet shape change. Note the process of self-amplification. *'Abans,'* dabigatran, rivaroxaban, apixaban; *ADP,* adenosine diphosphate; *Ca2+*, calcium; *ER,* endoplasmic reticulum; *Gp,* glycoprotein; *TXA2*, thromboxane A2; *vWF,* von Willebrand factor.
(Figure © L.H. Opie, 2012.)

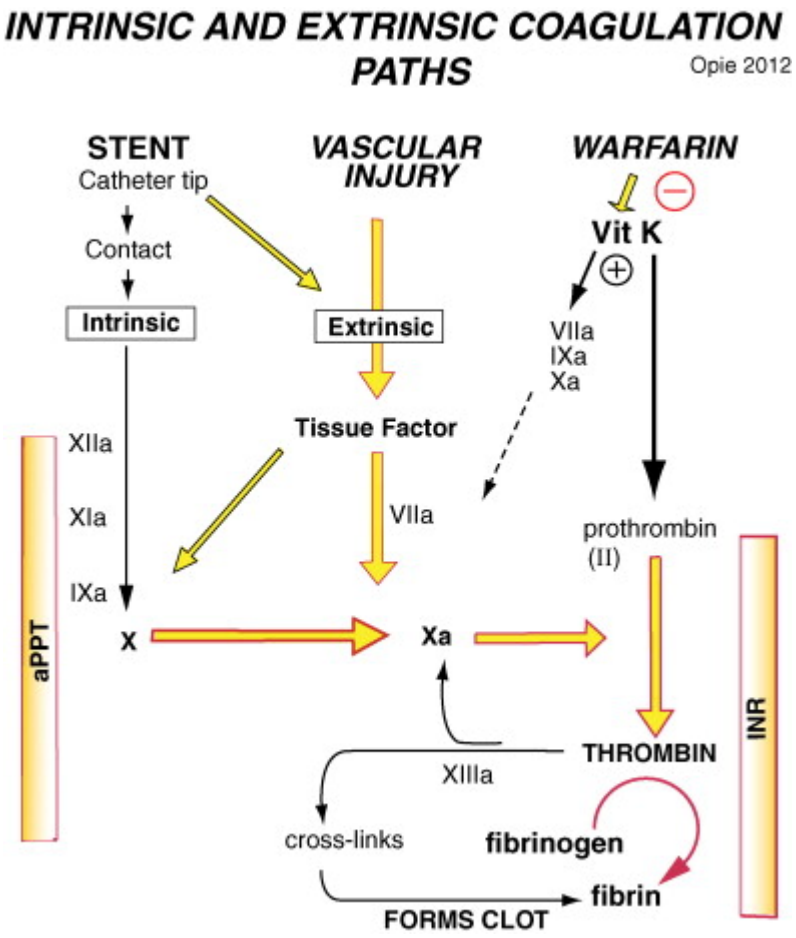

Figure 9-5 Intrinsic contact and extrinsic coagulation pathways. Note major sites of action of heparin and low-molecular-weight heparin. Note which processes are measured by activated partial prothrombin time (aPPT) and by international normalized ratio (INR).
(Figure © L.H. Opie, 2012.)

Does the intrinsic pathway have a role?

Traditionally, the extrinsic and intrinsic pathways are distinguished. The intrinsic coagulation pathway involves a series of interactions starting with activation of factors XII to XIIa, XI to XIa, IX to IXa, and X to Xa, which acts on prothrombin to form thrombin. The activation of X to Xa is where the traditional extrinsic and intrinsic pathways converge (Fig. 9-5), and marks the start of the “common pathway.” Although the extrinsic coagulation pathway takes the lead in vivo,[2] there is interpathway interaction,[7] and the traditional model helps in interpretation of in vitro coagulation tests.

Von willebrand factor and collagen platelet receptors.

Superficial platelet injury activates many platelet receptors, which are membrane Gps.[5] Since our last edition in 2005, more receptors have been identified (see Table 9-1), all basically promoting platelet participation in clotting, but without new clinically available antiplatelet agents. At medium and high shear rates, activated platelet receptors bind more readily to the subendothelial matrix, exposed by plaque rupture or tissue trauma, containing *von Willebrand factor* (vWF) and collagen. A large multimeric protein, vWF is normally present in high levels but inactive in the plasma. At the site of vessel injury, vWF becomes immobilized and activated. The vWF interacts with its platelet receptor glycoprotein Ib-alpha (GpIbα) to tether the platelets to the site of injury. The vWF platelet receptors also help to activate platelets by releasing calcium from the endoplasmic reticulum (not shown in Fig. 9-3). Collagen interacts with the platelet *collagen receptor,* GpVI (not shown in Fig. 9-3), which powerfully induces platelet activation,[8] thereby liberating more vWF from platelet granules.

Platelet activation and receptor self-amplification.

Platelets play a pivotal role in the pathophysiologic findings of AMI. They are involved not only in the initiation of clot formation after plaque fissuring or rupture, but also in the propagation of clot, the secretion of plasminogen activator inhibitor (PAI)–1, which causes clots to become resistant to lysis, and the secretion of thromboxane A_2 (TXA_2), which causes vasoconstriction. They may also embolize to cause plugging of the microvasculature. Platelet aggregates are resistant to fibrinolytic therapy

A critical aspect of platelet activation is the transition from the low- to high-affinity binding state of the platelet receptors,[9] sometimes called “inside-outside” activation (see Table 9-1). Thrombin, readily generated at the site of plaque rupture (see Fig. 9-2), is a potent activator, which leads to release of more thrombin from platelets, followed by release of adenosine diphosphate (ADP) and TXA_2. These three bind to their respective platelet receptors and promote further activation (see Fig. 9-3), a process called *self-amplification.*[9] Activated receptors bind more readily to vWF factor, subendothelial collagen, and fibrinogen. These macromolecules bind platelets to each other (platelet aggregation) and to the platelets already adhering to the vessel wall.

Platelet shape change.

Activated platelets have activated contractile proteins. New actin filaments are formed, and myosin light chain kinase responds to signals from the TXA_2 and thrombin receptors (see Fig. 9-3) to promote platelet shape change (see Figs. 9-2 and 9-4). The shape change results in increased surface membrane available for platelet activation and promotion of receptor conformational changes to further activate platelets. The shape change also releases platelet ADP, TXA_2, and thrombin, which in turn activate other platelets,[10] like a whirlwind effect.

Platelet calcium.

A critical event during platelet activation is the rise in the intracellular platelet calcium level. Several mediators (including collagen from endothelial injury, thrombin, ADP released from injured platelets) mobilize calcium from the endoplasmic reticulum (see Fig. 9-3). Enhanced platelet calcium has several consequences, including (1) stimulation of formation of TXA_2 (see Figs. 9-3 and 9-4), (2) activation of platelet contraction and shape change to promote the conformational activation of GpIIb/IIIa so that fibrinogen and other adhesive proteins can interlink platelets, and (3) enhanced release of ADP from platelet granules to act on their receptors further to promote platelet activation.[11]

Platelet rapid propagation.

The adherent, activated, and aggregated platelets continue to stimulate further thrombus formation. The large concentration of local thrombin, derived both from platelet release and both coagulation pathways, produces local fibrin that polymerizes in “end-to-end” and “side-to-side” reactions to form a fibrin clot. Thrombin also changes circulating factor XIII to active XIIIa, which cross-links the fibrin units. The cross-linked polymers and entrapped platelets make up the thrombus (clot).

Drugs inhibiting platelets.

Only some of the many platelet receptors can be blocked by aspirin, clopidogrel, the GpIIb/IIIa antagonists, and the blockers of the platelet $P2Y_{12}$ and PAR receptors (see Figs. 9-3 and 9-4; Table 9-1). Antagonists to several major receptors such as those to which collagen, the vWF, thrombin, and TXA_2 bind, have yet to be developed. Indirectly many of these receptors could be inhibited by blocking tissue factor, so new agents are in development.

Therapeutic activation of coagulation.

When urgent activation of the clotting mechanism is essential (for example, traumatic hemorrhage with life-threatening bleeding), then powerful activation of thrombosis can be attempted by giving recombinant factor (rF) VIIa. Its only approved use is for hemophiliacs with inhibitors to factors VIII and IX (licensed in the United States as *Novoseven*). rF VIIa is increasingly used for off-label indications. Limited available evidence from 28 studies for five off-label indications suggests no mortality reduction with rFVIIa use.[12] Rather, there is risk of increased thromboembolism. For factor Xa–induced bleeding, prothrombin complex

concentrate (PCC) immediately and completely reverses the anticoagulant effect of *rivaroxaban* but not dabigatran in healthy human subjects.[13] For dabigatran, PCC slows hematoma expansion in experimental brain hematoma in murine intracerebral hemorrhage.[14]

Tranexamic acid.

Tranexamic acid inhibits plasmin. Recent large-scale trial evidence has shown reduced bleeding when administered after trauma and especially in the first 3 hours after trauma.[15],[16] Importantly, deaths and cardiovascular deaths were reduced without an increase in MI, venous thrombosis, or pulmonary embolism. This inexpensive one-time treatment has the potential to reduce bleeding and mortality. However, there was a trend to increased mortality when given more than 3 hours after the onset of the trauma.

Expert CONSULT

DRUGS FOR THE HEART
LIONEL H. OPIE | BERNARD J. GERSH

Antiplatelet agents: Aspirin and cardiovascular protection

Platelet inhibition.

Acetylsalicylic acid (aspirin) irreversibly acetylates cyclooxygenase (COX; see Fig. 9-3), and activity is not restored until new platelets are formed. The COX isoform is COX-1, the inhibition of which gives both the cardiovascular therapeutic benefit and the toxic gastric side effects. In contrast, aspirin does not strongly inhibit COX-2; this pathway produces the prostaglandins (PGs), including PGE_2, that contribute to the inflammatory response. By inhibiting COX-1, aspirin interferes with the synthesis of prothrombotic TXA_2, important in the platelet activation cycle (see Fig. 9-3) and at a low dose permits the continued secretion of PGI_2 (prostacyclin).[17] Being very primitive cells, platelets cannot synthesize new proteins, hence aspirin prevents all platelet COX-1 activity for the lifespan of the platelet, which is 8-10 days. Aspirin also has important nonplatelet effects. In the vascular endothelium it inactivates COX, which may diminish the formation of antiaggregatory prostacyclin as well as TXA_2.

Despite these potentially conflicting effects of aspirin, the overwhelming clinical effect is antithrombotic. Also note that vascular COX can be resynthesized within hours, whereas platelet COX can only reform with the birth of new platelets in the absence of aspirin. On the negative side, aspirin can cause gastric irritation, and gastrointestinal (GI) bleeding requiring hospitalization occurs in 2 per 1000 patients treated per year,[18] with a small increase in risk of hemorrhagic stroke.[19],[20] However, in the secondary prevention of MI, aspirin is approximately 100 times more effective in preventing cardiovascular events than in provoking major bleeding[21] although aspirin resistance may limit the response (see later). Bleeding is related to the dose of aspirin, with major bleeding doubling as the dose is increased from less than 100 mg to less than 200 mg/day.[22] (See “Low-Dose Aspirin and Efficacy” later in this chapter for discussion of ideal doses.)

Additional effects.

Aspirin blocks aggregation only in response to stimulation by thromboxane. Its effects can be overcome by other stimuli, particularly thrombin, which is the most powerful stimulus of platelet aggregation.[23] However, aspirin may have important additional effects on platelet-neutrophil interactions,[24] and on inflammation, but many of these effects require concentrations much higher than currently used for secondary prevention.[25]

Aspirin nonresponsiveness (“resistance”).

Resistance is a commonly used but loosely defined and controversial term. Of patients with arterial thrombosis, 5% to 20% or more experience a recurrent vascular event during long-term follow-up despite an apparently adequate therapeutic dose.[26] Nonadherence must first be eliminated.[27] “Resistance” may occur in 16% of patients with prior MI, and was associated a fourfold risk of death, reinfarction, or rehospitalization over 12 months.[28] Antiplatelet responsiveness (to aspirin or thienopyridines) is not an “all or nothing” phenomenon. Rather, there is a continuous spectrum. In addition, the clinical response depends on the potency of the thrombogenic stimulus. When aspirin resistance is defined as failure of suppression of thromboxane generation with high urinary concentrations of a metabolite of TXA_2, then the risk of MI is doubled.[26] When defined by platelet function tests and presumed clinical unresponsiveness to aspirin, there is a long-term trebling of the risk of death, myocardial infarct, or stroke.[29] The diverse mechanisms of aspirin resistance include platelet Gp polymorphisms, activation of platelets by pathways other than the COX pathway, and enhanced inflammatory activity with increased expression of COX-2 that is not strongly inhibited by aspirin.[26] Laboratory diagnosis is not easy, as there is no accepted definition, so that clinical suspicion usually provides the cue. Clopidogrel, as an add-on or replacement, may help,[10] but aspirin-resistant patients may also have a reduced response to clopidogrel.[30]

Clinical use of aspirin

Because platelets play such an important role in vascular disease of all kinds, there are many clinical

indications for aspirin. A meta-analysis of 135,000 patients in 287 studies confirmed its prophylactic effects after a previous MI, in effort and unstable angina, after a stroke, and after coronary artery bypass surgery, while establishing its efficacy in women as well as in men.[21] The major problem is balancing the benefits of aspirin versus the risks, the chief being major GI bleeding and a smaller risk of hemorrhagic stroke. When aspirin is used for secondary prevention, the balance strongly favors benefit. In primary prevention assessing potential risk versus overall benefit (including cancer prevention) is the key.

Secondary prevention by aspirin.

All patients with a prior cardiovascular event should be considered for aspirin therapy, which on average reduces the risk of any further vascular event by approximately one-quarter. *In stable angina* in β-blocked patients, aspirin 75 mg daily reduced AMI or sudden death by 34% compared with placebo.[31] The risk reductions extend to those with unstable angina (46%), coronary angioplasty (53%), prior MI (25%), prior stroke or TIA (22%), and peripheral arterial disease (23%).[21]

Primary prevention by aspirin: Only for those at high risk?

Our previous recommendation, supported by a metaanalysis on more than 30,000 subjects, was that aspirin is indicated only in high-risk populations.[21] In a small but well-designed trial on 1276 diabetic persons with peripheral vascular disease followed for up to 8 years, and judged to have higher cardiovascular risk, aspirin, disappointingly, failed in the primary prevention of cardiovascular events including deaths from heart disease or stroke.[32] The largest study on aspirin and bleeding comes from the Italian National Health System on new users of low-dose aspirin (≤300 mg) from 2003 to 2008.[33] The study authors selected 186,425 patient's using propensity-score matching and compared them with an equal number not currently taking low-dose aspirin. During a median follow-up of 5.7 years, there were 1.6 million person-years of observation. For those currently taking aspirin, the rate of total hemorrhagic events per 1000 person-years was 5.58, whereas the rate was 3.60 per 1000 person-years in those not taking aspirin, with an incidence rate ratio (IRR) of 1.55 (confidence interval [CI], 1.48-1.63). The excess aspirin-induced bleeding was similar in numbers to the expected aspirin-induced reduction of major cardiovascular events for those with a 10-year risk of between 10% and 20%. Of note, an increased intake of proton pump inhibitors (PPIs) was associated with reduced major bleeding. A major problem with this study is that "low dose" could be 300 mg daily, much higher than our recommendation.[34]

Aspirin to prevent cancer.

In a series of papers Rothwell's group at Oxford has shown a remarkable effect of aspirin in lessening the development of cancer, including early metastases. In eight primary and secondary prevention trials allocation to aspirin reduced death resulting from cancer by 21% (CI 0.68-0.92, p = 0·003).[35] Even though this study is a retrospective analysis, in three large UK trials long-term posttrial follow-up was obtained from death certificates and cancer registries. Strong support for the inhibitory effect of aspirin on colorectal cancer comes from a prospective randomized study in which aspirin 600 mg daily (a dose normally not used because of the bleeding risk) for a mean of 25 months substantially reduced cancer incidence in carriers of hereditary colorectal cancer.[36]

Furthermore, in an analysis of 51 trials with 77,549 participants, allocation to aspirin gave fewer nonvascular deaths overall (p = 0.003;) and decreased cancer deaths (odds ratio [OR] 0.85, p = 0.008; 34 trials, 69,224 participants).[37] The lower risks were initially offset by increased major bleeding, but both effects decreased with increasing follow-up, leaving only the reduced risk of cancer (absolute reduction 3.13 per 1000 patients per year) from 3 years onward. As the effect of both low and high doses of aspirin in decreasing cancer metastases convincingly (all P values <0.005) started at approximately 4-5 years after initiation of aspirin, the proposal is that aspirin inhibits the growth of metastases.[38]

What should we recommend to our patients? From the earlier studies, we calculate that there is a strong case for prevention of GI cancers that vastly outweigh the risks of major bleeds in those at low cardiovascular risk.[39] In the light of the recent Rothwell analysis on 51 trials, we agree with the editorialists in the *Lancet* that the case for prolonged aspirin use is now very convincing.[40] Benefit exceeds harm (Fig. 9-6). Without clear data for guidance, aspirin could be started at a low dose of 75 mg perhaps in the patient's early 50s to allow for both the early and the delayed anticancer benefit shown in this study.

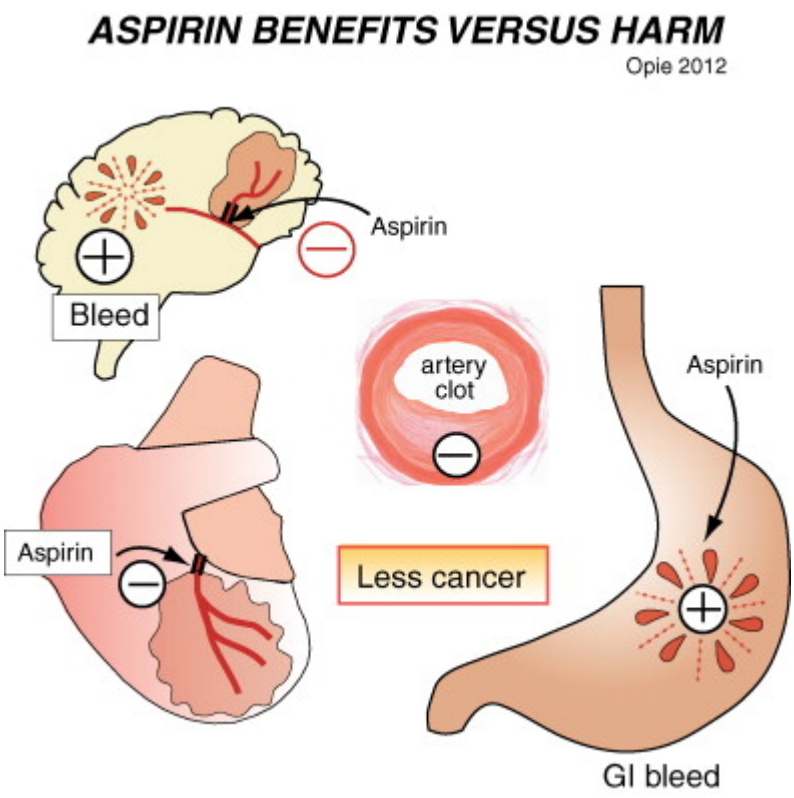

Figure 9-6 Aspirin benefit exceeds harm. Besides the well-known arterioprotective effects of aspirin on heart and brain, balanced to some extent by increased cerebral bleeding, the newly reported decreased risk of cancer argues for its use in primary prevention. *GI,* Gastrointestinal.
(Figure © L.H. Opie, 2012.)

Thus we change our previous opinion that prophylactic aspirin for the general apparently healthy population should not be encouraged. We remain concerned about starting aspirin in older adults in whom decreased renal function is a possible side effect. Nonetheless, in the absence of data for aspirin use for primary prevention at different severities of chronic kidney disease (CKD), in practice low-dose aspirin less than 100 mg is often used even in the presence of severe CKD.[41]

Aspirin for cardiovascular indications.

In acute coronary syndromes (ACS), including AMI with fibrinolytic therapy or primary PCI, and unstable angina with either conservative or invasive strategies, aspirin should be given in both the acute and follow-up phases, and is part of triple antiplatelet blockade. A large trial comparing 300-325 mg daily doses with lower-dose aspirin (75-100 mg daily) showed no outcome differences and no differences in bleeding.[42] Aspirin 160 mg was the dose used in the first large AMI trial in 1988[43] and was also favored by a retrospective analysis.[44]

Aspirin as an antiinflammatory drug.

Although the Framingham-based risk factor calculation is an excellent guide, it does not factor in the role of the inflammatory response in the genesis of vascular disease. In the Physicians' Health Study, the benefit of aspirin in primary prevention was largely localized to men with high blood levels of C-reactive protein.[25] Logically, but without prospective trial support, aspirin by its antiinflammatory effect should be more effective than expected from current risk factor calculations, and might be considered for primary prevention in those with high C-reactive protein levels. However, the benefits of this approach remain to be proven.

Other indications for aspirin.

(1) *In postcoronary bypass surgery,* aspirin should be started within 48 hours of surgery, which reduces total

mortality by about two-thirds,[45] and continued indefinitely. (2) Use for *prevention of stroke in atrial fibrillation (AF),* when warfarin is contraindicated or the patient has a CHADS-VASc score of less than 2 (congestive heart failure; hypertension; age 75 years or older [2 points]; diabetes mellitus; stroke, TIA, or thromboembolism [2 points]; vascular disease; age 65-74 years; sex category; graded 0–9)[46] and thus is not at modest risk of stroke (6%-10% 10-year risk).[34] (3) For *arteriovenous shunts,* aspirin decreases thrombosis. (4) For *stroke prevention* in intracranial arterial stenosis, high-dose aspirin (325-1300 mg daily) was better than warfarin (see "Possible Indications for Warfarin"). (5) For urgent therapy in *TIAs and minor stroke,* aspirin is part of a comprehensive strategy (with clopidogrel, a statin, blood pressure lowering, and anticoagulation if indicated).[46] (For dual therapy with clopidogrel, see p. 348.)

Low-dose aspirin and efficacy.

Low doses theoretically retain efficacy yet limit GI side effects and bleeding. Metaanalysis suggests that the dose range should be 75-150 mg daily for a wide range of indications.[21] In a follow-up study of patients with non–ST-elevation (NSTE) ACSs the optimal dose of aspirin was 75 to 100 mg.[22] Aspirin 80 mg/day completely blocks platelet aggregation induced by COX.[47] Doses of only 30 mg daily were as effective as higher doses in preventing TIAs,[48] but other endpoints were not tested. The problem with very low doses is that the full antithrombotic effect takes up to 2 days to manifest, explaining why higher dose aspirin (approximately 160 mg) should be given urgently at the onset of symptoms of AMI or unstable angina. Much higher dose aspirin, formerly used to prevent recurrences of stroke or TIAs, is seldom appropriate.[18],[48],[49]

Bleeding, gastrointestinal, and renal side effects of aspirin.

Whereas bleeding is the most serious side effect, GI side effects are much more common. Dyspepsia, nausea, or vomiting may be dose-limiting in approximately 10%-20% of patients. Such side effects may be reduced by buffered or enteric-coated aspirin, or by taking aspirin with food. Low-dose enteric coated aspirin (Ecotrin 81 mg in the United States) is often prescribed to avoid GI side effects, yet by delivering aspirin to the small intestine rather than the stomach, bioavailability is reduced with risk of suboptimal clinical response.[27] Standard "low"-dose aspirin (75-300 mg daily) more than doubles the risk of major GI bleeding (relative risk, 2.07; CI 1.61-2.66) and increases intracranial bleeds by 65%.[50] In absolute terms, however, the risk is low: 769 patients must be treated for 1 year to cause one major bleed.[50] *Impaired renal function and decreased excretion of uric acid* with risk of gout are less commonly emphasized, but are frequent in older adults even with low-dose aspirin.[51]

Contraindications to aspirin.

The major contraindications are aspirin intolerance, history of GI bleeding, and peptic ulcer or other potential sources of GI or genitourinary bleeding. Hemophilia is not an absolute contraindication to aspirin when there are strong cardiovascular indications. Because it retards the urinary excretion of uric acid and creatinine, blood uric acid, and creatinine should be monitored, especially in older adults.[52] Relative contraindications include gout, dyspepsia, iron-deficiency anemia, and the possibility of increased perioperative bleeding.

Drug interactions with aspirin.

Concurrent warfarin and aspirin therapy increases the risk of bleeding, especially if aspirin doses are high. Aspirin inhibits COX-1 activity approximately 170 times more than COX-2[53] so that interaction with COX-2 inhibitors is unlikely. Among nonsteroidal antiinflammatory drugs (NSAIDs), those with dominant COX-1 activity (ibuprofen and naproxen) but not those with dominant COX-2 activity (diclofenac [Voltaren]) interfere with the cardioprotective effects of aspirin.[27],[54] Angiotensin-converting enzyme (ACE) inhibitors and aspirin have potentially opposing effects on renal hemodynamics, with aspirin inhibiting and ACE inhibitors promoting the formation of vasodilatory PGs.

When ACE inhibitors are chronically used for heart failure, postinfarct protection, or high-risk prevention, they are still beneficial even when aspirin is added. Two metaanalyses have addressed this issue. Aspirin did reduce but not eliminate the ACE inhibitor's beneficial effect on major clinical events. The risk reduction in those also receiving aspirin at baseline was an OR of 0.80 versus 0.71 in those given an ACE –inhibitor only.[55] In 96,712 patients with AMI, there was no interaction over 30 days.[56] A practical policy is to keep the aspirin dose low, especially in those with hemodynamic problems such as heart failure.[57] The risk of aspirin-induced GI bleeding is increased by alcohol, corticosteroid therapy, and NSAIDs. Phenobarbital,

phenytoin, and rifampin decrease the efficacy of aspirin through induction of the hepatic enzymes metabolizing aspirin. The effect of oral hypoglycemic agents and insulin may be enhanced by aspirin. Aspirin may reduce the efficacy of uricosuric drugs such as sulfinpyrazone and probenecid. Both thiazides and aspirin retard the urinary excretion of uric acid, increasing the risk of gout.

Treatment of aspirin-induced gastrointestinal bleeding.

In those with healed ulcers, aspirin plus a PPI reduces recurrent bleeding more effectively than a change to clopidogrel.[58] Could primary use of clopidogrel avoid or lessen the incidence of GI bleeding that occurs with aspirin? Indirect evidence suggests that almost 1000 patients would have to be treated for 1 year with clopidogrel instead of aspirin to avoid one major bleed at the cost of more than $1 million.[50]

Other antiplatelets: Clopidogrel and dipyridamole (used as single antiplatelet therapy)

ADP is released from platelets during platelet activation and, when externalized, interacts with two G protein–coupled platelet receptors ($P2Y_1$, $P2Y_{12}$), which act through different intracellular signals (see Fig. 9-3). $P2Y_1$ activation induces platelet shape change and initiates GpIIb/IIIa activation, whereas $P2Y_{12}$ perpetuates GpIIb/IIIa activation and critically stabilizes platelet aggregation.[27] $P2Y_{12}$ antagonism may not only prevent platelet aggregation but also promote disaggregation.[27] Another indirect effect of ADP is to rapidly activate intravascular tissue factor. Therefore ADP antagonists may not only decrease platelet thrombosis, but may directly affect coagulation.[27] Clopidogrel is the most widely used agent of this group, with the more recent agents being prasurgel and ticagrelor (see Fig. 9-3). Ticlopidine was the first agent of this group, yet now is seldom used because of potentially serious side effects. First, we present a brief review of ticlopidine.

Ticlopidine

Ticlid and clopidogrel are both thienopyridine derivatives that irreversibly inhibit the binding of ADP to the $P2Y_{12}$ receptor (see Fig. 9-7). Ticlopidine can cause neutropenia, liver abnormalities, and thrombotic thrombocytopenic purpura (TTP), making it much less safe than clopidogrel. Both agents when added to aspirin give added antiaggregatory effects and improve clinical outcomes.[21] The neutropenia associated with ticlopidine occurs within the first 3 months of treatment. It is therefore essential that a complete blood cell count and white cell differential be performed before starting treatment, and every 2 weeks until the end of the third month, according to the manufacturer's information. Ticlopidine has two licensed indications in the United States, to prevent repeat stroke or TIA in those intolerant of or resistant to aspirin and for coronary artery stenting for up to 30 days with aspirin. In practice, ticlopidine is rarely used in countries where clopidogrel is available except in cases of clopidogrel resistance or allergy.

Pharmacokinetics of ticlopidine.

The kinetics of ticlopidine tablets are nonlinear, with a markedly decreased clearance on repeated dosing. Thus it takes 4-7 days to achieve maximum inhibition of platelet aggregation when given with aspirin.[59] However, a quicker response can be achieved by oral loading. Ticlopidine is largely metabolized by the liver, followed by renal excretion. The plasma half-life during constant dosing is 4-5 days.

Clopidogrel

Clopidogrel is a widely used inhibitor of the platelet ADP receptor $P2Y_{12}$.[7] It is substantially safer than ticlopidine with a low rate of myelotoxicity (0.8%, package insert). There is no study that compares the rate of GI bleeding to that with placebo, but there is less major GI bleeding than with aspirin.[50] Clopidogrel acts at a different site from aspirin by *irreversibly* inhibiting the binding of ADP to the $P2Y_{12}$ receptor, thereby preventing the transformation and activation of the GpIIb/IIIa receptor (Figs. 9-3 and 9-7). Thus clopidogrel has gained considerable importance in the treatment of ACS. Compared with ticlopidine, metaanalysis suggests a superior reduction of major adverse cardiac events[60] to which may be added better tolerability (fewer GI and allergic side effects). As with aspirin, clopidogrel resistance also occurs.

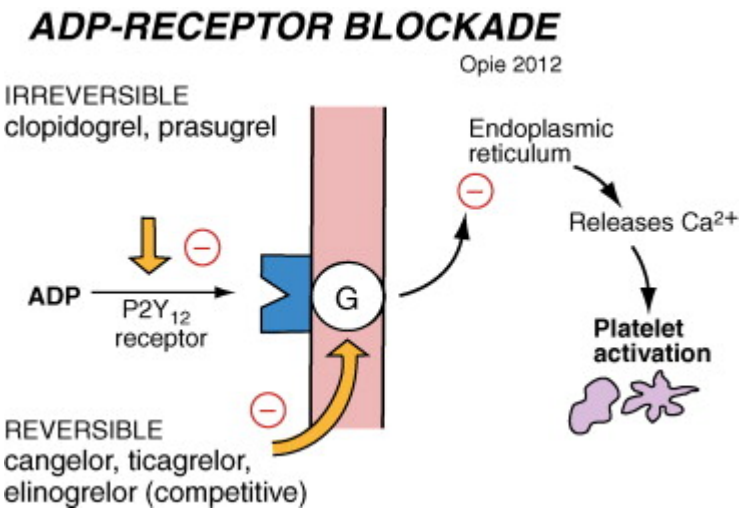

Figure 9-7 Sites of adenosine diphosphate (ADP)–receptor (P2Y12) block, either irreversible (e.g., by clopidogrel) or reversible (e.g., by ticagrelor). Gi protein, inhibitory form. For role of P2Y12 also see Figure 9-3. *Ca2+*, Calcium.
(Figure © L.H. Opie, 2012.)

Pharmacokinetics and dosage.

Clopidogrel is an inactive prodrug that requires in vivo oxidation by the hepatic or intestinal cytochrome CYP3A4 and 2C19 isoenzymes (Fig. 9-8).[61] The onset of action on platelets is within hours of a single oral dose,[62] but steady state inhibition requires between 3 and 7 days (package insert).[63] When given upstream before PCI, a 600-mg oral *loading dose* of clopidogrel achieves maximal inhibition of platelets after 2 hours,[64] compared with 24-48 hours with a 300-mg loading dose, both doses achieving greater inhibition than ticlopidine.[64] In a prospective trial, in a secondary analysis double-dose clopidogrel (a loading dose of 600 mg and then150 mg for 7 days) was superior to standard-dose prior (a loading dose of 300 mg and then 75 mg/day) for PCI for ACS at 30 days.[65] Kinetics of clopidogrel are nonlinear and variable, with a markedly decreased clearance on repeated dosing. When dosing is stopped, it takes approximately 5 days for the generation of new platelets and the bleeding to be reduced, so that cessation for 5 days is recommended before coronary artery bypass grafting (CABG) to avoid major bleeding that may require 30 transfusions per 1000 patients.[63] No dose adjustment of clopidogrel is needed for older adults or for patients with renal impairment (package insert).

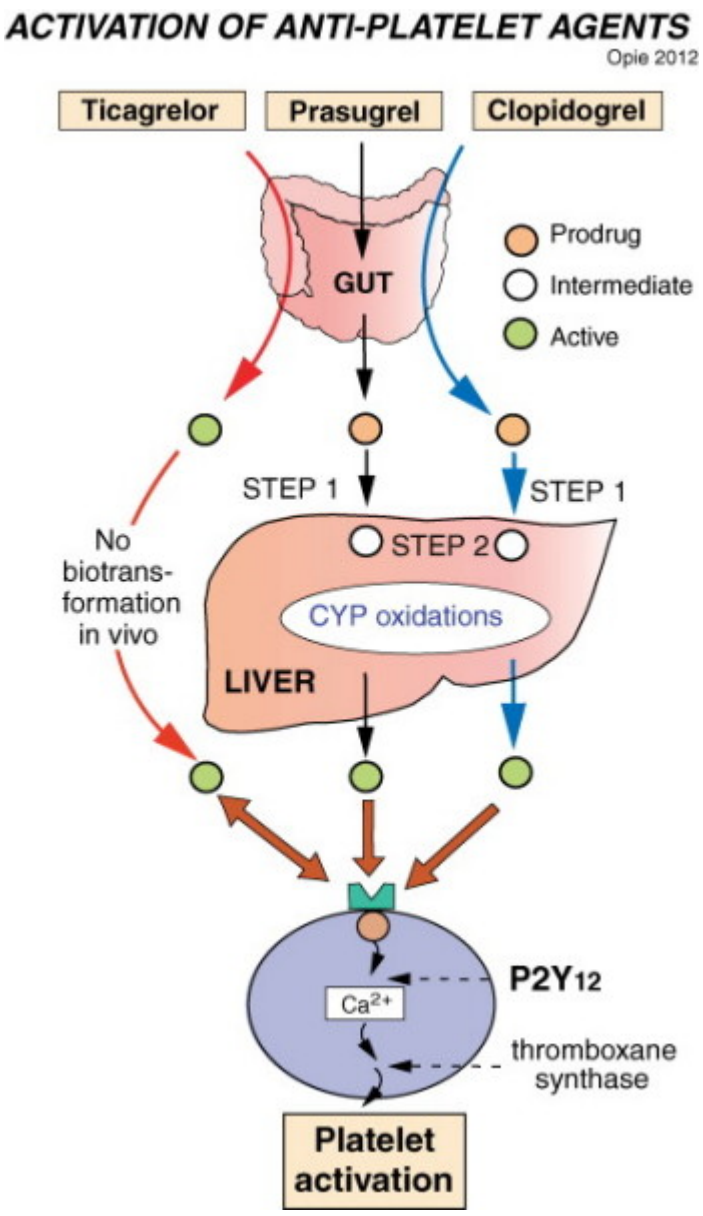

Figure 9-8 Activation of antiplatelet agents. Note that both prasurgel and clopidogrel require hepatic activation with risk of interactions with other drugs at that site. Ticagrelor requires no hepatic step and was superior to clopidogrel in the PLATO trial.[61] *Ca2+*, Calcium; *CYP,* cytochrome P-450.
(Figure © L.H. Opie, 2012.)

Major side effects.

Neutropenia occurs in 0.02% versus 2.4% for ticlopidine (package inserts). The major side effect of clopidogrel is increased major bleeds (approximately 1% excess), without an increase in intracranial bleeds.[21] A *contraindication* is active bleeding.

Clopidogrel genetic testing.

Clopidogrel is a prodrug that requires metabolic activation by hepatic cytochrome P450 (see Fig. 9-8). The CYP2C19*2 allele is a common genetic variant and is associated with increased rates of ischemic events and stent thrombosis after PCI. This and other genetic variants are carried by nearly 30% of individuals of western European ancestry and approximately 40% of those of Asian descent and of blacks. On-site genetic testing completed within 1 hour can now identify those with specific genetic variants.[66] Prasugrel or ticagrelor can be given instead of clopidogrel in those individuals. Although this is a promising approach,

prospective genetic-based trials are now needed to determine whether clinical outcome benefit of such rapid genetic testing is achieved. A recent *Lancet* editorial concludes, “Funders await evidence establishing the value of genetic testing–guided antiplatelet treatment before making reimbursement decisions.”[66] Of note, the US Food and Drug Administration (FDA) has controversially stated that CYP2C19 genotyping be considered prior to prescribing clopidogrel.

Drug interactions.

Atorvastatin and omeprazole competitively inhibit hepatic activation of clopidogrel, reducing clopidogrel responsiveness.[67] Despite such theoretical concerns and ex vivo testing suggesting a potential negative interaction with concomitant clopidogrel and CYP3A4-metabolized statins (atorvastatin, simvastatin, pravastatin), there was no evidence of a clinical interaction in a large placebo-controlled trial with long-term follow-up.[68] Nonetheless, higher doses of clopidogrel (600 mg) and atorvastatin (40-80 mg as currently used) may interact, as is being tested in the prospective SPICE trial.[67]

PPIs, and particularly the ones that effect the cytochrome P450 pathway, may decrease the efficacy of clopidogrel.[69] Reassuringly, in a randomized trial that stopped early because of lack of funding, in 3761 patients given clopidogrel with or without omeprazole, there was a reduction in upper GI tract bleeding with omeprazole (hazard ratio [HR]: 0.13; CI: 0.03-0.56; p = 0.0001) with no apparent interaction with cardiovascular events (HR: 0.99; CI: 0.68-1.44).[70]

Reduced response to clopidogrel resistance and effects of platelet reactivity.

According to the test used, the incidence varies. There is no simple classification into responders and nonresponders, but rather a gradation of responses. Increased on-treatment platelet reactivity, as measured by a direct sensitive $P2Y_{12}$ assay, is related to serious clinical outcomes. There were increased long-term cardiovascular events after PCI, including death, MI, and stent thrombosis. These events were all increased in half of 3000 patients who had increased platelet reactivity, as shown by metaanalysis.[71] When giving a loading dose of 600-mg at the time of PCI, followed by 150 mg/day versus 75 mg/day of clopidogrel over 6 months, there is modest 22% reduction in the rate of high platelet reactivity at 30 days, but that did not translate into any change in the primary endpoint nor in the incidence of death from cardiovascular causes at 6 months.[72] There are no data on appropriate therapy of such increased platelet reactivity, but the current European Society of Cardiology (ESC) guidelines prefer other $P2Y_{12}$ blockers.[73]

Preferred use of other $P2Y_{12}$ blockers.

Of $P2Y_{12}$ blockers, ticagrelor has some advantages over prasugrel, which requires hepatic activation (see Fig. 9-8), so that the issue of the effects of hepatic genetic variations does not arise. In case of excess bleeding, ticagrelor may be more readily reversible with a shorter duration of action of 3-4 days versus 5-10 days for prasugrel. Furthermore, ticagrelor has strong trial data with mortality reduction in ACS in PLATO.[74] Prasugrel gives more effective platelet inhibition than does clopidogrel in patients with high residual platelet reactivity, but without change in outcome events, a trial stopped early because of low event rates.[75] This was a trial with high residual platelet reactivity and low event rates e.g.: 1 vs 0.

Indications, dose, and use.

Clopidogrel is licensed in the United States for (1) *reduction of atherosclerotic events* (MI, stroke, vascular death) in patients with recent stroke, recent MI, or with established peripheral arterial disease; and (2) for *ACS* whether or not PCI (with or without stent) or CABG is performed. For loading, 600 mg is better.[65] For *prevention of late poststent thrombosis* after drug-eluting stent (DES), clopidogrel should be used for at least 12 months post-DES insertion,[76] and aspirin must be kept on indefinitely. *For aspirin resistance,* clopidogrel often replaces aspirin; however, there is no outcome study.

How long to keep on after PCI?

The standard recommendation is to use clopidogrel for 1 year with DES and 1 month with bare metal stents. However, there are no definitive data. An observational study suggests an increased risk of an adverse cardiovascular event when stopping after a mean of 278 days.[77]

Aspirin intolerance.

Clopidogrel can be used in place of aspirin and has modest superiority in a chronic population at broad vascular risk (9% relative risk reduction versus aspirin).[78]

Summary.

Clopidogrel is an effective agent, but with variable metabolism and a relatively high rate of in vitro platelet resistance. The precise frequency of clinical resistance is unknown, but greater variation in platelet reactivity is seen with clopidogrel than with newer platelet antagonists (see “Prasugrel” and “Ticagrelor,” both later in this chapter). In acute vascular injury it should be added to aspirin to obtain better platelet inhibition and clinical results but not routinely for stable coronary disease; it can replace aspirin in cases of intolerance. Upstream clopidogrel has replaced routine administration of GpIIb/IIIa blockers for high-risk patients with NSTE ACS. The ESC guidelines recommend the use of ticagrelor with discontinuation of clopidogrel if already used for pretreatment.[73]

Dipyridamole and sulfinpyrazone

In general, platelet inhibition by dipyridamole (site of action the same as prostacyclin, see Fig. 9-3) with or without aspirin or sulfinpyrazone, produces results very similar to those seen with aspirin alone.[21] By contrast, clopidogrel or ticlopidine added to the effects of aspirin, reducing vascular events by approximately 20%.[21] Therefore *dipyridamole* is no longer the nonaspirin antiplatelet agent of choice even in the cerebrovascular circulation for which data are stronger. Dipyridamole helps to reduce recurrent stroke when given with aspirin as in the ESPRIT trial, and when combined with earlier studies the overall risk ratio of vascular death, stroke, or MI was 0.82 (CI: 0.74-0.91).[79] The only cardiovascular-licensed indication of dipyridamole is for prosthetic mechanical valves, in combination with anticoagulation by warfarin.[80] Note the dangerous drug interaction of dipyridamole with the antiarrhythmic adenosine (see Fig. 8-7). *Sulfinpyrazone* inhibits COX, with effects similar to those of aspirin, yet is more expensive. It requires multiple daily doses and has no benefit in patients already on aspirin. However, in contrast to aspirin it is also a uricosuric agent. In the United States, the only licensed indication is chronic or intermittent gouty arthritis.

Expert CONSULT

DRUGS FOR THE HEART
LIONEL H. OPIE | BERNARD J. GERSH

Dual antiplatelet therapy

Aspirin-clopidogrel combined.

As aspirin and clopidogrel act differently (see Fig. 9-3), better results should logically be obtained by using the combination in higher-risk patients. The general principle is as follows. Substantial data shows that adding clopidogrel to aspirin is beneficial in the setting of acute vascular injury, whether procedure-induced as in stenting, or spontaneous as in ACS,[81] including AMI.[82] In high-risk subgroups of CHARISMA, dual antiplatelet therapy appeared protective.[83]

For STEMI or unstable angina and non–ST-elevated myocardial infarction (NSTEMI) *with intended invasive therapy* by PCI, the revised American College of Cardiology (ACC)–American Heart Association (AHA) 2011 guidelines[84] advise clopidogrel 300-600 mg given as soon as possible as a loading dose, then 75 mg daily for at least 1 year.[84] In the large OASIS-7 trial that randomized 17,263 patients who had PCI to a 7-day double-dose clopidogrel regimen (600 mg on day 1; 150 mg on days 2-7, then 75 mg daily) reduced cardiovascular events and stent thrombosis compared with standard doses at 30 days (300 mg on day 1 then 75 mg daily).[42] Efficacy and safety did not differ between high-dose and low-dose aspirin.[65]

Clopidogrel added to aspirin reduced the composite of combined death, MI, and stroke at 1 year by 27% ($p < 0.02$).[85] Dual antiplatelet resistance has been reported but optimal therapies have not been defined.[30] *Drug interaction:* PPIs, advised in guidelines to prevent GI bleeding especially when clopidogrel is given with aspirin, may counteract platelet inhibition, but the evidence is not robust.[86]

In atrial fibrillation at high risk of stroke.

In patients with AF at high risk of stroke, maximal benefits are found with the new direct thrombin or factor Xa inhibitors (Fig. 9-9). For those with *prior TIAs or minor stroke,* aspirin added to clopidogrel (both 75 mg daily over 18 months in the MATCH trial) increased life-threatening bleeds from 1% to 3% ($p < 0.0001$) without improving cardiovascular outcomes,[87] thus making the case for only one antiplatelet agent in these patients.

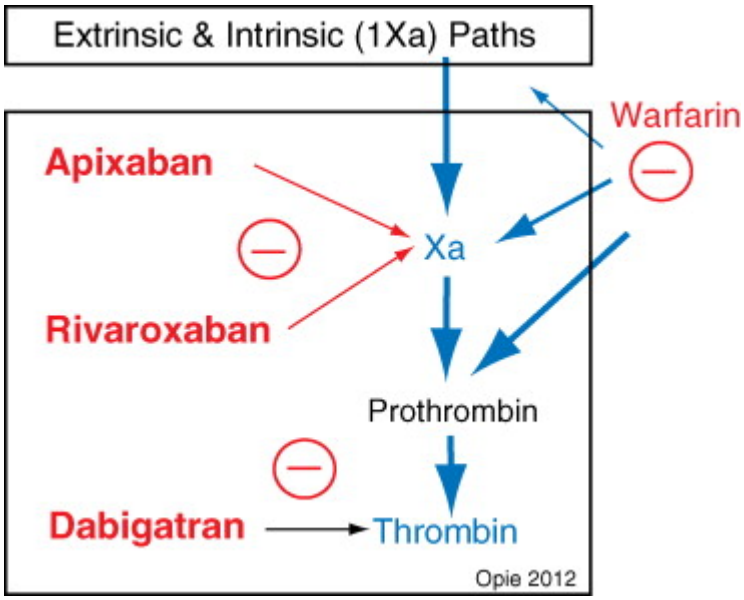

Figure 9-9 Extrinsic and intrinsic paths (see Fig. 9-10) showing sites of action of various indirect and direct thrombin inhibitors. *(Figure © L.H. Opie, 2012.)*

Clinical summary.

In *NSTE ACS,* regardless of whether management is conservative or invasive, clopidogrel provides benefit (combined with aspirin). In the CURE trial of 12,562 patients, clopidogrel added to aspirin reduced the combined incidence of death, nonfatal MI, and stroke by 20% versus aspirin alone ($p < 0.001$) over an average 9-month period.[88] Clopidogrel increased major bleeding (3.7% versus 2.7%, $P = 0.003$). Loading with upstream clopidogrel is used for PCI for ACS at moderate to high risk,[89],[90] as now recommended by ESC guidelines.[73]

Expert CONSULT

DRUGS FOR THE HEART
LIONEL H. OPIE | BERNARD J. GERSH

Newer antiplatelets added to aspirin: Prasugrel, ticagrelor, and vorapaxar

Prasugrel

Prasugrel (Effient) is a newer-generation thienopyridine (the first generation is ticlopidine and the second is clopidogrel) that irreversibly and noncompetitively inhibits the $P2Y_{12}$ receptor at the same site as clopidogrel (see Fig. 9-7). Prasugrel is a prodrug. It is not detected in plasma following oral administration, being rapidly hydrolyzed in the intestine to a thiolactone, which is then converted in the liver (see Fig. 9-8) to the active metabolite by a single step, primarily by CYP3A4 and CYP2B6. For the role of onsite genetic and residual platelet reactivity testing to decide between clopidogrel and prasugrel for PCI, see “Clopidogrel” earlier in this chapter. The active metabolite has an elimination half-life of approximately 7 hours (range 2-15 hours). Unexpectedly, CYP3A inhibitors such as verapamil and diltiazem do not appear to alter prasugrel activity, but may decrease the maximum concentration (Cmax) by 34% to 46%. Prasugrel-mediated inhibition of platelet aggregation is approximately five to nine times more potent than that of clopidogrel,[91] achieving greater platelet inhibition than 600 mg of clopidogrel with an onset of action within 1 hour.[92]

Major clinical trial.

In the TRITON-TIMI 38 Trial[92] prasugrel (60 mg loading dose, then 10 mg daily) was compared with clopidogrel (300 mg loading dose followed by 75 mg daily) in patients undergoing PCI and followed for 6-15 months. Prasugrel reduced the primary endpoint of cardiovascular death, MI, and stroke from 12% to 9.9% ($p < 0.001$). Stent thrombosis fell from 2.4% to 1.1% ($p < 0.001$). Forty-six patients would have to be treated for 5 months to avoid one primary endpoint, compared with 167 treated to result in one major hemorrhage (not CABG related). Overall, greater efficacy came at the price of greater bleeding. The FDA and the European Medicines Agency (EMA) have both approved prasugrel with warnings about the bleeding risk. The EMA also warns of hypersensitivity reactions with prasugrel, affecting anywhere from 0.1% to 1% of patients.

FDA-approved indications.

Prasugrel is indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with ACS who are to be managed with PCI for unstable angina or NSTEMI, or STEMI when managed with either primary or delayed PCI. Note, however, that the approval did not include superiority to clopidogrel. The FDA states that prasugrel’s greater treatment effect and greater bleeding rate in TRITON might in part be explained by the decreased conversion of clopidogrel to active metabolites in approximately 30% of white patients, and also because the concurrent use of PPIs in an unspecified number of the subjects in the trial might have led to a genetically based interaction that also decreased clopidogrel’s effective activity. Another factor is that clopidogrel was intentionally given at the same time as prasugrel in TRITON, whereas ideally it should have been given earlier for an optimal effect.[93]

Bleeding risk.

The black box FDA warning on the label states that prasugrel can cause serious bleeding and occasionally TTP. Bleeding should, if possible, be managed without stopping prasugrel, particularly in the first few weeks after ACS, which would increase the risk of subsequent cardiovascular events. Further analysis of the TRITON-38 reveals that the major predictors of serious bleeding were a combination of the patient and procedural characteristics and antiplatelet therapies.[94] Although serious bleeding was strongly associated with mortality within the first month of the bleeding event, this association was not significant beyond 40 days (HR for mortality 1.38; 95% CI 0.72 to 2.66; $P = 0.33$). Factors increasing the risk were (1) the use of a GPIIb/IIIa inhibitor which, when given even only for a short period, showed a stronger association with serious bleeding than did assignment to prasugrel (HR 1.59; $p < 0.001$); (2) a history of stroke or TIA (HR 1.58; $P = 0.01$); (3) age 75 years or older (HR 2.58; $P < 0.001$); (4) female gender (HR 1.77; $p < 0.0001$); (5) body weight of less than 60 kg (HR 2.30; $P < 0.001$); and (6) femoral access (HR 1.60; $P = 0.02$). Patients

with a history of stroke or TIA or low body weight (<60 kg) should not receive prasugrel.

Ticagrelor

Ticagrelor belongs to a novel chemical class, cyclopentyl-triazolopyrimidine, and is an oral reversibly binding noncompetitive inhibitor of the $P2Y_{12}$ receptor with a plasma half-life of approximately 12 hours.[73] The level of $P2Y_{12}$ inhibition is determined by the plasma ticagrelor level and, to a lesser extent, an active metabolite. Like prasugrel, it has a more rapid and consistent onset of action than clopidogrel, but additionally it has a quicker offset of action so that recovery of platelet function is faster. Unlike prasugrel, it requires no hepatic activation (see Fig. 9-8).

Drug interactions.

Ticagrelor inhibits hepatic CYP3A to increase blood levels of drugs metabolized through CYP3A, such as amlodipine and two commonly used statins (simvastatin and atorvastatin), whereas moderate CYP3A inhibitors such as diltiazem, verapamil, and amlodipine increase the levels of ticagrelor and reduce the speed of its offset. (For a proposed interaction with high dose aspirin, see “Approval Status” later in this chapter.)

Clinical studies.

In the PLATO trial, patients with either moderate to high risk NSTE-ACS (planned for either conservative or invasive management) or STEMI planned for primary PCI were randomized to either clopidogrel 75 mg daily, with a loading dose of 300 mg, or ticagrelor 180 mg loading dose followed by 90 mg twice daily.[74] In this trial over 12 months ticagrelor given to 9333 patients reduced deaths compared with clopidogrel given to 9291 patients (4.5% versus 5.9%, $p < 0.0001$). In the overall cohort, in which 61% of patients came to PCI either early or within 24 hours the primary composite endpoint (death from vascular causes, MI, or stroke) was reduced from 11.7% in the clopidogrel group to 9.8% in the ticagrelor group (HR 0.84; CI 0.77-0.92; $P < 0.001$). The primary endpoint in patients undergoing a planned invasive strategy, the primary composite endpoint occurred in 9% of patients in the ticagrelor group, versus 10.7% in the clopidogrel group ($P = 0.0025$)[95] of the benefit in terms of reduced MI and death accrued progressively with continued separation of event curves at 12 months

Adverse effects of ticagrelor.

Adverse effects are reviewed in Hamm et al.[73] In addition to increased rates of minor or non–CABG-related major bleeding with ticagrelor, adverse effects include dyspnea, increased frequency of ventricular pauses, and asymptomatic increases in uric acid. Dyspnea occurs most frequently (up to 14%) within the first week of treatment and may be transient or persist until cessation of treatment, but is usually not severe enough to stop treatment. The dyspnea does not seem to be linked to deterioration in cardiac or pulmonary function. Ventricular pauses of 3 seconds or more occurred more frequently (but not significant for ≥5 second pauses) and were mostly asymptomatic nocturnal sinoatrial pauses occurring in the first week. Caution is required in advanced sinoatrial disease or second- or third-degree atrioventricular block, unless already treated by a permanent pacemaker. The mechanisms of the dyspnea and ventricular pauses remain uncertain.

Approval status.

Health Canada and the European Union have granted approval to ticagrelor for the secondary prevention of atherothrombotic events in patients with ACS. The FDA approval is to reduce the risk of cardiovascular death and MI in patients with ACS, but with a boxed warning stating that use of ticagrelor with aspirin in doses exceeding 100 mg/day decreases the effectiveness of the medication. This dose limitation might be explained by a drug-drug interaction with high-dose aspirin such as 300-mg daily that is thought to account for the lesser effectiveness of ticagrelor in the North American component of the PLATO trial.

Cangrelor

Cangrelor is a rapid-acting, reversible, potent, competitive inhibitor of the $P2Y_{12}$ receptor (see Fig. 9-7). Given intravenously, it acts within 20 minutes to achieve 85% inhibition of ADP-induced platelet aggregation. In a pooled analysis of the two large phase 3 CHAMPION trials, with the use of the universal

definition of MI, cangrelor was associated with a significant reduction in early ischemic events when compared with clopidogrel in patients with NSTE ACS undergoing PCI.[96] A third phase 3 trial, the PHOENIX trial, is underway. In a small trial, when added to clopidogrel, cangrelor decreased platelet reactivity but did not alter cardiac surgery–related bleeding.[97]

Vorapaxar and atopaxar

Vorapaxar.

Vorapaxar is a potent, competitive PAR-1 antagonist (see Fig. 9-3) that was tested in two large outcome trials. In 12,944 patients with ACS (NSTE),[98] vorapaxar did not significantly reduce the primary endpoint of a composite of major cardiovascular events (P = 0.07), although it did reduce the secondary endpoint of cardiovascular death, MI, or stroke (P = 0.02). Unfortunately, it significantly increased the risk of major bleeding, including intracranial hemorrhage (P < 0.0001), so that the trial was terminated early after a safety review.[98] In the second study, a secondary-prevention study in 26,449 patients with MI, ischemic stroke, or peripheral vascular disease,[99] vorapaxar reduced by 12% (p = 0001) the protocol-specified primary endpoint of the composite of cardiovascular death, MI, stroke, or urgent coronary revascularization compared with standard of care, but again at the cost of increased bleeding (4.2% versus 2.5%, P < 0.001), including intracranial hemorrhage (ICH). However, there was a lower risk of ICH in patients without a history of stroke.

Atopaxar.

Atopaxar is still under evaluation. In one phase 2 trial on patients with ACS (NSTE), no major cardiovascular benefits were detected, hepatic enzymes rose, and QTc was prolonged.[100] However, Holter-detected ischemia decreased 48 hours following dosing.

Expert CONSULT

DRUGS FOR THE HEART
LIONEL H. OPIE | BERNARD J. GERSH

Glycoprotein IIb/IIIa receptor antagonists

GpIIb/IIIa blockers inhibit one of the platelet integrin adhesion receptors known as the αIIbβ3 receptor (see Fig. 9-3 and Table 9-1).[10] Thereby they block final platelet activation and cross-linking by fibrinogen and vWF. Importantly, the trials of GpIIb/IIIa antagonists were conducted before the advent of dual antiplatelet therapy so that recent guidelines have given them less strong recommendation. Thus according to current ESC guidelines it is reasonable to withhold GpIIb/IIIa receptor inhibitors until after angiography.[73] Maximum platelet inhibition should logically consist of three types of agents acting at three different sites: aspirin, $P2Y_{12}$ blockers, and GpIIb/IIIa inhibitors (see Fig. 9-3). However, high doses of all three combined with anticoagulant therapy should only be reserved for ACS with continuing ischemia while awaiting PCI because of the increased risk of bleeding.[73]

Risk of thrombocytopenia and bleeding.

The three commonly used GpIIb/IIIa antagonists are abciximab, tirofiban, and eptifibatide, each with somewhat different approved indications in the United States (Table 9-2). They have all been studied on a background of aspirin and antithrombotic therapy, but the main trials were conducted prior to the use of thienopyridines and the current $P2Y_{12}$ blockers. The major problem with these agents is acute thrombocytopenia at rates ranging from 0.3% to 6%[101] with added risk of delayed thrombocytopenia after 5-11 days; both acute types are thought to be caused by drug-dependent antibodies. Abciximab more than doubles the incidence of severe thrombocytopenia, which can rarely be fatal, with much lower risks for eptifibatide or tirofiban.[73] Thus all three are contraindicated in the presence of a bleeding site or increased bleeding potential, or preexisting thrombocytopenia. All are administered with either low-molecular-weight heparin (LMWH) or low-dose intravenous unfractionated heparin (UFH). All are given intravenously and only for a limited time, to cover the intervention.[73] For patients who are not at high risk and in the absence of PCI, their effect is modest or neutral and no current guidelines recommend their use in such settings.

Table 9-2 -- GpIIb/IIIa Receptor Antagonists: Key Properties

Compound and US Licensed Indications	Supporting Trials	Pharmacokinetics	Doses (all with aspirin and heparin)*	Special Points	Side Effects and Contraindications
Abciximab 1. PCI 2. Unstable angina requiring PCI within 24 h	CAPTURE, EPIC, EPILOG, EPISTENT, TARGET	Monoclonal antibodyHigh affinity to platelet receptor (low KD); 67% bound to receptor; plasma t½ 10-30 min; remains platelet-bound in circulation up to 15 days with some residual activity	0.25 mg/kg bolus 10-60 before PCI, then 0.125 mcg/min up to max of 10 mcg over 12 h, up to 24 h if ACS with planned PCI	Keep vials cold (not frozen); filter bolus injection before use, use in-line filter for infusion; discard vial after use.	Bleeding—most contraindications relate to risk of bleeding. Use extra care at puncture sites.Thrombocytopenia—Caution: obtain platelet count before starting, 2-4 h after bolus and 24 h before discharge of patientHypersensitivity—rare.
Eptifibatide 1. PCI 2. Non-ST elevation ACS	IMPACT-II, PURSUIT, ESPIRIT	Cyclic heptapeptideLower receptor affinity than others; plasma t½ 2-3 h; renal clearance 50%	180 mcg/kg bolus, then 2 mcg/kg/min up to 72 hReduce dose to 0.5 mcg/kg/min at time of PCI, then for 20-24 h post-PCI. If no prior ACS but PCI, 135 mcg/kg bolus then 0.5 mcg/kg/min	Store vials at 2°-8° but can keep at room temperature up to 2 months.	Bleeding, as for abciximab.Renal disease: C/I if serum creatinine > 4 mg/dL (350 μmol/L). If serum creatinine 2-4 mg/dL (175-350 μmol/L) reduce dose to 135 mcg/kg bolus then 0.5 mcg/kg/min. Thrombocytopenia: no excess is claimed in package insert, but real risk probably similar to

Compound and US Licensed Indications	Supporting Trials	Pharmacokinetics	Doses (all with aspirin and heparin)*	Special Points	Side Effects and Contraindications
					other agents (see text).
Tirofiban 1. Non-ST elevation ACS 2. ST-elevation MI	PRISM, PRISM-Plus RESTORE On-TIME 2	Peptidomimetic nonpeptideIntermediate affinity for receptor, closer to abciximab; hence 35% unbound in circulation, renal (65%) and fecal (25%) clearance	1. Non-STEMI, Two stage infusion: 0.4 mcg/kg/min for 30 min, then 0.1 mcg/kg/min up to 48 min 2. STEMI, 25-mcg/kg bolus and 0.15-mcg/kg/min maintenance infusion	Store vials at room temperature, 25 °C or 77 °C protected from light (easiest to store)	Bleeding, as for abciximab.Renal disease: ↓ dose if creatinine clearance <30 mL/min. Thrombocytopenia: 1.5% vs 0.6% heparin alone. Do platelet count before (C/I if count < 150,000/μL), 6 h after initial dose, then daily, stop if platelets <90,000//μL.

Berg JM, et al., J Am Coll Cardiol 2010;55:2446.

ACS, Acute coronary syndrome; *C/I,* contraindications; *MI,* myocardial infarction; *PCI,* percutaneous intervention; *STEMI,* ST-elevation myocardial infarction; $t_{½}$, half-time.

* For heparin doses, see text.

Combination with unfractionated or lmwhs or other anticoagulants.

The GpIIb/IIIa blockers must be combined with aspirin and anticoagulant therapy, the latter being UFH in most major trials. This in turn calls for constant monitoring of the heparin dose by activated clotting time (ACT) testing. However, current practice usually prefers LMWH to UFH. Based on the results of the ACUITY trial, bivalirudin may be used in place of GpIIb/IIIa inhibition plus UFH and LMWH.[63],[102] Fondaparinux is recommended by the ESC in nonurgent situations,[63] although there has been no formal test of its combination with GpIIb/IIIa inhibitors.

Intracoronary administration.

Compared with intravenous administration, intracoronary administration of GpIs has favorable effects on thrombolysis in myocardial infarction (TIMI) flow, target vessel revascularization, and short-term mortality after PCI, with similar rates of bleeding. Data regarding mid- and long-term outcomes are inconclusive. Large trials with longer follow-up are required to determine long-term safety and efficacy.[103]

Abciximab

Abciximab *(ReoPro)* is a monoclonal antibody against the platelet GpIIb/IIIa receptor. It consists of a murine variable portion of the Fab fragment combined with the human constant region. Abciximab also blocks the binding of vitronectin to its receptor ($\alpha_v\beta_3$) on endothelial cells, but it is not known whether this has any therapeutic advantage. Inhibition of platelet aggregation is maximal at 2 hours after a bolus injection, and returns to almost normal at 12 hours. However, the antibody is transmitted to new platelets and can be detected 14 days after administration. Its action can be reversed by platelet transfusions. Abciximab is very effective in patients undergoing PCI,[90] which is currently its only license in the United States, unless dealing with NSTE ACS with known angiographic findings and requiring PCI within 24 hours (see Table 9-2). When given very early, in the ambulance, to those with STEMI it only decreased distal embolization during PCI.[104]

Dose, side effects, and contraindications.

An initial bolus is followed by an infusion to a maximum of 24 hours (see Table 9-2). High-risk patients are pretreated with clopidogrel (see previous paragraph). Careful control of heparin is important to lessen bleeding, using a reduced dose as with all GpIIb/IIIa inhibitors. In EPILOG[105] heparin was given as an initial bolus of 70 U/kg, or less according to the initial ACT (maximum initial bolus, 7000 units), followed by 20 U/kg boluses as needed to keep the ACT at 200 seconds (see package insert). Acute severe *thrombocytopenia* (platelet count of <20,000), occurs in approximately 0.5% to 1% of patients.[106] Therefore platelet counts are required in the first few hours after beginning the infusion. Readministration of abciximab may provoke antibodies to cause severe thrombocytopenia in approximately 2.4%.[107] Thus previous thrombocytopenia is a clear *contraindication* to readministration; use

alternative IIb/IIIa blockers. It can be given intracoronary.

Tirofiban

Tirofiban *(Aggrastat)* is a highly specific nonpeptide peptidomimetic GpIIb/IIIa inhibitor, which is inherently less likely to cause hypersensitivity than a monoclonal antibody. Nonetheless, the end result of both methods of blockade is inhibition of binding of fibrinogen and vWF to the GpIIb/IIIa receptor (see Fig. 9-3). It has an acute onset and a half-life of approximately 2 hours. Indications, dosage, side effects, and contraindications are in Table 9-2. In the TACTICS trial on patients with unstable angina, tirofiban with PCI was compared with tirofiban alone, and the combination was better except for the low-risk group of patients, arguing for the value of risk assessment in ACS (see Fig. 12-3). Tirofiban is only licensed for unstable angina and NSTEMI, but is the easiest of the three agents to store (vials at room temperature). The European approval is for unstable angina or non–Q-wave MI with the last episode of chest pain occurring within 12 hours and with electrocardiogram (ECG) changes or elevated cardiac enzymes. Increased bleeding is given in the tirofiban package insert as the most common adverse event. In those who received heparin and tirofiban, the incidence of thrombocytopenia (defined as <50,000/mm^{3}) was 0.3% versus 0.1% for those who received heparin alone (package insert).

Comparison with abciximab.

In the TARGET trial of patients receiving triple antiplatelet therapy (aspirin, clopidogrel, and a GpIIb/IIIb inhibitor) plus heparin, tirofiban was compared with abciximab in 4809 patients undergoing PCI for an ACS or for stable angina.[108] Both drugs were given according to the package inserts. By 30 days, MI had occurred in 6.9% of tirofiban patients versus 5.4% of abciximab patients (p = 0.04). Minor bleeding was more frequent with abciximab. At 12-month follow-up there was no difference in the composite endpoint of death, MI, or urgent revascularization.[109] Thus, overall, at these doses used and long-term the agents were equal although very different in price.

Use of tirofiban in STEMI.

The new higher doses (25 mcg/kg bolus and 0.15 mcg/kg/min maintenance infusion)[110] were given to patients with STEMI in the ambulance or referral center in the On-TIME 2 Study.[111] All patients also received an intravenous bolus of UFH (5000 IU), together with intravenous aspirin 500 mg and an oral 600-mg loading dose of clopidogrel. Then, before primary PCI, an additional 2500 IE UFH was administered only if the ACT was less than 200. Major adverse cardiac events at 30 days were significantly reduced (5.8% versus 8.6%, p = 0.043). There was a strong trend toward a decrease in mortality (2.2% versus 4.1%, p = 0.051) in patients who were randomized to tirofiban pretreatment, which was maintained during the 1-year follow-up (3.7% versus 5.8%, p = 0.08). Tirofiban pretreatment reduced major adverse cardiac events at 30 days (5.8% versus 8.6%, p = 0.043), with a strong trend toward a decrease in mortality.[111]

Summary.

For STEMI tirofiban pretreatment reduced major adverse cardiac events at 30 days.

Eptifibatide

Eptifibatide *(Integrilin)* is a synthetic cyclic heptapeptide. Structural differences from tirofiban mean that they bind at different sites on the GpIIb/IIIa receptor, yet with the same end result. The affinity for the receptor is, however, lower than with the other GpIIb/IIIa blockers, which explains the higher dose in absolute terms. Indications, dosage, side effects, and contraindications are in Table 9-2. UFH was given with eptifibatide in the PURSUIT trial as a bolus of 5000 units (weight adjusted), and then infused at 1000 U/hour to keep the activated partial prothrombin time (aPPT) at between 50 and 70.[112] As for all GpIIb/IIIa blockers, the major problem is increased bleeding. Although the package insert claims that thrombocytopenia (<100,000/mm^{3}) is not augmented, in PURSUIT[112] profound platelet depression (<20,000/mm^{3}) occurred within 0.3% eptifibatide versus 0.1 % in controls, both groups receiving aspirin and heparin. Thus thrombocytopenia is a risk as with other GpIIb/IIIa blockers. Eptifibatide is currently the only GpIIb/IIIa blocker that is licensed for both ACS and for PCI. It can be given by the intracoronary route.

Expert CONSULT

DRUGS FOR THE HEART
LIONEL H. OPIE | BERNARD J. GERSH

Oral anticoagulants: Warfarin, antithrombin, and anti-Xa agents (dabigatran, rivaroxaban, apixaban)

Oral anticoagulation by warfarin

Warfarin (Coumarin, Coumadin, Panwarfin) is the most commonly used oral anticoagulant. Warfarin also has few side effects, except for the major complication associated with over-anticoagulation, which is bleeding including serious risk of intracranial hemorrhage. The metabolism of warfarin is influenced by many other drugs. In general, when comparing warfarin with aspirin, higher-intensity warfarin (international normalized ratio [INR] 3-4) is more effective, but associated with more bleeding that may be unacceptable. Moderate-intensity warfarin (INR 2-3) still has the risk of bleeding but protects better than aspirin from stroke prevention in AF.[113] Currently there is a strong trend away from warfarin toward the new antithrombin agents (dabigatran, rivaroxaban, apixaban). Yet in carefully managed situations as in Finland,[114] the risk of intracranial hemorrhage with warfarin is declining. Patients currently already stabilized on warfarin with INR 2-3 are currently best left on warfarin.

Cost-effective considerations.

Thus an important contemporary question is whether a new candidate for anticoagulant therapy for nonvalvular AF should receive one of the newer antithrombin agents or warfarin. One of the deciding factors may be cost effectiveness, suggesting that dabigatran is superior to warfarin. Dabigatran was associated with 4.27 quality-adjusted life-years compared with 3.91 quality-adjusted life-years with warfarin.[115] Dabigatran provided 0.36 additional quality-adjusted life-years at a cost of $9000, yielding an incremental cost-effectiveness ratio of $25,000. This conclusion is, however, limited as it is based on a substudy of a single randomized trial. Furthermore, these results may not apply to good stabilized INR control using warfarin.

Mechanism of action.

As a group, the warfarin-like oral anticoagulants inactivate vitamin K in the hepatic microsomes, thereby interfering with the formation of vitamin K–dependent clotting factors such as prothrombin (see Fig. 9-5). In addition, factor X may be reduced.[113] The onset of therapeutic levels of anticoagulation is delayed by 2-7 days.

Pharmacokinetics.

After rapid and complete absorption, oral warfarin is almost totally bound to plasma albumin, with a half-life of 37 hours. It is metabolized in the hepatic microsomes by the enzymes cytochrome P450(CYP)2C9 and vitamin K epoxide reductase (VKORC1) to produce inactive metabolites excreted in the urine and stools. *Genetic variation* in these enzymes probably account for much of the variability of the warfarin dose from patient to patient.[116] For pharmacogenetic testing, see below.

Dose.

A standard procedure is to give warfarin 5 mg/day for 5 days, checking the INR daily until it is in the therapeutic range, and then to check it three times weekly for up to 2 weeks. *Lower starting doses* should be given to older adults and to those with increased risk of bleeding (including prior aspirin use). Genetic variations in hepatic enzymes explain lower doses for persons of Asian descent[117] and higher doses for black and some Jewish populations.[117],[118] In those transitioning from parenteral anticoagulation, warfarin should be commenced at least 4 days before heparin is discontinued to allow for the inactivation of circulating vitamin K–dependent coagulation factors; the heparin can be discontinued once the INR (next section) has been in the therapeutic range for 2 days.[113] Avoiding a large primary dose helps prevent an excessively high INR. Patients with heart failure or liver disease require lower doses. The usual dose

maintenance is 4-5 mg daily, but may vary from 1 mg to 20 mg daily. Warfarin resistance is largely genetic in origin.[118] This wide range means that doses must be individualized according to the INR. In the United States, genetic-based testing is available to identify those with very low warfarin requirements.[116] In the first trial of warfarin dosing guided by genetic testing, more accurate early control of anticoagulation was achieved. However, the primary endpoint of reduced out-of-range INRs was not achieved.[119]

Inr range.

The effect of warfarin is monitored by reporting the INR (see Fig. 9-5), which represents the prothrombin time according to international reference thromboplastin, as approved by the World Health Organization. In general clinical practice, the aim is moderate intensity of inhibition with an INR of 2-3. Thus an INR of 2-3 is also appropriate for patients who have deep vein thrombosis (DVT) with pulmonary embolism, those at risk of thromboembolism, and for AF. Patients with *prosthetic heart valves* require the greatest intensity of safe anticoagulation, and the recommended INR range is variable, from 2 to 4.5, with lower values for those with bioprosthetic valves and mechanical aortic rather than mitral valves.[113] A metaanalysis on 23,145 patients recommended a target of more than 3.[120] As Asian populations have a higher rate of intracranial hemorrhage, a lower INR target may be needed.[117] Once the steady-state warfarin requirement is known, the INR need only be checked once every 4-6 weeks. Importantly, variation in INR control and variation in warfarin requirements may be influenced in individual patients by dietary changes and alcohol intake (modifying metabolism) and by drug interactions (see p. 358).

Self-monitoring and self-guided warfarin therapy.

Selected patients who can both self-monitor and self-guide have less thromboembolic events and lower mortality than those who only self-monitor.[121] Thus with computer-guided dose adjustment the educated patient may achieve control superior to that achieved even by the experienced physician.

Pharmogenetic-guided dosing.

Bleeding risks are highest within the first 1-3 months of starting warfarin, up to 10 times more than later risk. In the CoumaGen-II study of VKORC genotype-guided warfarin dosing, the prior analysis of VKORC gave the genetically appropriate first dose. The result was 10% absolute reduction in the out-of-range INRs, 66% lower rate of DVT, and a reduction in serious adverse events at 90 days from 9.4% in controls to 4.5%. These data argue for the pharmacogenetic approach, if available and if rapid and affordable, prior to the initiation of warfarin.[122]

Dose reduction.

The dose should be reduced in the presence of congestive heart failure; liver damage from any source, including alcohol; renal impairment (which increases the fraction of free drug in the plasma); and malnutrition (which leads to vitamin K deficiency).Thyrotoxicosis enhances the catabolism of vitamin K, reducing the dose of warfarin needed, whereas myxedema has the opposite effect. In older adults, the dose should be reduced because the response to warfarin increases with age. A high intake of dietary vitamin K (e.g., green vegetables such as broccoli) reduces the efficacy of warfarin. Some fad diets alternate high and low salad periods, which causes INR control to fluctuate.

Drug interactions with warfarin.

Warfarin interacts with approximately 80 other drugs. It is inhibited by drugs such as barbiturates or phenytoin that accelerate warfarin degradation in the liver. Potentiating drugs include the cardiovascular agents allopurinol and amiodarone, and cephalosporins that inhibit the generation of Vitamin K.[113] Drugs that decrease warfarin degradation and increase the anticoagulant effect include a variety of antibiotics such as metronidazole *(Flagyl)* and co-trimoxazole *(Bactrim)*.

Antiplatelet drugs such as aspirin, clopidogrel, and NSAIDs may potentiate the risk of bleeding, but this varies considerably. Sulfinpyrazone powerfully displaces warfarin from blood proteins, reducing the required dose of warfarin down to 1 mg in some patients. The safest rule is to tell patients on oral anticoagulation not to take any over-the-counter nor any new drugs without consultation, and for the physician to checklist any new drug that is used. If in doubt, the INR should be monitored more frequently. This is also necessary when dietary changes are anticipated, as during travel.

Contraindications.

Contraindications include recent stroke; uncontrolled hypertension; hepatic cirrhosis; and potential GI and genitourinary bleeding points such as hiatus hernia, peptic ulcer, gastritis, gastroesophageal reflux, colitis, proctitis, and cystitis. If anticoagulation is deemed essential, the risk-benefit ratio must be evaluated carefully. Old age is not in itself a contraindication against anticoagulation, although older adults are more likely to bleed, particularly if prone to falls.

Renal impairment.

The warfarin doses for moderate reduction in renal function may need reduction (approximately 25% in a small study for a mean creatinine clearance [CrCl] of 47 mL/min) while watching for increased warfarin instability.[113]

Pregnancy and warfarin.

Warfarin is contraindicated in the first trimester because of its teratogenicity, and 2 weeks before birth because of the risk of fetal bleeding. The alternative, UFH, may be less effective than warfarin and the FDA has issued a warning against LMWH. One approach is to use heparin or LMWH in the first trimester; warfarin in the second trimester until about 38 weeks; and changing to heparin or LMWH, which is discontinued 12 hours before labor induction, restarted postpartum, and overlapped with warfarin for 4-5 days. Heparin should be regularly monitored by aPPT and LMWH by anti-Xa levels. Heparin requirements increase in the third trimester because heparin-binding proteins increase.

Complications and cautions.

The most common complication is bleeding with increased risk of intracranial hemorrhage, especially in older adults.[123],[124] This finding has accelerated the trend toward replacement of warfarin by direct thrombin inhibitors; yet they, too, are relatively contradicted in much older adults. Although rare, a very serious complication is *warfarin-associated skin necrosis.* The cause is not well understood; it may possibly be acute depletion in protein C, a natural anticoagulant. The skin necrosis may occur between the third and the eighth day of therapy, especially when high-dose warfarin is initiated after cardiopulmonary bypass. The best protection is to start with lower doses under the cover of heparin. If it is necessary to carry on with warfarin despite the necrosis, the dose should be reduced to approximately 2 mg daily, covered by heparin, and gradually increased over several weeks.[113] Long-term use of warfarin (>1 year) may be complicated by osteoporotic fracture, which is more marked in men.[125]

Warfarin overdose and bleeding.

Bleeding is more common in older adult patients soon after starting therapy, which is a high danger period.[126] During chronic therapy, the risk of bleeding can be reduced dramatically by lowering the intended INR from 3-4.5 down to 2-3.[113] Even high INR values up to 9 may (in the absence of bleeding) be managed by dose omission and then reinstating warfarin at a lower dose. If bleeding becomes significant, or if the INR is more than 9, 3-5 mg of oral vitamin K_1 should be given to reduce the INR within 24-48 hours. The subcutaneous route gives variable results and should be avoided, rather than using the slow intravenous route (5-10 mg over 30 min) for an emergency.[113] In patients with *prosthetic valves,* vitamin K should be avoided because of the risk of valve thrombosis, unless there is a life-threatening intracranial bleed. A comparison between fresh frozen plasma (FFP) and vitamin K in patients with mechanical heart valves and mild to moderate over-anticoagulation showed quicker response within 6 hours to FFP.[127] In patients unresponsive to vitamin K or with life-threatening bleeding, the intravenous treatment could be (1) a concentrate of the prothrombin group of coagulation factors including II, IX, and X; or (2) FFP (15 mL/kg).

Indications for warfarin

Acute myocardial infarction.

We maintain the viewpoint expressed in our previous editions that we do not advise using oral anticoagulants routinely after infarction; rather, there should be a careful evaluation of the needs of each individual patient, with a preference for aspirin started as soon as possible after the onset of myocardial ischemia and continued indefinitely unless there are clear contraindications. We also recommend a $P2Y_{12}$

blocker for 12 months. The downside is the risk of increased bleeding with warfarin[128] and with triple therapy.

In chronic heart failure post-MI (mean ejection fraction, 25%) in sinus rhythm, there was no significant overall difference in the primary outcome between treatment with warfarin and treatment with aspirin.[129] In this 6-year study of 2305 patients, 48% with previous MI with low and in sinus rhythm, there was no difference in the composite of death, ischemic stroke, or intracranial bleed. The reduced rate of ischemic stroke with warfarin was offset by an increased risk of major hemorrhage. The authors concluded that choice between warfarin and aspirin should be individualized. Because aspirin is cheap and requires no monitoring, it wins the day in most instances. Aspirin was provided by Bayer HealthCare; thus the likely dose was 100 mg daily.

Venous thromboembolism.

In patients with DVT, warfarin should be initiated concurrently with intravenous heparin or LMWH. Thereafter, oral anticoagulation alone should be continued for at least 3 months. A less intensive regimen (INR 2-3) is effective and safer than a more intensive regimen (INR 3-4.5).[113] Long-term follow-up by low-intensity warfarin (INR 1.5 to 2) reduces repeat events.[130] Indefinite treatment should be considered in patients with recurrent venous thrombosis, or with risk factors such as antithrombin-III deficiency, protein-C or protein-S deficiency, persistent antiphospholipid antibodies, or malignancy. For documented *pulmonary embolism,* either LMWH or UFH should be given, followed by oral warfarin continued for approximately 6 months in the absence of recurrences. However, should there be a recurrence, indefinite therapy should be considered.

Atrial fibrillation.

AF is strongly associated with thromboembolism and the risk rises additively in those with congestive heart failure, left ventricular (LV) dysfunction, hypertension, older age, diabetes, TIA, previous thromboembolism, prior MI, peripheral atrial disease, the presence of aortic plaques, and especially stroke. Treatment should be guided by the use of the European guidelines[46] taking into account the $CHADS_2$ score[131] and the CHADS-VASC or CHA_2DS_2-VASc scores.[132] (For assessment of these scoring systems, see Chapter 12, p. 498.) The benefits of warfarin far exceed the risk of hemorrhage. The only clear indications for withholding warfarin are (1) lone AF in younger patients (aged <65 years) without risk factors; (2) bleeding diathesis; and (3) older adult patients with high risk of bleeding, which can be quantified by the HAS-BLED[133] or ATRIA bleeding risk scores.[134] Cardioversion increases the risk of an embolus in patients with AF. After 48 hours of AF, anticoagulation for 3 weeks is strongly recommended (if feasible) prior to elective cardioversion. Transesophageal echo may be used to look for atrial thrombus with the aim of proceeding to cardioversion in the absence of thrombus, and where the duration is uncertain. In most patients the duration of anticoagulation even after resumption of sinus rhythm should be lifelong.[135] Patients with paroxysmal AF have increased risk of stroke, the same as persistent AF.[136]

Paroxysmal atrial fibrillation.

The choices vary from no treatment in “lone” AF to warfarin in those older adult patients at higher risk of stroke.[137] For the latter, one of the newer antithrombins would be preferred because of their lower risk of stroke (see later, Table 9-6). Treatment should again be guided by the use of the European guidelines,[46] taking into account the $CHADS_2$ score[131] or the CHADS-VASC or CHA_2DS_2-VASc scores.[132] (For assessment of these scoring systems and the HAS-Bled indexes, see Chapter 12, p. 499.) We recommend the CHA_2DS_2-VASc scores.

Atrial fibrillation presenting with acute embolic stroke.

Although anticoagulation is required, cerebral hemorrhage must first be excluded by computed tomography or magnetic resonance imaging. In the case of large strokes, warfarin should be delayed for approximately 1 week to allow full evolution to occur.

Atrial fibrillation: Proposals.

There is strong evidence for the use of moderate-intensity anticoagulation (INR target 2-3) in “high-risk” patients, in whom warfarin is much more effective than aspirin in preventing stroke ($CHADS_2$ >1).[46],[137]

Patients should be risk-stratified CHA_2DS_2-VASc scores, and aspirin (or no antithrombotic) should only be used in those at low stroke risk (score of 0 or 1). The clinical assessment required to assess the need for warfarin is shown in Table 7 of the European recommendations on anticoagulation.[138] The major risk factors are age older than 65 years, a history of hypertension, diabetes, congestive heart failure, and a history of stroke or TIA. Increased left atrial (LA) dimension, a mitral valve gradient, or regurgitation indicate higher risk.[138] Patients with a recent TIA or minor stroke are at particularly high risk of a recurrence.[139]

Atrial fibrillation in older adults.

This common combination requires careful balancing of the advantages of reduced thromboembolism versus the risk of serious hemorrhage, especially in those with increased risk of hemorrhage and those with an inadvertent INR of 4 or more.[126]

Mitral stenosis or regurgitation.

In patients with mitral valve disease, the risk of thromboembolism is greatest in those with AF, marked LA enlargement, or previous embolic episodes; anticoagulation is strongly indicated in patients with any of these features. In contrast, anticoagulation is not indicated in patients with mitral stenosis with sinus rhythm. *Percutaneous mechanical LA appendage closure* with the Watchman device is a new approach. In a comparison of such closure against warfarin in AF patients with $CHADS_2$ of 1 or more,[140] the procedure was noninferior to warfarin therapy for the prevention of stroke, systemic embolism, and cardiovascular death. Yet there was a significantly higher risk of complications, predominantly pericardial effusion and procedural stroke related to air embolism. These complications could be decreased by meticulous care and increased operator experience.[140] Peri-device flow occurred in 32% of implanted patients at 12 months but was not associated with an increased risk of thromboembolism.[141]

Dilated cardiomyopathy.

There is a substantial risk of systemic embolism, particularly if there is AF. Although anticoagulants are effective in reducing thromboembolism, the risk versus benefit is the subject of ongoing trials. In heart failure, aspirin is as protective as warfarin.[129] Thus we do not recommend routine anticoagulation in the absence of additional thrombotic risk or evidence of mural thrombus.

The tachycardia-bradycardia syndrome.

Tachycardia-bradycardia syndrome may be complicated by AF and thromboembolism. Anticoagulation should be considered, especially if there is underlying organic heart disease, such as ischemic heart disease, hypertension, or cardiomyopathy.

Atrial septal defects.

In older patients with atrial septal defects and pulmonary hypertension, anticoagulation is strongly recommended as prophylaxis against in situ pulmonary arterial thromboses or, rarely, paradoxical emboli. Anticoagulation is also required for patients with repaired septal defects who subsequently develop AF.

Warfarin for prosthetic heart valves.

Warfarin is recommended in patients with mechanical prosthetic heart valves, usually at a level of 2.5 to 3.5.[113] However, a metaanalysis proposed a relatively high target INR of 3 to 4.5, with aortic mechanical valves at the lower end and mitral valves at the higher end of the INR range.[120] In patients with bioprosthetic mitral valves, the risk of thromboembolism is highest in the first 6-12 weeks, when warfarin is mandatory. Thereafter, aspirin may be given or antithrombotic therapy may be discontinued if there are no other indications. There is strong evidence supporting the continuation of warfarin when mitral bioprosthetic valves are combined with AF, a large left atrium, or LV failure. In patients with bioprosthetic aortic valves the risk is low, and aspirin for 6-12 weeks is appropriate.[142]

Warfarin for moderate chronic kidney disease: Warfarin-related nephropathy.

CKD is associated with both a lower warfarin maintenance dose and decreased stability of anticoagulation, requiring tighter anticoagulation management.142A In those with stage 3 CKD, AF is associated with double the rate of adverse events,[143] including increased bleeding.[41] Adjusted-dose warfarin compared with

aspirin and very-low-dose warfarin reduced ischemic stroke and systemic embolism by 76% (P < 0.001), yet without increased major hemorrhage.[143] However, note that for this degree of stage 3 renal impairment, dabigatran or rivaroxaban can also be used, whereas apixaban also seems safer, although without comparative trials (see later, Table 9-6).

Warfarin-related nephropathy is a newly described entity in those with an acutely increased INR of more than 3 soon after the initiation of warfarin.[144] This, if confirmed, is especially serious in patients with CKD in whom it is more often associated with an unexplained acute increase in serum creatinine and an accelerated progression of CKD. In 4006 patients with CKD and an INR exceeding 3, the 1-year mortality was 31.1% compared with 18.9% without warfarin-related nephropathy.[144] The *bottom line* is that INR should be kept below 3 in all patients soon after starting warfarin, but especially in those with CKD or who use antithrombin inhibitors (see later, Table 9-6).

Possible indications for warfarin.

Cerebrovascular accidents and transient ischemic attacks.

There is no evidence to support anticoagulation in patients who have had a completed stroke (in the absence of AF). When patients present with an acute stroke and AF, warfarin is indicated providing cerebral hemorrhage is excluded by computed tomography. In patients with recent TIAs, warfarin is only recommended when symptoms persist despite aspirin or clopidogrel therapy, or when there is a major cardiac source of embolism. In symptomatic intracranial arterial stenosis, high-dose aspirin is better than warfarin (same stroke outcomes, less bleeding and death).[145]

Mitral valve prolapse.

In patients with definite echocardiographic documentation of mitral valve prolapse and evidence suggestive of thrombotic or thromboembolic events, warfarin or platelet inhibitors may be indicated.

Low-dose warfarin: Is it indicated to prevent thromboembolism?

As reviewed in the seventh edition of this book, low-dose warfarin is theoretically attractive for a variety of thromboembolic conditions, yet not supported by trial data. In secondary prevention after venous thromboembolism (VTE), low-intensity warfarin (INR 1.5-1.9) was better than placebo[130] but inferior to the conventional intensity (INR 2-3).[146] For patients with unprovoked VTE, a low level of anticoagulation with *rivaroxaban* was noninferior to warfarin for the primary efficacy outcome (symptomatic recurrent VTE) and reduced major bleeding from 2.2 to 1.1% (HR, 0.49; 0.31 to 0.79; P = 0.003). Rates of other adverse events were similar.[147]

Oral anticoagulation by warfarin: Summary.

Oral anticoagulants are indicated in many *patients with AF and in those with prosthetic heart valves.* They are used in both the treatment and prevention of venous thrombosis and pulmonary embolism. *A small minority of patients with AMI qualify for limited anticoagulation with warfarin for 3-6 months.* Very few require prolonged anticoagulation. Long-term anticoagulation requires careful consideration of the risk-benefit ratio (bleeding versus decreased thromboembolism) for each individual patient. There is the increasingly recognized risk of increased intracranial bleeding with warfarin. For example, although a patient with chronic AF may benefit from meticulous anticoagulation, aspirin may be a safer choice for a relatively noncompliant or frail older adult patient. The major problem with warfarin is the large variation in the doses needed to achieve and maintain the required INR. Genetic-based dosing is gaining ground but is costly and not straightforward.

Expert CONSULT

DRUGS FOR THE HEART
LIONEL H. OPIE | BERNARD J. GERSH

Anticoagulation with direct thrombin inhibitors and anti-X a agents

As noted in Chapter 7, with the recognition of the importance of stroke as the principal clinically significant complication of AF, stroke prevention by new oral anticoagulants has moved to the fore. These agents are at least as effective as warfarin in preventing embolic stroke among patients with AF and are safer with less intracranial bleeding or complicating hemorrhagic strokes.[148] There may be a small increase in the incidence of MI with dabigatran, with an HR of 1.27 versus warfarin; the mechanism is unknown.[149] On offer are more convenient and potentially safer ways of maintaining optimal anticoagulation, which should encourage physicians to use these agents more widely for patients with AF. These agents are discussed here. The major remaining issues are cost effectiveness versus warfarin and the lack of any clinically established antidotes to inadvertent uncontrolled bleeding. However, the risk of bleeding may have been over emphasized (see discussion of the EMA under “Doses and Approval” in “Dabigatran”), the exception being in the much older adults.

Dabigatran

Dabigatran etexilate (Pradaxa) is a new direct thrombin inhibitor.[150] Dabigatran and its acyl glucuronides are competitive, direct thrombin inhibitors (see Fig. 9-9). Because thrombin enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents thrombosis. Both free and clot-bound thrombin as well as thrombin-induced platelet aggregation are inhibited by the active moieties. Dabigatran etexilate mesylate is absorbed as the ester, which is then hydrolyzed, forming dabigatran, the active moiety. Dabigatran is metabolized to four different acyl glucuronides, which have similar pharmacokinetics and activity to dabigatran. These have similar dose-proportional pharmacokinetics in healthy subjects and patients in the range of doses from 10 to 400 mg. Dabigatran etexilate is a substrate of the efflux transporter P-Gp. However, there appear to be no significant drug interactions with P-Gp inducers or inhibitors. After oral administration of dabigatran etexilate in healthy volunteers, Cmax occurs at 1 hour postadministration in the fasted state. The half-life of dabigatran in healthy subjects is 12 to 17 hours; its bioavailability is 6.5%, and 80% of the drug is excreted by the kidneys. Gastric discomfort is a potential side effect.

Clinical studies.

In the RE-LY study dabigatran 150 mg twice daily reduced the combined endpoint of stroke and systemic embolism in patients with AF when compared with warfarin, yet with approximately similar rates of bleeding and four fewer intracranial hemorrhages per 1000 patients.[151] With dabigatran there was a trend toward increased MI, more than balanced by the major finding that stroke or systemic embolism was reduced compared with warfarin.[152] At a dose of 110 mg twice daily dabigatran gave similar rates of stroke and systemic embolism as warfarin, yet with 30% lower rates of major hemorrhage and five fewer intracranial hemorrhages per 1000 patients.[153] A major advantage over warfarin is that dabigatran reduces stroke or systemic embolism more effectively than warfarin. A broader composite that included “net clinical benefit” of all major events (all strokes, systemic embolism, MI, pulmonary embolism, major bleeding, and all-cause death) occurred at annual rates of 4.76% with dabigatran 110 mg, 4.47% with dabigatran 150 mg, and 5.10% with warfarin. The HRs versus warfarin were 0.93 ($P = 0.24$) for dabigatran 110 mg and 0.88 (95%, CI 0.78-0.98, $P = 0.03$) for dabigatran 150 mg. Thus the higher dose was better than warfarin at reducing all adverse cardiovascular events.[154]

Coadministration.

Coadministration of aspirin and dabigatran increased the risk of major bleeding compared with dabigatran alone (HR 1.91; $P < 0.001$) without any evidence of benefit in reducing stroke and other serious vascular events.

Risks in older adults.

Impaired renal function and low body weight are hazards. There must be a careful evaluation of the risks and possible benefits of treatment before starting dabigatran. In RE-LY, dabigatran at the higher dose of 150 mg twice daily was superior to adjusted-dose warfarin in reducing ischemic and hemorrhagic stroke. The risk for major bleeds was similar across subgroups.

Doses and approvals.

Doses and approvals are complex. The FDA has licensed the higher dose (150 mg twice daily) for prevention of stroke in patients with AF and the lower dose of 110 mg twice daily is also licensed in Europe. In May 2012 the FDA-approved new label stated that the 150-mg twice-daily dose is superior to warfarin in preventing ischemic and hemorrhagic stroke in nonvalvular AF.[155]The FDA also approved the 75 mg twice-daily dose for severe renal impairment. The Canadian Health authority approved dabigatran for the prevention of stroke and systemic embolism in patients with AF in whom anticoagulation is appropriate. The 150-mg twice-daily dose was recommended and the 110-mg twice-daily dose was specifically for patients more than 80 years of age and for patients at high risk of bleeding. Dabigatran 150 and 110 mg are both approved by the EMA for prevention of stroke or embolism in patients with nonvalvular AF and one or more risk factors, as well as the prevention of venous thromboembolic events in total hip- and knee-replacement surgery. In patients older than 75 or with renal impairment, renal function should be assessed after 1-3 months and then at least annually, and the drug should not be given to patients with CrCl less than 30 mL/min. Although more expensive than warfarin, the great cost of having a stroke often followed by lifelong physical impairment must be taken into account in financial analyses.

In renal impairment.

In the presence of renal impairment, the dose must be reduced because dabigatran and its moieties are renally excreted (80%) and should not be given to those with CrCl of less than 30 mL/min. However, these populations were excluded in RE-LY. Thus the FDA recommends a 75-mg dose[156] and the EMA suggests the 110-mg dose available in Europe.[41] Note that with time renal function may deteriorate, leading to increased plasma concentrations of dabigatran.[150]

Risk of bleeding.

Dabigatran increases the risk of bleeding and can cause significant and sometimes fatal bleeding. In January 2012, in response to the reports of bleeding, the FDA revised the dabigatran label, stressing the need to monitor renal function and adjusting the dabigatran dose if necessary. In May 2012, the EMA noted that the incidence of bleeding with dabigatran had significantly fallen during postregistration use.[157] More information will be available from RELY-ABLE, a long-term safety study, the results of which will soon be available and from GLORIA-AF, a patient registry, the second phase of which was recently launched.

Risk factors and contraindications for bleeding include much advanced age and the use of drugs that increase the risk of bleeding in general (e.g., antiplatelet agents, heparin, and chronic use of NSAIDs). Overall in the RE-LY study there was similar risk of major bleeds during dabigatran as with warfarin use, with a higher rate of major GI bleeds with dabigatran 150 mg than with warfarin (1.85% versus 1.25%, respectively),[153] and a higher rate of any GI bleeds (6.1% versus 4%, respectively) but lower rates of intracranial bleeding.

Active therapy for major bleeds.

With a short half-life, minor bleeds are treated by dose reduction or omission. Dabigatran etexilate is a lipophilic molecule successfully adsorbed in vitro by activated charcoal therapy. Although not clinically tested, it is reasonable to administer charcoal within 1 to 2 hours of overdose before dabigatran etexilate is absorbed from the GI tract.[150] In experimental brain hematoma in a murine intracranial hematoma model associated with dabigatran, PCC and, less consistently, FFP prevented excess hematoma expansion.[14] PCC was not effective in reversing anticoagulation with dabigatran in a small clinical trial.[13]

Dabigatran versus warfarin.

Hankey and Eikelboom[150] argue as follows. Warfarin will probably remain the treatment of choice for compliant patients well stabilized on warfarin, in those with a CrCl less than 30 mL/min, those who cannot afford dabigatran, those suffering from gastric discomfort, and when there are concerns about compliance

with the twice-daily dose of dabigatran. In addition, even patients taking warfarin and achieving good INR control may prefer dabigatran because dabigatran 150 mg twice daily reduces stroke and intracranial bleeding compared with warfarin. *Switching* from warfarin to dabigatran requires warfarin to be stopped and the INR to be monitored daily. When the INR falls below 2, usually 2 to 3 days later, dabigatran can be started.

Dabigatran: Summary.

Dabigatran, a direct thrombin inhibitor, is the first of the oral antithrombin agents; hence it has the largest and longest experience. The advantages of dabigatran versus warfarin are that it is rapidly effective, does not interact with foods nor with most medications (which are particularly problematic for patients taking warfarin), does not require monitoring, and is associated with a lower risk of ischemic stroke and intracranial bleeding than warfarin. It is more expensive than warfarin, but is more cost effective.

Rivaroxaban

Rivaroxaban (Xarelto) is an oral inhibitor of factor Xa (10a) and, like dabigatran and apixaban, it does not require monitoring. Unlike dabigatran or apixiban, it is given only once daily in AF. It is well tested in chronic nonvalvular AF.[158]

Pharmacokinetics.

Unchanged rivaroxaban is the most important compound in human plasma, with no major or active circulating metabolites present. The absolute bioavailability of rivaroxaban is approximately 100% for the 10-mg dose. Rivaroxaban is rapidly absorbed with Cmax appearing 2-4 hours after tablet intake. Rivaroxaban has a half-life of approximately 5 to 13 hours. Plasma protein binding in humans is high at approximately 92% to 95%. Approximately two thirds of rivaroxaban is cleared by the liver and the other one third is cleared by direct renal excretion of unchanged compound. Hepatic metabolism is mediated by cytochromes P450-(CYP3A4, CYP2J2). Renal excretion of the unchanged drug involves the P-Gp–breast cancer resistance protein transporter systems. Rivaroxaban does not induce nor inhibit CYP3A4. In cirrhotic patients with moderate hepatic impairment, rivaroxaban clearance is impaired so that inhibition of Factor Xa is increased by a factor of 2.6. Thus the dose needs reduction. For renal impairment see next section.

Drug interactions.

Rivaroxaban must be used with caution in patients receiving concomitant systemic treatment with azole antimycotics (e.g., ketoconazole) or human immunodeficiency virus (HIV) protease inhibitors (e.g., ritonavir) or rifampin (rifampicin). These drugs are strong inhibitors of both CYP3A4 and P-Gp. Co-administration of rivaroxaban with the strong CYP3A4 and P-Gp inducers (e.g., phenytoin, carbamazepine, phenobarbitone, or St. John's Wort) may also lead to a decreased rivaroxaban plasma concentration.

Use in nonvalvular atrial fibrillation.

To prevent stroke or systemic embolism in patients with a $CHADs_2$ score of 2 or more the dose was 20 mg once daily,[158] reduced to 15 mg daily in those with moderate to severe renal impairment.[159] In the ROCKET-AF study rivaroxaban was at least noninferior to warfarin (superior while on treatment).[158] There was no difference between groups in the risk of major bleeding, yet intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.

Use in recent acute coronary syndrome.

Because factor 10a (Xa) plays a central role in thrombosis, the inhibition of factor Xa by low-dose rivaroxaban was tested with the aim of showing improved cardiovascular outcomes in patients with a recent ACS.[160] In the ATLAS ACS 2–TIMI 51 trial 15,526 patients with a recent ACS received low-dose aspirin and a thienopyridine (almost all clopidogrel) plus 2.5-mg rivaroxaban twice daily (one fourth of the daily dose used in AF). Results were better than with 5 mg twice daily, with reduced rates of cardiovascular death (2.7% versus 4.1%, P = 0.002) and all-cause deaths (2.9% versus 4.5%, P = 0.002). The same dose reduced the risk of the composite endpoint of death from cardiovascular causes, MI, or stroke. Rivaroxaban, however, increased the risk of major bleeding (2.1% versus 0.6%, P < 0.001) and intracranial hemorrhage (0.6% versus 0.2%, P = 0.009), but not the risk of fatal bleeding. There were no hepatic side effects. The

problem with this otherwise impressive trial is that FDA approval for patients with ACS was declined in May 2012 because of imperfect follow-up of a small number of trial patients. Nonetheless, this study shows that a much lower dose than before could be used and that rivaroxaban has the potential to improve outcome in those with recent ACS.

Prevention of pulmonary embolism.

In 4832 patients who had acute symptomatic pulmonary embolism with or without deep vein thrombosis, rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) equaled standard therapy.[147] Rivaroxaban was noninferior to warfarin for the primary efficacy outcome (symptomatic recurrent VTE), and reduced major bleeding from 2.2% to 1.1% (HR, 0.49; 0.31 to 0.79; P = 0.003). Rates of other adverse events were similar.

Renal disease.

In the ROCKET-AF trial, the reduced dose of 15 mg once daily was given to those with moderate to severe renal impairment and a CrCl of 30-49 mL/min.[159] The outcomes in this cohort were similar to those with warfarin, as were rates of major and nonmajor bleeding.

Bleeding as a side effect.

Should bleeding occur, delay the next dose or discontinue. For serious bleeding, consider procoagulant PCC as tested on human volunteers.[13] If not available, resort to activated prothrombin complex concentrate (rF VIIa).

FDA and european union approvals.

The FDA approved rivaroxaban in standard doses for the prevention of stroke and systemic embolism in nonvalvular AF and to reduce the risk of blood clots, DVT, and pulmonary embolism following knee- or hip-replacement surgery. Rivaroxaban is approved in the European Union for the prevention of nonvalvular-related AF, stroke, and systemic embolism, and for the treatment of DVT.

Rivaroxaban: Summary.

The major advantage compared with other agents is the once-daily dose, whereas the major problem is that such a wide range of doses from 20 mg once daily to 2.5-mg twice daily appears to have clinical activity.

Apixaban

Apixaban (Eliquis), a direct factor Xa inhibitor, is a relatively new drug and is still being assessed by regulatory agencies. Apixaban has one high-grade study, ARISTOTLE,[161] so that it may become among the first choices for anticoagulation in patients with AF.

Pharmacokinetics.

Maximum plasma concentrations are 3 to 4 hours after an oral dose. The bioavailability of the drug is approximately 50% for a 10-mg dose. The half-life is 8-15 hours (see later, Table 9-6). It is given twice daily for all indications. Liver metabolism is by CYP3A4-dependent and CYP3A4-independent mechanisms, with approximately 25% of the dose excreted unchanged in the urine. For *drug interactions,* see Table 9-6, later. Apixaban is not recommended in patients receiving concomitant treatment with strong inhibitors of both CYP3A4 and P-Gp, such as azole antimycotics and HIV virus protease inhibitors.

Dosage.

For stroke prevention in AF, 5 mg twice daily is standard, with a recommended 2.5-mg twice-daily dose for patients with two or more of the following criteria: age 80 years and older, body weight less than 60 kg, or a serum creatinine level of 1.5 mg/dL (133 micromol/l) or more.

Outcome studies.

This oral direct factor Xa inhibitor, given 5 mg twice daily, was clearly better than warfarin in 18,201 patients

with AF and at least one additional risk factor for stroke ($CHADS_2$ score mean of 2.1).[161] It does not require anticoagulant monitoring. Apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality (see Chapter 8, p. 316). In a separate study of those with AF at increased risk of stroke ($CHADS_2$ score mean 2.1), but considered unsuitable for warfarin, apixaban was clearly superior to aspirin without increased bleeding.[162] However, in thromboprophylaxis, as for DVT, a prolonged course of apixaban was inferior to a short course of enoxaparin and gave more bleeding.[163] Apixaban is *contraindicated* in high-risk patients after an ACS. When added at a dose of 5 mg twice daily to standard antiplatelet therapy, major bleeding events increased without reduction in recurrent ischemic events.[164]

Severe renal impairment.

There are limited clinical data in patients with a CrCl of 15 to 29 mL/min; thus only use with caution in such patients.

Overdose or excess bleeding.

There is currently no specific reversal agent or antidote for apixaban. The same considerations as for rivaroxaban apply.

Apixaban: Summary.

As this agent in still being assessed for registration by the FDA and European authorities, widespread clinical experience is still to come. Yet it has attractive properties such as the low rate of renal elimination, and, of note, reduced mortality in a major trial in patients with nonvalvular AF.

Novel anticoagulants (NOACS).

These have ben summarized in the current European Society of Cardiology –Europace Guidelines as follows (Camm et al., 2012). The NOACs offer better efficacy, safety, and convenience compared with OAC with VKAs. Thus, where an OAC is recommended, one of the NOACs—either a direct thrombin inhibitor (dabigatran) or an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)—should be considered instead of adjusted-dose vitamin K antagonists such as warfarin (with INR 2–3) for most patients with AF.

There is insufficient evidence to recommend one NOAC over another, although some patient characteristics, drug compliance and tolerability, and cost may be important considerations in the choice of agent.[164A]

Expert CONSULT

DRUGS FOR THE HEART
LIONEL H. OPIE | BERNARD J. GERSH

Acute anticoagulation: Heparin

Mechanism of action and use.

Heparin, traditionally the backbone of antithrombotic therapy, is a heterogeneous mucopolysaccharide with extremely complex effects on the coagulation mechanism and on blood vessels. The major effect of UFH is on the interaction of antithrombin and thrombin (factor IIa) to inhibit the thrombin-induced platelet aggregation that initiates ACS and venous thrombosis (see Fig. 9-6).

Mode of action: Comparison with LMWH.

Inhibition of thrombin by heparin requires (1) binding of heparin to antithrombin by a unique pentasaccharide segment of the heparin molecule, and (2) simultaneous binding of heparin to thrombin by 13 additional saccharide units (see Fig. 9-6).[165] Heparin-antithrombin also inhibits factor Xa, to a lesser extent Xia, and others in the contact “intrinsic” path. Antithrombin contains an active center (arginine) that inhibits the active center serine not only in thrombin but also in several of the coagulation proteases, so the name *antithrombin* means more than a specific interaction only with thrombin. The dose-effect relationship is difficult to predict because heparin is a heterogeneous group of molecules extracted by a variety of procedures, and its strength varies from batch to batch. Heparin also binds variably to plasma proteins, endothelial cells, and macrophages. Such binding inactivates some of the heparin. Furthermore, there is the risk of heparin-induced thrombocytopenia (HIT; see section following).These complexities, added to the difficulty of controlling the dose and the need for monitoring, mean that heparin is far from ideal as an intravenous anticoagulant. However, its advantages compared with LMWH are that the anticoagulant effects can be promptly discontinued by stopping the intravenous infusion and it is completely and readily reversed by protamine. Also, in clinical doses it is not cleared by the kidneys; hence it is safer in renal failure.[165] Furthermore, it has a wider spectrum of antithrombotic activity (see Fig. 9-6).[165]

Controlling the dose of intravenous heparin.

When heparin is administered after fibrinolytic therapy to patients with ACS, meticulous laboratory control of the heparin dose is required. The heparin may be diluted in either isotonic saline or dextrose water. European dosage recommendations are an intravenous bolus of 60-70 IU/kg up to 5000 IU, followed by an infusion of 12-15 IU/kg/hour (maximum 1000 IU/hour).[63] The dose should be adjusted to an aPPT of 1.5-2.5 times the upper limit of normal, or 50-75 seconds with monitoring at 6, 12, and 24 hours. The AHA-ACC more cautiously recommend lower doses: an initial bolus of 60 U/kg (maximum 4000 U), with an initial infusion rate of 12 U/kg/hour (maximum 1000), aiming at aPPT levels of 60-80 seconds.[166]

Higher aPPTs increase the risk of cerebral bleeding without conferring any survival advantage. The use of nomograms results in fewer subtherapeutic aPPTs, and there may also be less bleeding. If the aPPT is three times the control value, the infusion rate should be decreased by 50%; if 2-3 times the control value, the infusion rate should be decreased by 25%; if 1.5-2 times the control value, there should be no change. If the aPPT is less than 1.5 times the control value, the infusion should be increased by 25% to a maximum rate of 2500 IU/hour. At the same time, overheparinization should be guarded against to avoid cerebral bleeding. The inherent limitation of the aPPT is that different commercial reagents and laboratory instruments give different aPPT values. The ACT is preferred in the catheterization laboratory (see p. 369).

Heparin: Precautions and side effects.

To reduce the risk of HIT (next section) current guidelines stress that intravenous heparin should not be given for longer than 48 hours.[167] There is an increased risk of heparin-induced hemorrhage in patients with subacute bacterial endocarditis or hematologic disorders such as hemophilia, hepatic disease, or GI or genitourinary ulcerative lesions. There is a narrow therapeutic window for the use of heparin in conjunction with fibrinolytic therapy. To avoid intracerebral hemorrhage, the recommended doses of heparin should not

be exceeded. Some patients are *resistant to heparin,* and in these patients administration of high-dose heparin with aPPT monitoring every 4 hours is advised. Heparin is derived from animal tissue, and occasionally causes allergy. *Heparin overdosage* is treated by stopping the drug and, if clinically required, giving protamine sulfate (checking first for salmon allergy) as a very slow infusion of a 1% solution, no more than 50 mg in any 10-minute period.

Heparin-induced thrombocytopenia and thrombosis syndrome.

HIT and heparin-induced thrombocytopenia-thrombosis syndrome (HITTS) occurs in approximately 3%-5% of patients during or after UFH treatment for 5 days or more. The incidence is much lower, less than 1% during and after LMWH therapy (see later, Table 9-4). A subset of these patients develop venous or arterial thrombosis (HITTS).[168] A retest clinical scoring system (the *"4 Ts"*) is used to assess the likelihood of this syndrome: the platelet count drops by 50% or more (thrombocytopenia), 5-10 days after commencing UFH (timing), there is new thrombosis, and other causes of thrombocytopenia have been excluded.[169] HIT is an immune-mediated potentially fatal syndrome in which the heparin-induced immunoglobulins bridge platelets causing both thrombocytopenia and thrombosis. In most patients the onset occurs during heparin therapy; however, in less than 5% onset is after discontinuation of heparin therapy (delayed-onset HIT).[86] Heparin or LMWH must be discontinued on suspicion. Laboratory tests are available to support the diagnosis. As the condition is prothrombotic, these patients require alternative anticoagulation, and most patients are treated with direct thrombin inhibitors or heparinoid and later commenced on warfarin when the platelet count has recovered.

Hit therapy.

In the United States, *lepirudin, argatroban, and bivalirudin,* are licensed for HIT therapy (see later, Table 9-4). In patients with suspected or proven HIT who need PCI for ACS, argatroban (direct thrombin inhibitor, 240 mcg/kg bolus followed by 20 mcg/kg/min infusion, doses rounded) can cover the intervention, even without added GpIIb/IIIa blockade.[170] Valid alternatives in ACS are fondaparinux, an indirect antithrombin (see later),[171],[172] or bivalirudin, a direct thrombin inhibitor[173] that is licensed for use when HIT or HITTS complicates PCI (see later, Table 9-4). The heparinoid danaparoid is also used elsewhere but has molecular overlap with heparin. Of note, the British Society of Haematology advises that *all patients receiving prolonged heparin of any sort should have platelet counts on day 1 and every 2-4 days.*[174]

Indications for heparin

In acute myocardial infarction.

In AMI heparin is given together with thrombolysis or primary percutaneous coronary intervention. *In ACS,* UFH was the reference standard,[165] but this is no longer the case now that LMWH, fondaparinux, and bivalirudin are available. Reinfarction may occur following the cessation of intravenous heparin usually as a result of "heparin rebound" and the procoagulant state that ensues. *In elective PCI,* no placebo-controlled trials have been performed with UFH; the standard regimen is 70-100 IU/kg, with additional weight-adjusted boluses to achieve and maintain an ACT of 250-300 seconds.[106] If a GpIIb/IIIa antagonist is co-administered, the initial heparin dosage is reduced to 70 IU/kg (bolus) followed by 100 U/kg infused to maintain an ACT of at least 250-300 seconds.[106] In Europe and other countries, bolus-reduced heparin doses may be used (e.g., 70-100 IU/kg without monitoring of the ACT[175] and no additional heparin is given during the procedure[106]). Heparin should be discontinued immediately after the interventional procedure. In the *prevention and treatment of DVT,* subcutaneous heparin has been replaced by LMWH or fondaparinux.

Anticoagulation in pregnant women.

UFH may be used (Category C, see Table 12-10), but can cause osteoporosis if given in doses of more than 20,000 IU daily for more than 5 months.[142],[176] Alternatives are fondaparinux or LMWH (Category B) (also see p. 374).

Low-molecular-weight heparins

LMWHs are approximately one third of the molecular weight of heparin, and are also heterogeneous in size. LMWHs have greater bioavailability and a longer plasma half-life than standard heparin (see later, Table

9-4). They bind to antithrombin, effectively to inhibit factor Xa with also some direct inhibition of thrombin (see Fig. 9-6). Approximately 25%-30% of the molecules of various preparations contain the crucial 18 or more saccharide units needed to bind to both antithrombin III and thrombin; hence inhibition of thrombin is less powerful than that of heparin. The ratio of LMWHs binding to antithrombin III and inhibition of factor Xa:IIa (where IIa is thrombin) varies with each agent, for example, 2:1 with dalteparin and 3:1 with enoxaparin. The bleeding side effects of LMWHs can be reduced but not completely reversed by protamine (residual anti-Xa activity remains). LMWHs given subcutaneously in a fixed dose are much easier to use than standard UFH, and risk of HIT is less (see Table 9-2). Regular platelet counts are required, and the LMWH should be stopped if the count falls to less than 100,000/mm[2].

LMWH for acute coronary syndromes.

Several trials show the superiority or equivalence of LMWH to UFH. A meta-analysis on more than 49,000 patients in 12 trials showed superiority of enoxaparin as adjunct therapy in those with STEMI. For every 1000 patients treated, 21 deaths or MI events were prevented at the cost of four nonfatal major bleeds, thus showing net clinical benefit.[177] In NSTEMI, nine death or MI events were prevented for every 1000 patients treated by enoxaparin, at the cost of eight nonfatal major bleeds, showing a net neutral clinical effect.[177]

In elective PCI, in the STEEPLE trial, intravenous doses of enoxaparin 0.5-0.75 mg/kilo gave less major bleeding than UFH.[178] Furthermore, 0.75 mg/kg achieved better target anti-factor Xa levels (92%) than did the lower dose (79%), both much better than with UFH (20%). Concurrent GpIIb/IIIa use increased bleeding substantially (OR 2.28, $p < 0.001$). Sheath removal occurred 4-6 hours after the end of PCI with 0.75 mg/kg and immediately at the end of PCI with the lower dose. This trial was not powered for outcome events, which were similar in UFH- and enoxaparin-treated patients. No adjustment is needed for *renal dysfunction* if only a single bolus is given for elective PCI (for other situations, see Table 9-4).[179] SYNERGY demonstrated that switching between UFH and LMWH increases bleeding risks.[179]

Dalteparin.

Dalteparin (Fragmin) comes in a single-dose prefilled syringe or as multidose vials. Each syringe contains 2500 to 10,000 international units antifactor Xa (see Fig. 9-6) equal to 16-64 mg of dalteparin. It is given as a deep subcutaneous injection and NOT intramuscularly. In the FRISC study the dose was 120 IU twice daily plus aspirin for 6 days, then 7500 IU for 35-45 days, starting after admission for unstable angina. At 6 days the composite endpoint of death or MI was reduced from 4.8% with aspirin to 1.8% with dalteparin plus aspirin ($p = 0.001$),[180] but by 6 months these differences were no longer apparent. In the United States, dalteparin is licensed for prevention of ischemic complications in unstable angina and non–Q wave MI, and for prevention of DVT. It is contraindicated by major bleeding or thrombocytopenia or past HITTS (Heparin-induced thrombocytopenia and thrombosis syndrome). There is a boxed warning against its use with spinal anesthesia and pregnancy, category B (see Table 12-10).

Choice of LMWH or UFH.

LMWH is in general preferred to UFH because it is convenient, overall less expensive, eliminates the need for aPPT monitoring, avoids the problem of intravenous site infections, and gives superior results.[177],[181] The inability to monitor the degree of anticoagulation with LMWH in contrast to UFH, and the lack of a complete antidote are potential disadvantages, especially when urgent PCI is undertaken in high-risk ACS.[90]

Bivalirudin

Bivalirudin (Angiomax) is the only intravenous anticoagulant that reduces ischemia similarly to UFH, yet with a consistent reduction in bleeding complications associated with PCI. Bivalirudin binds directly to thrombin (factor IIa) and thereby inhibits the thrombin-induced conversion of fibrinogen to fibrin (Fig. 9-10). It inactivates fibrin-bound as well as fluid-phase thrombin.

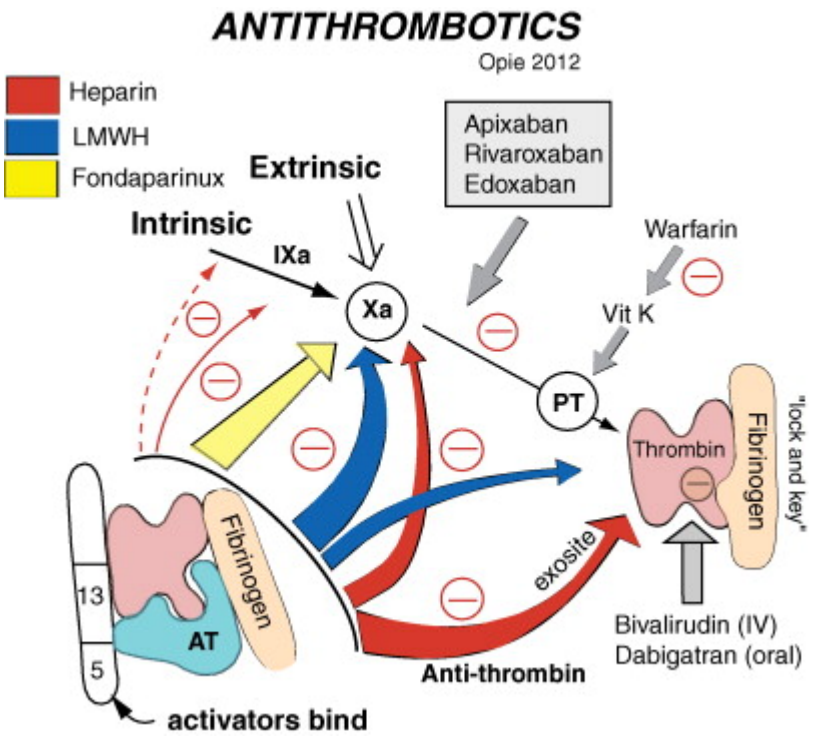

Figure 9-10 Sites of action of antithrombotics. Crucial to the formation of the clot is the interaction between thrombin and fibrinogen to form fibrin (see Fig. 9-5) that cross-links the platelets (see Fig. 9-1). The thickness of the arrows indicates the strength of the binding of the antithrombotics to various molecular sites. *AT,* antithrombin; *IV,* intravenous; *LMWH,* low-molecular-weight heparin; *PT,* prothrombin.
(Figure © L.H. Opie, 2012.)

Pharmacokinetics.

Bivalirudin is easy to use, has linear kinetics, and, because it is not protein-bound, has few drug interactions. It inhibits both soluble and clot-bound thrombin and blocks thrombin-mediated platelet activation and aggregation.[182] Elimination is predominantly achieved by proteolytic cleavage and, to a lesser extent, by renal excretion so that clearance is reduced by only approximately 20% in moderate and severe renal impairment (FDA information). This may be particularly advantageous in *CKD* as the risk of bleeding is approximately doubled.[183] Coagulation tests (activated partial thromboplastin time and ACT) correlate well with plasma concentrations.

Nonurgent PCI.

In nonurgent PCI and almost half for ACS, the long-term outcome events with bivalirudin and selective adjunctive GpIIb/IIIa blockade (7.2%), was similar to that of UFH plus planned GpIIb/IIIa blockade.[184] In the acute phase, major bleeding was less common with bivalirudin (2.4% versus 4.1%, $p < 0.001$). The bivalirudin dose was 0.75 mg/kg prior to the intervention followed by an infusion of 1.75 mg/hour for the duration of the procedure.

ACS with planned PCI.

In ACS with planned PCI, the ACUITY trial showed that bivalirudin alone gave similar outcome rates to heparin plus GpIIb/IIIa inhibition with less bleeding. [102],[185],[186]

Urgent PCI in high-risk non–ST elevation ACS.

For urgent PCI in non-STE ACS, bivalirudin is a cost-effective alternative to UFH plus GpIIb/IIIa blockade and gives less bleeding.[186] In this trial (ACUITY), GpIIb/IIIa antagonists added to bivalirudin increased bleeding but gave no outcome benefit.[102] Despite absence of firm data,[187] the AHA-ACC guidelines

suggest that bivalirudin should be combined with clopidogrel to optimize outcomes.[166] Given the adverse relationship of bleeding[185],[188] to long-term mortality, bivalirudin is a reasonable alternative to UFH or LMWH with added GpIIb/IIIa antagonists. The current preferred approach for *non-STE ACS* is to use bivalirudin in patients at high risk of bleeding (Fig. 12-3).

Primary PCI in STEMI.

For primary PCI in STEMI, in the HORIZONS study on 3602 patients bivalirudin reduced major bleeding by 40% (4.9 versus 8.3%, p < 0.001) and also reduced 30-day mortality (1.8% verus 2.9%, p = 0.035) as compared with UFH and a GpIIb/IIIa receptor antagonist.[189] Thus this agent is an attractive antithrombotic option for primary PCI compared with UFH plus GpIIb/IIIa antagonists and can be given to all those with ACS, but trial data in those whom PCI is not planned are not superior to heparin.[190] Long-term final 3-year results of the primary PCI trial HORIZONS-AMI show continued mortality benefit of bivalirudin and also suggest possible late benefits on stent thrombosis and repeat MI (Fig. 9-11).[191]

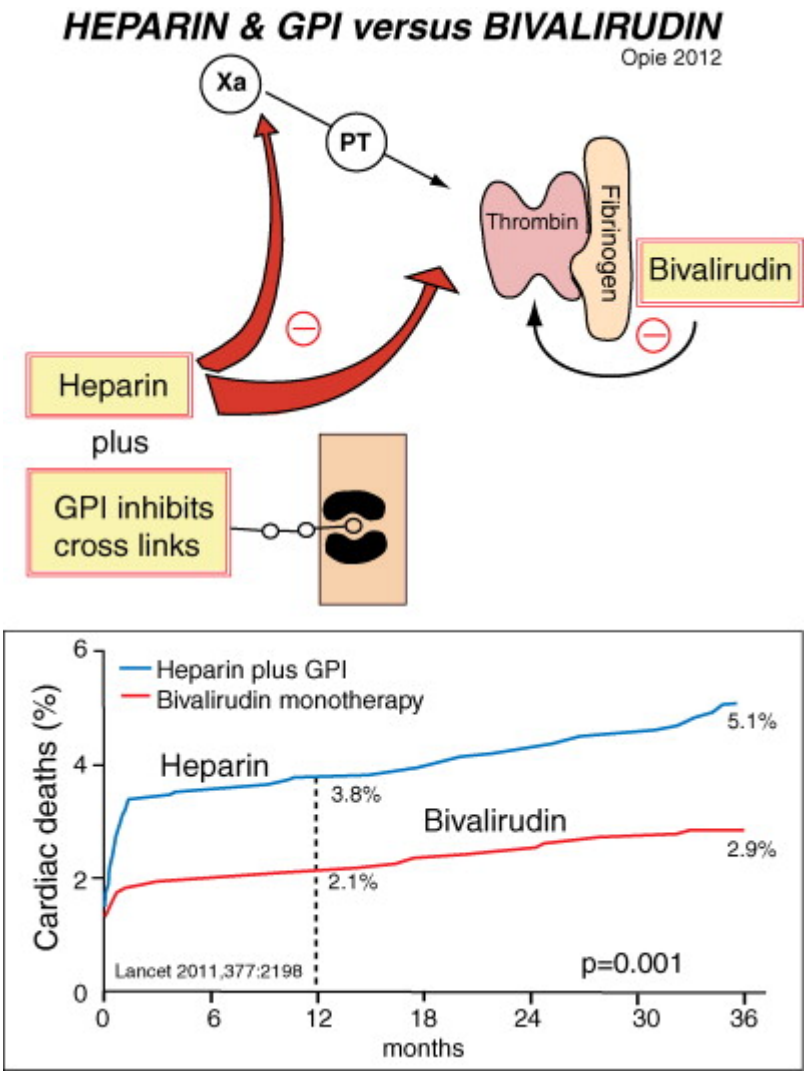

Figure 9-11 Comparison of effects of heparin plus glycoprotein IIb/IIIa inhibitor (GPI) versus bivalirudin. *Upper panel* shows mechanisms of action. *Lower panel* shows superior effects of bivalirudin in decreasing deaths in acute myocardial infarction. *PT,* Prothrombin.
(Figure modified from Stone GW, et al. HORIZONS-AMI Trial Investigators. Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial. Lancet 2011;377:2193-2204; © L.H. Opie, 2012.)

Less bleeding VS. heparin.

At similar ACTs in patients undergoing PCI, bivalirudin had consistently less bleeding than did heparin or heparin plus a Gp inhibitor.[192]

Chromic kidney disease.

The ESC recommends an infusion rate of 1.75 mg/kg/hour for moderate renal impairment (CrCl, 30-59 mL/min); if the clearance is less than 30 mL/min, reduce to 1 mg mg/kg/hour.[73]

Bivalirudin, licensed use.

The FDA license is for use with aspirin for patients with unstable angina undergoing percutaneous transluminal coronary angioplasty. Bivalirudin is also licensed for patients with or at risk of HIT or HITTS who are undergoing PCI.[173]

Bivalirudin evaluation.

Bivalirudin is a valuable agent to replace heparin or UFH during PCI. An important outcome study shows mortality reduction versus heparin and a GpIIb/IIIa antagonist when used for acute STEMI. It causes relatively less bleeding than does heparin in unselected patients undergoing PCI.

Enoxaparin

Enoxaparin (Lovenox, Clexane) is the most used and most tested LMWH. It predominantly inhibits factor Xa but also inhibits thrombin to some degree. It is given by subcutaneous injection, and comes in concentrations of 100 or 150 mg/mL, in prefilled single-dose syringes or as ampules. Indications are similar to dalteparin, including treatment of acute DVT. Warnings are similar to dalteparin plus warning against use with prosthetic valves, especially in pregnant women (pregnancy category B) risk of thrombocytopenia, although this is rare. This drug has been well studied in several major trials. It is excreted renally.

Use in AMI.

Enoxaparin was superior to UFH in STEMI as shown in a metaanalysis on more than 49 000 patients.[177] Although bleeding was increased with enoxaparin, this increase was offset by a reduction in death or MI. In the NSTEMI patients, the comparison was neutral. In a current metaanalysis, 23 trials representing 30,966 patients were selected, including 10,243 patients (33.1%) undergoing PCI for STEMI and 8750 (28.2%) undergoing secondary PCI after fibrinolysis.[193] Enoxaparin was superior to UFH in reducing mortality and bleeding outcomes during PCI and particularly in patients undergoing PCI for STEMI.

Comparisons with oral thrombin inhibitors.

Compared with apixaban in patients undergoing hip replacement, enoxaparin was associated with higher rates of VTE, without differences in bleeding rates.[194] In this study, apixaban compared with enoxaparin reduced all VTE and death from any cause ($P < 0.001$). Regarding rivaroxaban, also for prevention of VTE, it gave better protection than enoxaparin at similar rates of bleeding.[194] Dabigatran in a similar setting and given at a high dose (220 mg daily) reduced the primary efficacy outcome ($p < 0.0001$) as also major VTE plus VTE-related death (<0.03) when compared with subcutaneous enoxaparin 40 mg once daily.[195] On the positive side, enoxaparin was superior to apixaban for medically ill patients requiring prophylaxis for VTE in that outcomes were similar but enoxaparin had fewer major bleeding events than apixaban ($P = 0.04$).[163]

Dosage.

The standard dose for ACS is 1 mg/kg subcutaneously every 12 hours with aspirin and clopidogrel and, sometimes, a GpIIb/IIIa inhibitor. For thromboprophylaxis, the standard dose is 40 mg subcutaneously daily. Enoxaparin is given until PCI or throughout hospitalization or for 8 days. In older adult patients the dose should be reduced (e.g., omit the intravenous bolus and give 0.75 mg/kg twice daily[179]). In CKD with a CrCl less than 30 mL/min, the ESC recommendation is that the dose be reduced to 1 mg/kg once daily.[73]

Summary: Enoxaparin.

Enoxaparin given subcutaneously is the standard LMWH, predominantly inhibiting factor Xa. It is superior to UFH for AMI (specifically STE) and superior to apixaban for prophylaxis against thromboembolism for medical patients. In patients undergoing major hip or knee operations, enoxaparin is being displaced by the new oral thrombin inhibitors (apixaban, dabigatran, rivaroxaban).

Fondaparinux

Fondaparinux (Arixtra) is the only selective activated factor X (factor Xa) inhibitor available for clinical use in ACS.

Pharmacokinetics.

It is a synthetic pentasaccharide structurally similar to the antithrombin-binding sequence found in heparin.

It inhibits the coagulation factor Xa (see Fig. 9-10) by binding with a high affinity and reversibly and noncovalently to antithrombin, thereby catalyzing and promoting antithrombin-mediated inhibition of factor Xa. It increases the ability of antithrombin to inhibit factor Xa 300-fold. The specific anti-Xa activity is approximately sevenfold higher that of LMWH.[138] Fondaparinux has 100% bioavailability after subcutaneous injection, with an elimination half-life of 17 hours, and can therefore be given once daily. For use in PCI it needs no monitoring. The risk of hemorrhage increases with impaired hepatic or renal function (contraindicated if CrCl less than 30 mL/min), in patients with very low body weight, or in for older adult patients for whom the dose must be reduced according to the FDA-approved package insert. Thrombocytopenia can occur but HIT has not yet been reported (see Table 9-2); thus monitoring of platelet count is unnecessary.[63]

License in the united states.

In the United States fondaparinux is licensed only for prevention of DVT and (with warfarin) for acute pulmonary embolism, although the large trials in ACS[196] suggest that additional off-license use could be appropriate. A boxed warning introduced in 2010 warns of the risks of epidural or spinal hematomas in patients given neuraxial anesthesia or undergoing spinal punctures.

Non-STE ACS.

In non-STE ACE, in 20,078 patients in OASIS-5, fondaparinux was similar to enoxaparin, both usually given with clopidogrel, in reducing death or MI at 9 days (the primary endpoint), but also reduced deaths at 30 days and 6 months.[197] Major bleeding was much less (approximately halved) with fondaparinux (dose 2.5 mg subcutaneously once daily, extra 2.5 or 5 mg intravenously before PCI). In a subgroup of those who underwent PCI,[196] death, MI, and stroke as separate endpoints were not reduced at any time. Rather, it was when major bleeding was added to the rates of death, MI, and stroke that fondaparinux was superior to enoxaparin at 9 days, 30 days, and 6 months of follow-up. For PCI, European guidelines suggest the addition of UFH to fondaparinux initiated prior to the procedure.[63] Specifically, catheter thrombosis[196] can be thereby avoided.[196] *In the conservative management of ACS,* fondaparinux is superior to heparin.[190]

STEMI.

In STEMI in OASIS-6, fondaparinux was compared in a large complex trial conducted in 41 countries in 12,092 patients with either no anticoagulation or UFH who may or may not have received a fibrinolytic agent.[197] The most commonly used fibrinolytic agent was streptokinase (without UFH).[197] In patients undergoing primary PCI, there was no advantage of fondaparinux given as an intravenous bolus (2.5 or 5 mg, the latter if no GpIIb/IIIa) followed by subcutaneous dosing up to 8 days, but there was an excess of catheter thrombosis and coronary complications. (By extrapolation from OASIS-5, added UFH at the time of PCI might have avoided the thrombosis).[196] In others without PCI but receiving thrombolysis, subcutaneous fondaparinux was superior to UFH for reducing death or reinfarction at 90-180 days by 23% ($p = 0.008$). Of note, fondaparinux was given for approximately 8 days, whereas UFH was given for approximately 2 days. Fondaparinux was also superior to placebo in patients that received no reperfusion therapy. Thus the benefit of fondaparinux over UFH in STEMI is less clear and the longer duration of therapy could have accounted for part of the benefit. However, fondaparinux is clearly easier to administer than UFH.

Catheter thrombosis.

A problem with fondaparinux is the low albeit real risk of catheter thrombosis at the time of PCI. This risk is countered by a covering bolus injection of UFH given at PCI,[73] as studied in the FUTURA/OASIS-8 trial.[198] The standard-dose UFH, namely 85 IU/kg (reduced to 60 IU/kg in the case of the use of GP IIb/IIIa receptor inhibitors) was better than a lower bolus (50 IU/kg), because there was more favorable net clinical benefit and lower risk of catheter thrombosis compared with low-dose UFH.[198]

Chronic renal disease.

For chronic renal disease, fondaparinux is the drug of choice in moderately reduced renal function (CrCl 30-60 mL/min) but contraindicated in severe renal failure (CrCl <20 mL/min).[73]

Summary: Fondaparinux.

Fondaparinux is superior to placebo (but not to UFH) in STEMI (treated with thrombolytic agent or without reperfusion). Fondaparinux is superior to LMWH in non-STE ACS (lower bleeding and fewer deaths). The ESC guidelines favor fondaparinux in non-STE ACS unless the patient is planned for early intervention.[63] The ACC-AHA guidelines recommend either UFH or enoxaparin.[166]

Lepirudin.

Lepirudin (Refludan) is a recombinant hirudin licensed only for HIT and the associated thromboembolic disorder to prevent further thromboembolism. It is contraindicated in pregnancy (category B) and in breast feeding, with a warning against use with thrombolytic agents or in bleeding disorders. The infusion dose (0.15 mg/kg after an initial bolus of 0.4 mg/kg) is adjusted by the aPPT (1.5 to 2.5). It is almost exclusively cleared in the kidneys, so that renal impairment requires lower doses (see package insert for table).

Which regimen is better?

There are several approved options (UFH versus LMWH versus bivalirudin versus fondaparinux). The chosen regimen may differ between interventional and noninterventional centres. When intervention is likely, bivalirudin has excellent data, whereas if a conservative strategy is employed, fondaparinux is well tested. If bleeding is a concern, bivalirudin and fondaparinux (if PCI is unlikely) are good choices. Some factors guiding choice are shown in Tables 9-2, 9-3, 9-4, and 9-5.

Table 9-3 -- Antiplatelets, Antithrombotics, and Fibrinolytics in Acute Coronary Syndromes and in Percutaneous Coronary Intervention

Condition	Antiplatelet Agents	Antithrombotics	Fibrinolytics
ACS, low-risk or conservative strategy	Aspirin, clopidogrel (if no CABG)	Heparin/LMWH or fondaparinux or bivalirudin	None
ACS, high-risk* invasive strategy	Previous, plus GpIIb/IIIa (Eptifibatide/tirofiban/if continuing ischaemia; abciximab if anatomy known)	Heparin/LMWH; bivalirudin may replace both IIb/IIIa and heparin/LMWH	None
ACS, ST-elevation MI, PCI not available	Aspirin plus clopidogrel‡	Heparin/LMWH or fondaparinux (OASIS-6)	TNK/tPA /rPA/streptokinase
Primary PCI	Aspirin, clopidogrel ± abciximab (may consider selective IC abciximab or eptifibatide)	Bivalirudin/UFH	
Elective PCI, low risk	Aspirin, clopidogrel	Heparin/LMWH/bivalirudin	None
Elective PCI, high risk	Above, plus abciximab or eptifibatide	Heparin/LMWH/bivalirudin	None

ACS, Acute coronary syndrome; *CABG,* coronary artery bypass graft; *IIb/IIIa,* glycoprotein IIb/IIIa inhibitor; *LMWH,* low-molecular-weight heparin; *MI,* myocardial infarction; *PCI,* percutaneous coronary intervention; *rPA,* reteplase; *TNK,* tenecteplase; *tPA,* tissue plasminogen activator; *UFH,* unfractionated heparin.

* Elevated troponins, ischemic ST-depression or similar ongoing ischemia.

‡ Aspirin 162 mg, clopidogrel 75 mg in COMMIT trial.[82],[236]

Table 9-4 -- Aspirin, Clopidogrel, and Warfarin for Secondary Prevention and Risk Reduction for Coronary and Vascular Disease: Class I Recommendations from the AHA and ACC Foundation

1.	Aspirin 75-162 mg daily recommended in all patients with CAD unless contraindicated. **(Level of Evidence: A)**

Clopidogrel 75 mg daily if intolerant or allergic to aspirin. **(Level: B)**

2. A P2Y12 receptor antagonist in combination with aspirin is indicated for patients after ACS or PCI with stent placement. **(Level: A)**
   Give clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor* 90 mg twice daily for at least 12 months. **(Level: A)**
3. For patients undergoing CABG, give aspirin within 6 hours after surgery, 100-325 mg daily for 1 year. **(Level: A)**
4. For patients with atherosclerosis, use antiplatelet therapy rather than warfarin. **(Level: A)**
5. Compelling indications for anticoagulant therapy: atrial fibrillation, prosthetic heart valve, LV thrombus, or concomitant venous thromboembolic disease; add warfarin to the low-dose aspirin (75-81 mg daily). **(Level: A)**
6. Warfarin with aspirin and/or clopidogrel: increased risk of bleeding. Monitor closely. **(Level: A)**

From Smith SC Jr, et al. World Heart Federation and the Preventive Cardiovascular Nurses Association. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. Circulation 2011;124:2458–73.

ACC, American College of Cardiology; *ACS,* acute coronary syndrome; *AHA,* American Heart Association; *CABG,* coronary artery bypass grafting; *CAD,* coronary artery disease; *LV,* left ventricular; *PCI,* percutaneous coronary intervention.

* We prefer ticagrelor as in the PLATO trial (Wallentin et al., *New Engl J Med* 2009;361:1045).[61] Ticagrelor has proven outcome benefit including mortality reduction in ACS, which remains a repeat risk despite secondary prevention.

Table 9-5 -- Unfractionated Heparin Versus Low-Molecular-Weight Heparin, Fondaparinux, and Bivalirudin

	UFH	LMWH	Fondaparinux*	Bivalirudin (Hirulog)
Molecular weight	5000-30,000 Da	Mean 5000 Da	1728 Da	2180
Mechanism of action	Major antithrombin (IIa) activity, less on Xa and on Xia[165]	Greater anti Xa activity: also antithrombin (IIa) activity	Specific conformational change in antithrombin, factor Xa strongly inhibited	Inhibits both soluble and clot-bound thrombin[237]
Mode of administration	IV infusion or SC 2-3 times daily	SC only, 1-2 times daily	SC daily; added IV bolus for PCI in ACS	IV infusion
Therapeutic dose	Bolus, then IV infusion with monitoring of aPTT	Fixed dose by body weight for creatinine clearance <60-30 mL/min 1 mg/kg daily; if <30 mL/min avoid unless single-bolus dosing for elective PCIAge ≥75 yr reduced dosing; no bolus and 0.75 mg/kg b.i.d. with fibrinolysis Care if liver disease	2.5 mg; reduce dose in older adults or renal impairment; C/I creatinine clearance <30 ml/min; body wt <50 kg	FDA: IV bolus 0.75 mg/kg; infuse 1.75 mg/kg/h for PCI duration[†]Reduce in renal disease
Bioavailable half-life	<1.5 h	<4 h	<17 h	25 min

	UFH	LMWH	Fondaparinux*	Bivalirudin (Hirulog)
Monitoring of anticoagulant activity	aPTT	Usually not necessaryAnti-Xa levels advised in renal failure, severe obesity, pregnancy	Usually none needed, anti-Xa possible	aPTT; ACT (not usually done)
Reversal	Reversed with IV injection protamine sulphate	Only partially reversible with protamine	rVIIa potential partial antagonist	Baseline coagulation times within 1 h of drug cessation; no single reversal agent; combinations may work
HIT; of these, 20%-50% develop HITTS	HIT incidence in those receiving therapy for ≥5 days 3%-5%	HIT incidence in those receiving therapy for ≥5 days <1%	Very low cross-reactivity with HIT antibodies; thrombotic HIT not yet found, package insert warns severe thrombocytopenia in 0.2%	FDA: indicated to treat HIT/HITTS or risk thereof during PCI; IV bolus 0.75 mg/kg; infuse 1.75 mg/kg/h

ACS, Acute coronary syndrome; *ACT,* activated clotting time; *aPTT,* activated partial thromboplastin time; *b.i.d.,* twice daily; *C/I,* contraindicated; *FDA,* Food and Drug Administration; *HIT,* heparin-induced thrombocytopenia; *HITTS,* heparin-induced thrombocytopenia thrombosis syndrome; *IV,* intravenous; *LMWH,* low-molecular-weight heparin; *PCI,* percutaneous coronary intervention; *SC,* subcutaneous; *UFH,* unfractionated heparin.

* Fondaparinux: package insert; Wester, 2007.[172]

† Alternate dosage: bolus 0.1 mg/kg, then infused at 0.25 mg/kg/h; before PCI added bolus 0.5 mg/kg, infusion increased to 1.75 mg/kg/h.[102]

Expert CONSULT

DRUGS FOR THE HEART
LIONEL H. OPIE | BERNARD J. GERSH

Fibrinolytic (thrombolytic) therapy

Although primary PCI is superior to thrombolytic therapy for STEMI, there are many regions where this is not feasible (especially within 3 hours of presentation). Hence, internationally, fibrinolysis remains the most commonly used reperfusion therapy.

Role of plasmin.

Thrombolytic agents have a common goal: the generation of plasmin that lyses the clot (Fig. 9-12). Physiologically, the plasminogen activator system forms plasminogen that binds to the clot surface to lyse the clot,[199] opposing thrombus formation. PAI-1, made by adipose tissue, inhibits the formation of plasmin. Chronic inhibition of fibrinolysis by PAI-1 can promote accumulation of intravascular fibrin, which may be invaded by proliferating vascular smooth muscle cells and circulating progenitor cells gradually to form a cellular neointima (see Fig. 9-8). These effects may be important in provoking a thrombotic response in the presence of minor endothelial damage.[199] Future inhibitors of PAI-1 may help to control slow thrombus formation, which could be effective as long-term preventative therapy[200] as opposed to the rapid therapeutic effects of current agents such as tissue plasminogen activator (tPA), and tenecteplase (TNK) or reteplase (rPA) used to achieve clot lysis in acute thrombotic conditions (Fig. 9-13).

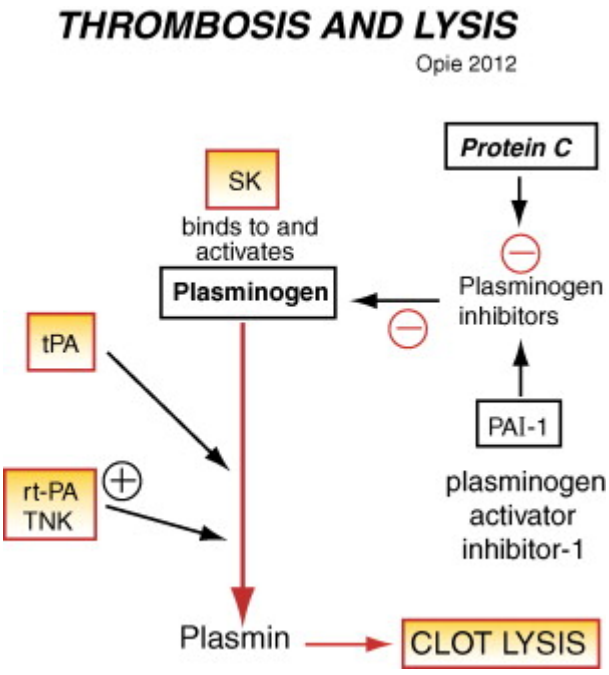

Figure 9-12 Sites of action of thrombolytic agents. *PAI,* Plasminogen activator inhibitor; *rt-PA,* reteplase; *SK,* streptokinase; *tPA,* tissue-type plasminogen activator; *TNK,* tenecteplase.
(Figure © L.H. Opie, 2012.)

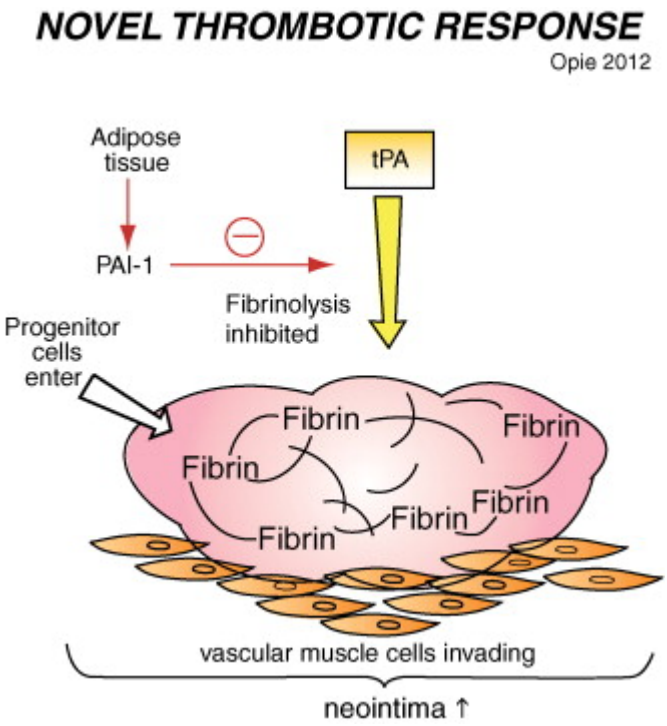

Figure 9-13 Novel thrombotic mechanisms. Plasminogen activator inhibitor-1 (PAI-1), made by adipose tissue, inhibits fibrinolysis and thus the formation of plasmin from tissue plasminogen activator (tPA). This process, when chronic, can promote accumulation of intravascular fibrin, which may then be invaded by proliferating vascular smooth muscle cells and circulating progenitor cells gradually to form a cellular neointima in the fibrin-rich clot. These effects could provoke a delayed thrombotic response in the presence of minor endothelial damage.
(Figure © L.H. Opie, 2012.)

Goals of fibrinolysis.

The goals of reperfusion therapy are early patency, increased myocardial salvage, preservation of LV function, and lower mortality.[201],[202] The major aim is to achieve early reperfusion with short "symptom-to-needle'" and "door-to-needle" times in patients with suspected AMI and STE or new-onset left bundle branch block. Early reperfusion can be achieved by either fibrinolysis or by PCI. Primary PCI is established as providing better reperfusion than lysis, but for patients within the first 3 hours of symptom onset more prompt reperfusion with lysis may balance the delayed but more complete and sustained reperfusion with PCI.[203] Symptom-to-balloon time and door-to-balloon times are crucial. The principle of modern fibrinolytic therapy is the use of agents such as alteplase (tPA), rPA, TNK, and streptokinase (Table 9-6), which convert plasminogen into active plasmin. Because fibrinolytic agents simultaneously exert clot-dissolving and procoagulant actions and have significant serious side effects, *they must not be used in non-STE ACS (unstable angina and non-STEMI)* where they have no benefit and increase risks of bleeding.

Table 9-6 -- New Oral Anticoagulants: Pharmacologic Features and Major Trials

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Selective direct thrombin inhibitor	Selective direct Xa inhibitor	Selective direct Xa inhibitor	Selective direct Xa inhibitor
Doses, daily	110 or 150 mg b.i.d or 75 g b.i.d.	20 mg with evening meal (FDA)	5 mg b.i.d.	60 mg
Doses, renal impairment	CrCl <30 mL/min excluded	CrCl 30-49 mL/min, 15 mg	Half dose for increased serum creatinine; <80 yr; low BMI	Half dose for renal impairment
Renal eliminated	85%	66%	27%	50%*

Oral availability	6.5%	80%-100%	50%	62%
Half-life, h	12-17	5-13	8-15	6-11
Renal eliminated	85%	66%	27%	50%
Max inhibition, h	0.5-2	1-4	1-4	1-2
Drug interactions	Reduce dose: verapamil, dronedarone, amiodarone Avoid antifungals and protease inhibitors	Avoid verapamil, dronedarone, amiodaroneCaution: antifungals and protease inhibitors	Avoid verapamil, dronedarone, amiodaroneCaution antifungals and protease inhibitors	Reduce dose: verapamil, dronedarone, amiodaroneAvoid antifungals and protease inhibitors
Major phase III trial	RELY	ROCKETT (ATLAS ACS2[†])	ARISTOTLE	ENGAGE AF (under way)
$CHAD_2$ score mean in trial	2.1	3.5	2.1	2 or more
Primary endpoint result	150 mg HR 0.65,P < 0.001; 100 mg, NS	Noninferior to warfarin in high-risk patients with atrial fibrillation	HR 0.79; p = 0.01Stroke/systemic emboli; 0.81 mortality, p < 0.05	Aim: Noninferior to warfarin for stroke and systemic emboli
Safety	Intracranial bleeds less than warfarin; more GI bleeds (150 mg)	Intracranial bleeds less than warfarin; more GI bleeds	Less major bleeds and hemorrhagic stroke than warfarin; also in HF[†]	Not yet known
FDA approval	Stroke prevention in nonvalvular AF;DVT prevention after hip or knee replacement	Stroke prevention in nonvalvular AF;DVT prevention after hip or knee replacement; not FDA approved for ACS†, DVT		

Modified from De Caterina R, et al. Coordinating Committee. New oral anticoagulants in atrial fibrillation and acute coronary syndromes: ESC Working Group on Thrombosis-Task Force on Anticoagulants in Heart Disease position paper. J Am Coll Cardiol 2012;59:1413–1425.Also see Lip GY, et al. Indirect comparisons of new oral anticoagulant drugs for efficacy and safety when used for stroke prevention in atrial fibrillation. J Am Coll Cardiol 2012; 60:738-746.

ACS, Acute coronary syndrome; *AF,* atrial fibrillation; *b.i.d.,* twice daily; *BMI,* body mass index; *CrCl,* creatinine clearance; *CHAD,* congestive heart failure, hypertension, age, diabetes mellitus; *DVT,* deep-vein thrombosis; *FDA,* Food and Drug Administration; *GI,* gastrointestinal; *HF,* heart failure; *NS,* not significant.

* Of the absorbed drug.

† ATLAS-ACS TIMI 46 trial, theheart.org, May 23, 2012.

Early reperfusion: The golden hours.

Dramatic reductions in mortality can be achieved if treatment is obtained during the “golden” first hour. STE can resolve without the development of Q waves, and with very prompt reperfusion (usually within the first hour) there may be no elevation in biomarkers of necrosis (“aborted MI”). In the MITI trial, alteplase and aspirin were started as soon as possible either at home or in hospital.[204] Thrombolytic perfusion within 70 minutes reduced the early death rate from 8.7% to 1.2%, and infarct size fell from 11.2% to 4.9% when compared with a longer delay of up to 180 minutes. Among patients undergoing early primary PCI, the

relationship between symptom-to-balloon time and mortality is less striking, but this may relate in part to the relative lack of data as few patients achieve very early primary PCI.[205]

The window of opportunity.

In the FTT Collaborative Overview of 58,000 randomized patients in fibrinolytic trials,[206] mortality was reduced by 25% in patients randomized to fibrinolysis between 2 and 3 hours after symptom onset and by 18% in patients randomized to fibrinolysis between 4 and 6 hours. MI may also be "aborted."[207] Patients randomized between 7 and 12 hours still had a 14% reduction in mortality, the later improvement perhaps related more to the benefits of a patent infarct-related artery that to myocardial salvage.[208],[209] Gersh and colleagues describe the relationship between mortality reduction and the extent of myocardial salvage.[210] Within the first 60-90 minutes, mortality with reperfusion by fibrinolytic therapy can be reduced by 50%[203]; during the first 2-3 hours a striking but rapidly declining benefit of reperfusion is present; from 6-12 hours gains achieved by reperfusion are only modest as the curve flattens, so that there is almost no added benefit thereafter (see Fig. 12-5). Overall, during the first 1-3 hours of symptoms, the time to treatment is critical, whereas later when the patient is on the "flat" part of the curve time is less of a factor and opening the infarct-related artery is the priority. In this later time, a mechanical approach is superior to fibrinolytic agents that have lesser effectiveness on more mature coronary artery clots.

Alteplase (tPA)

Tissue plasminogen activator *(Activase in the United States, Actilyse in Europe)* is a naturally occurring enzyme that binds to fibrin with a greater affinity than streptokinase or urokinase; once bound, it starts to convert plasminogen to plasmin on the fibrin surface. Hence it is relatively "clot selective," although in clinical doses some systemic effects do occur. The very short half-life of alteplase mandates co-therapy with intravenous heparin to avoid reocclusion. In the GUSTO trial[211] mortality was 14% lower (1% absolute decrease) with tPA compared with streptokinase.

Dose of alteplase.

The US package insert states that alteplase is infused as 100 mg over 3 hours, with 60 mg in the first hour (of which 6-10 mg is given as a bolus), 20 mg over the second hour, and 20 mg over the third hour. For smaller patients (<65 kg), a dose of 1.25 mg/kg is administered. As with the other fibrinolytics (see later), aspirin 300 mg should be given as soon as possible. Any aspirin can be given, but if enteric should be chewed. Clopidogrel 300 mg followed by 75 mg per day (no loading dose in patients 75 years old or older) should also be commenced. An initial heparin bolus of 4000 IU is standard, although lower doses should be considered in older adults and in patients of low body weight. Intravenous heparin should be continued for at least 48 hours, adjusted to an aPPT of 50-75 seconds.

Use in stroke.

Intravenous alteplase is the only US-approved treatment for acute ischemic stroke. Alteplase was tested in doses of 0.9 mg/kg versus TNK, the first 10% administered as an initial bolus and the remainder over a 1-hour period, with a maximum dose of 90 mg. In a small trial high-dose TNK was better than alteplase (see TNK).[212]

Side effects and contraindications.

Side effects and hence contraindications relate chiefly to hemorrhage, for example, risk of hemorrhage or hemorrhagic stroke (Table 9-7). (For a full list of contraindications see *Drugs for the Heart,* sixth edition, Table 9-5). Gentamicin sensitivity is a specific exclusion for alteplase therapy because gentamicin is used in the preparation of alteplase.

Table 9-7 -- Clinical Factors in Choosing an Antithrombotic Agent

Condition	UFH	LMWH	Fonda	Bival
Severe renal impairment	Caution	Avoid	Avoid	Caution
↑ bleeding risk	Neutral	Selective use	Good*	Good*

Condition	UFH	LMWH	Fonda	Bival
Thrombocytopenia	Worst risk for HIT	Better: lower risk for HIT	Better, but some thrombocytopenia	Best
Early invasive strategy	Good*	Selective use[†]	Avoid[‡]	Good*

Bival, Bivalirudin; *Fonda,* fondaparinux; *HIT,* heparin-induced thrombocytopenia; *LMWH,* low-molecular-weight heparin; *UFH,* unfractionated heparin.

* Can use; positive data.

† Missed primary endpoint, positive data for fibrinolysis and rescue PCI.[177]

‡ Positive data for fibrinolysis, not for primary percutaneous coronary intervention.[188]

Cost effectiveness of alteplase.

An important disadvantage of alteplase is its cost, which is approximately five times that of streptokinase.

Tenecteplase

TNK is a genetically engineered mutant of native tPA with amino acid substitutions at three sites. These properties result in decreased plasma clearance, a longer half life (Table 9-8), increased fibrin specificity, and resistance to the PAI-1. In the ASSENT-2 trial, a single bolus of TNK (in a weight-adjusted dose of 0.5 mg/kg) was compared with accelerated alteplase. At 30 days, mortality was the same with both agents (6.18% with TNK versus 6.15% with alteplase), as was the stroke rate.[213] However, there was less major bleeding with TNK (4.7% versus 5.9%, $p < 0.01$). Thus the same or marginally better clinical results can be found with only one bolus of TNK-tPA versus the infusion required for alteplase, so that TNK is now preferred over tPA.

Table 9-8 -- Characteristics of Fibrinolytic Agents

	Streptokinase	Alteplase (tPA)	Reteplase (rPA)	Tenecteplase (TNK)
Fibrin selective	No	Yes	Yes	Yes > tPA
Plasminogen binding	Indirect	Direct	Direct	Direct
Duration of infusion (min)	60	90	10 + 10	5-10 sec
Half-life (min)	23	<5	13-16	20
Fibrinogen breakdown	4+	1-2+	Not known	>tPA
Early heparin	Probably yes	Yes	Yes	Yes
Hypotension	Yes	No	No	No
Allergic reactions	Yes	No	No	No
Approximate current cost/dose	$750* per 1.5 MU	$5863 per 100 mg	$5212 per 20-u kit	$3848 per 50-mg kit
TIMI flow grade 3, 90 min	32%	45%-54%	60%	<tPA
TIMI flow grade 2-3 at 90 minutes at 2-3 hours at 24 hours	53% 70%-73% 81%-88%	81%-88% 73%-80% 78%-89%	83% No data No data	No data No data No data

MU, Million units; *rPA,* reteplase; *TIMI,* thrombolysis in myocardial infarction; *TNK,* tenecteplase; *tPA,* tissue plasminogen activator.

Dollar prices for Mayo Clinic, 2012; TIMI flow grade 1 = some penetration of contrast material past prior obstruction; grade 2 = perfusion of entire infarct-related artery but delayed perfusion of distal bed; grade 3 = full perfusion, normal flow.

* Estimate.

Use in stroke.

In a phase 2B trial, 75 patients with early stroke received alteplase or TNK-tPA (0.1 mg/kg, administered as a single bolus, with a maximum dose of 10 mg; or 0.25 mg/kg, administered as a single bolus, with a maximum dose of 25 mg) less than 6 hours after the onset of ischemic stroke.[212] The higher dose of TNK-tPA was superior to the lower dose and to alteplase for all efficacy outcomes, including absence of serious disability at 90 days (in 72% of patients, versus 40% with alteplase; P = 0.02). Together, the two TNK-tPA groups had greater reperfusion (P = 0.004) and clinical improvement (P < 0.001) at 24 hours than the alteplase group.

Reteplase

Reteplase *(Retavase)* is a deletion mutant of alteplase with elimination of the kringle-1, finger, and epidermal growth factor domains, as well as some carbohydrate side chains. This results in prolonged plasma clearance, so that a double-bolus regimen (10 U+10 U intravenously, each over 10 minutes and 30 minutes apart) can be used. Heparin must not be given through the same intravenous line (physical incompatibility). In large trials, mortality was similar with rPA and streptokinase, and mortality and stroke rates were similar with rPA and alteplase.

Streptokinase

Streptokinase is the original thrombolytic agent (see Fig. 9-13). It has no direct effect on plasminogen, but rather works by binding with plasminogen to form a 1:1 complex that becomes an active enzyme to convert plasminogen to plasmin. In addition, streptokinase may increase circulating levels of activated protein-C, which enhances clot lysis. The second and third generation of thrombolytics are superior drugs, but streptokinase is cheap and still widely used in many parts of the world. The standard rate of infusion is 1.5 million IU of streptokinase in 100 mL of physiologic saline over 30-60 minutes.[214] The major problem with streptokinase is that the majority of generic preparations (13 of 16 tested) are underpowered with activities of 21%-87% of those claimed.[215]

Streptokinase and heparin or bivalirudin.

The combination of intravenous heparin with streptokinase remains controversial. We recommend heparin on the basis of the following trials. First, in an analysis of 68,000 patients (all of whom received aspirin, 93% of whom received fibrinolytic therapy and many of whom received streptokinase), the benefits of added heparin translates into a benefit/risk ratio of five deaths and three infarctions prevented at a cost of three transfusions per 1000 patients treated and a nonsignificant increase in stroke.[216] Second, in the 5-year follow-up of US patients in the GUSTO-1 Trial,[217] mortality was similar in the alteplase group and the streptokinase plus intravenous heparin group, but significantly higher in the streptokinase plus subcutaneous heparin group. Regarding streptokinase and bivalirudin in AMI, this combination was superior to streptokinase and UFH in prevention of reinfarction at the cost of modestly more bleeding.[218]

Side effects and contraindications of streptokinase.

In the GUSTO-I Trial,[211] there were two more hemorrhagic strokes per 1000 patients treated with alteplase than with streptokinase (p < 0.03; Table 9-9). Allergic reactions and hypotension were more common with streptokinase. The overall incidence of major bleeding was similar with both regimens. Major bleeding requires cessation of the fibrinolytic agent and adjunctive heparin, administration of protamine sulfate to reverse the actions of heparin, and FFP or whole blood. *Contraindications* are similar to those against alteplase, with the exception of gentamicin sensitivity. Additional contraindications are (1) major recent streptococcal infection, because antistreptococcal antibodies cause resistance to streptokinase; and (2) previous treatment by streptokinase, because the antibodies diminish efficacy and there is an increased risk of allergy.

Table 9-9 -- Side Effects of Streptokinase, Alteplase, and Tenecteplase in the GUSTO-I and ASSENT-2 Trials

	Streptokinase (GUSTO)*	Alteplase (GUSTO)*	Alteplase (ASSENT-2)[†]	Tenecteplase (ASSENT-2)[†]
Patient number	10,410	10,396	8,461	8,488
Mortality at 30 days	7.4%	6.3%*	6.2%	6.2%
Overall stroke	1.40%	1.55%	1.66%	1.78%
Hemorrhagic stroke[‡]	0.54%	0.72%*	0.93%	0.94%
Major bleeds	6.3%*	5.4%	5.9%	4.7%*
Allergic reactions	5.8%*	1.6%	0.2% (ana)	0.1% (ana)
Hypotension	12.5%	10.1%	16.1%	15.9%

ana, Anaphylaxis.

All three agents were used in conjunction with intravenous heparin.

* Significant difference.

† See Reference 213.

‡ For risk factors, see Simoons et al.[238] In patients with streptokinase and no risk factors, the probability of stroke is 0.3%. In patients with alteplase and three risk factors, the probability is more than 3%.

Which fibrinolytic?

Several large trials randomizing over 100,000 patients have compared the effects of streptokinase and alteplase. In the GUSTO-I Trial, there was a 14% relative and a 1% absolute mortality reduction with alteplase infused over 90 minutes compared with streptokinase,[211] at the cost of two extra strokes per 1000 patients randomized. Thus when stroke reduction is important (as in older adults), streptokinase may be better (and much cheaper). In the GUSTO-III trial, rPA was the equivalent to accelerated alteplase. In the ASSENT-2 trial, TNK was equivalent to alteplase, but with less major bleeding.[213] TNK and rPA have the advantage of bolus administration, TNK being given only once. The bolus agents are more convenient, simpler to use, and help to reduce medication errors. Alteplase, streptokinase, TNK, and rPA are licensed in the United States for mortality reduction in AMI. Of these, TNK is most widely used in the United States. All have similar contraindications.

Current trends.

Improvements have occurred with the addition of clopidogrel, enoxaparin, or fondaparinux, and more frequent use of rescue and systematic PCI or the pharmacoinvasive approach. Attention is also switching to improvements that can be achieved by lessening reperfusion injury.[219] Early studies in humans with reperfused AMI suggest that reperfusion injury can cause death of approximately one-third of the reperfused myocytes, and that postconditioning can limit such damage.[220]

Active intervention: Fibrinolysis or PCI?

The premise that the best form of reperfusion therapy is PCI is established as preferred treatment when door-to-balloon times are more than 90 minutes, but the outcomes depend on the expertise and logistics present in individual institutions. Primary PCI has the distinct advantage of lower bleeding rates than fibrinolytic therapy, and achieves higher TIMI grade 3 flow rates in the infarct-related artery. A metaanalysis of 23 randomized trials documented a benefit from primary PCI on both short- and longer-term mortality and morbidity.[221] However, fibrinolysis is likely to have been improved by the addition of clopidogrel, new antithrombotics and high rates of rescue or systematic PCI.

Goodbye to combined fibrinolysis and PCI?

The challenging hypothesis that reduced dose fibrinolytics could be combined with subsequent angioplasty, thereby helping to avoid the adverse effects of long delays to PCI, has been set aside by the FINESSE[222]

and ASSENT-4 studies.[223] However, very early thrombolysis with an average time delay of 100 minutes to the onset of therapy and preceding mandatory invasive study within 24 hours gave results similar to primary PCI in a small study.[224] Pharmacodynamic reperfusion strategy may make a comeback. Half-dose fibrinolysis, clopidogrel and UFH combined with transfer as soon as feasible to the nearest PCI-capable hospital is a practical strategy.[225]

"Rescue" or routine postthrombolytic PCI.

Some degree of resistance of thrombi to lysis can be expected in perhaps 10%-15% of patients; the cause may include deep fissuring or rupture of the plaque or platelet-rich thrombus, which is very resistant to lysis. Rescue PCI may be beneficial in patients with continuing pain or hemodynamic instability, or when very early fibrinolysis appears to have failed.[226] Rescue PCI is superior to repeat thrombolysis and to no treatment for failed reperfusion.[227] Following thrombolysis, routine early catheterization and frequent PCI within 24 hours appears to be more beneficial than a conservative strategy.[228] Thus if fibrinolytic agents are given, patients should ideally be rapidly transferred to a PCI-capable center if rescue PCI is required. Further studies are required to define whether all patients following fibrinolysis should undergo angiography and PCI regardless of symptomatic status and whether this should occur within 24 hours of fibrinolysis or at some later stage.

Effect of time delay.

PCI and fibrinolysis may be similarly effective in patients presenting within 3 hours, as shown in the PRAGUE-2 study,[229] and the CAPTIM data argue for fibrinolysis within the first 2 hours provided that prompt "rescue PCI" is available for failed reperfusion.[203] Other trials suggest that the advantage of PCI is greater in patients treated late.[230] Fibrinolytic therapy may be the treatment of choice in the first 2 hours, and PCI the treatment of choice both in patients with contraindications against fibrinolytic therapy and in those presenting after 3 hours, provided that the procedure can be performed with less than 60 minutes of PCI-related time delay. Nonetheless, the trend is toward increasing use of primary PCI where facilities are available. Much depends on how soon the patient can reach a center with high-quality emergency primary PCI facilities, and the door-to-balloon delay at those centers should be less than 90 minutes.[205],[231] *As the delay increases, the mortality advantage for primary PCI over fibrinolysis decreases.* Primary PCI is now the commonest form of reperfusion therapy in the United Kingdom. Unfortunately, however, less than 30% of patients in the United States and less than 20% in most of Europe have access to primary PCI, and probably even fewer in India or China, meaning that only thrombolytic reperfusion is available. Whenever facilities for primary PCI are available for STEMI, the current emphasis is on minimizing the door-to-balloon time.[231] Most emphasis should be placed on reducing the overall "ischemic time" (symptom onset to reperfusion). Effective and integrated prehospital systems (including paramedic ambulance with telemetry of the ECG and rapid coordination with the PCI center) can substantially reduce prehospital delays.[232],[233]

*Fibrinolysis versus PCI: Practical problems in developing countries**

Primary PCI ideally within 2-3 hours of presentation of AMI is the most desirable therapy. The Western world has established the necessary network to hasten the procedure with ever-shortening pain-to-balloon times. This policy is difficult to apply in the developing countries because of (1) problems in transportation in the form of well-equipped road or air ambulances; (2) slow traffic in bigger cities; (3) unavailability of PCI centers and well-trained operators across the country; (4) failure of insurance system to work efficiently, especially in countries like India where universal health insurance is not available. Within these limits, individual physicians and cardiologists as well as regional centres are putting efforts into optimizing the management of AMI both in urban and periurban areas in the developing countries. The following are important points:

1. Because the availability of catheter laboratory facilities and the finances for primary PCI are scarce, most of the patients in developing countries are treated in the coronary care unit (CCU) of a nearby hospital with thrombolysis. Although thrombolytic therapy remains the cornerstone treatment, 40% of STEMI patients in India did not receive any reperfusion therapy.[234]
2. This is the most important missed opportunity when it comes to improving the outcomes of STEMI. Even though tPA molecules have better evidence, most of the patients receive streptokinase because of its cost effectiveness.[234] Recently biosimilar tenecteplase has become less expensive in India, Asia, and some parts of South America, so that its use is increasing. β-Blockers and ACE inhibitors are also underused in developing countries during hospitalization in CCU.[234]

3. There is also a delay in the diagnosis of AMI when ECG is equivocal as few hospitals can provide troponin assays. “Point-of-care” troponin assays would tremendously enhance the early diagnosis and management of AMI.
4. *The potential for greater improvements in patient outcomes can be achieved with improved delivery of care rather than by the potential gains achieved by switching therapeutic strategies.* The ideal aim in the chain from patient to health care delivery provider is to shorten the time to thrombolysis and reperfusion and early transfer to PCI-available center as soon as possible, preferably within 6 hours.[235]
5. Pharmacodynamic reperfusion strategy: Half-dose fibrinolysis, clopidogrel, and UFH combined with transfer as soon as feasible to the nearest PCI-capable hospital is a practical strategy.[225]
6. Another area of opportunity is the early recognition of symptoms of AMI. Public education is the key to early reporting for chest pain. Physicians also need to be educated and motivated to participate in community activities to educate patients to not waste the “golden hour.”

* Section by Mardikar HM, et al. Management of AMI in the Indian scenario. In Opie LH, Gersh BJ, editors: *Acute myocardial infarction,* India, 2012, Elsevier.

Summary

1. ***Adherent, activated and aggregated platelets*** (the three As) form the thrombus by a series of events initiated by tissue factor, which becomes exposed when a plaque ruptures or the endothelium is injured. Antiplatelet agents are effective and widely used both prophylactically and in ACS, including STEMI.
2. ***Aspirin.*** This well-tested, widely used, and cheap antiplatelet agent is beneficial in a wide variety of vascular disorders, including the prevention and treatment of coronary heart disease. It inhibits platelet COX-1 over a wide dose range. Prophylactic aspirin is indicated for all stages of symptomatic ischemic heart disease, including chronic effort angina, unstable angina, AMI, postinfarction management, after CABG, and during PCI. In the past, primary prevention by aspirin was considered only for high-risk patients. In those at moderate risk, there are almost as many disabling side effects. In view of the series of papers by Rothwell's group that have shown a remarkable effect of aspirin in lessening the development of cancer, including early metastases, *we change our previous opinion that prophylactic aspirin for the general apparently healthy population should not be encouraged, but rather that prophylactic use of aspirin can be considered.*
3. ***ADP-receptor ($P2Y_{12}$) antagonists: Clopidogrel, ticlopidine and prasugrel.*** These ADP receptor antagonists decrease events in ACS and help to prevent acute thrombotic closure after coronary artery stenting and are used for stroke prevention in patients with aspirin intolerance or resistance. Clopidogrel has fewer serious side effects, especially thrombocytopenia, than ticlopidine. For elective PCI, high-dose clopidogrel is sufficient without GpIIb/IIIa receptor inhibitors. With planned PCI, upstream high-dose clopidogrel (300-600 mg loading) is commonly used without GpIIb/IIIa blockade, with ticagrelor being the preferred alternative. Clopidogrel should be continued together with aspirin for at least 12 months with ACS and following DES implantation.
4. ***Other antiplatelet agents.*** Other agents such as sulfinpyrazone and dipyridamole are used less. Dipyridamole plus aspirin reduces repeat stroke.
5. ***GpIIb/IIIa receptor blockers.*** GpIIb/IIIa receptor blockers, including intravenous abciximab, tirofiban, and eptifibatide, act by blocking the final pathway of platelet aggregation. In ACS, in high-risk patients, and in PCI, they give outcome benefit beyond that obtained by aspirin and heparin *or* LMWH. The current policy is to replace heparin plus GpIIb/IIIa antagonists by bivalirudin (see Fig. 12-3). Upstream IIb/IIIa receptor antagonists are no longer recommended except for recurrent ischaemia while awaiting PCI. Intravenous abciximab or eptifibatide may be given prior to primary PCI and are usually reserved for a high thrombus or poor coronary flow when they may be given by the intracoronary route. In STEMI treated by fibrinolytics, the GpIIb/IIIa blockers should not be used.
6. ***Intravenous UFH.*** Intravenous UFH has a rapid onset of action, and is widely used in acute MI with or without fibrinolysis. LMWH produces less reinfarction (with fibrinolysis) than UFH and is simpler to use. Other indications for heparin (or LMWH) are in ACS, PCIs, and VTE. In all of these situations it is combined with aspirin. The drawbacks of UFH are that (1) anticoagulation is seldom well controlled, so that over-anticoagulation and under-anticoagulation are frequent despite repetitive measurements of aPPT or ACT; and (2) rebound can occur on discontinuation.
7. ***LMWH.*** LMWH is easier to administer than UFH, being given in standard weight-adjusted doses subcutaneously without the need for aPPT testing. There is no complete antidote for overdosing although protamine reverses the antithrombin effect. Enoxaparin is superior to UFH as adjudicative therapy to fibrinolysis in STE ACS and similar in total outcome (events avoided versus bleeding) in NSTEMI.[177] Further data are required for primary PCI.
8. ***Bivalirudin.*** In patients with moderate- to high-risk ACS and planned early catheterization, bivalirudin infusion results in similar outcomes to UFH or enoxaparin plus GpIIb/IIIa antagonists, with less bleeding.[185] In primary PCI for STEMI, bivalirudin produces less bleeding (and a modest reduction in mortality) compared with heparin plus GpIIb/IIIa.

9. ***Fondaparinux.*** For conservative management, fondaparinux is convenient to use (2.5 mg subcutaneously once daily) and represents a preferred anticoagulant strategy in those at higher risk of bleeding, but must be avoided in renal impairment with CrCl less than 30 mL/min.[166] Added UFH appears to reduce catheter thrombosis.
10. ***Which regimen provides better therapy for ACS?*** There are several approved options (UFH versus LMWH versus bivalirudin versus fondaparinux). The chosen regimen may differ between interventional and noninterventional centers. When intervention is likely, bivalirudin has excellent data, whereas if a conservative strategy is employed, fondaparinux is well tested in combination with fibrinolysis. If bleeding is a concern, bivalirudin and fondaparinux (if PCI is unlikely) are good alternative choices.
11. ***Oral anticoagulation.*** *Warfarin* has a slow onset of action over several days. Anticoagulation with warfarin is essential for those with prosthetic mechanical heart valves. For most patients with AF, warfarin is superior to aspirin in stroke prevention. Two major problems with warfarin are, first, the genetically induced large interpatient variation in the dose required, and, second, the serious risk of intracranial hemorrhage as use of warfarin in older adults has increased as world populations age. The risk of brain hemorrhage can be predicted by genetic profiling where available and affordable, and lessened by using the new oral agents. Oral thrombin inhibitors such as *dabigatran, rivaroxaban, and apixaban* compare well with warfarin in large-scale studies, often giving better outcome reduction. Their major advantage is a fixed oral dose that needs no monitoring, and reduced intracranial bleeding versus warfarin. They are already widely used to prevent stroke in nonvalvular AF. Their major disadvantages are cost and renal excretion, requiring dose decrease or even exclusion. Increased bleeding is usually not serious, but if it occurs, there is no tested antidote.
12. ***Fibrinolytic agents*** form the basis of therapy in many situations in which primary PCI is not feasible, as in the early stages of STE AMI. They are usually given in combination with UFH or LMWH, together with oral aspirin and clopidogrel. TNK and rPA need only one or two (respectively) bolus injections versus the infusion over 90 min needed for alteplase, which is associated with more systemic bleeding than TNK. For those at high risk of intracranial bleeds, such as older women with hypertension, streptokinase lessens the risk, but the lowest risk of intracranial and other bleeding is achieved with primary PCI. If patients present within 12 hours of onset of AMI, and appropriate facilities are available, the best approach to opening the occluded infarct-related artery is primary PCI. The door-to-balloon time should be 90 minutes or less. Combined fibrinolysis and PCI is harmful and not helpful. The next development could be therapy aimed at reduction of reperfusion injury in the ambulance.
13. ***Ongoing trials.*** Ongoing trials are testing newer antiplatelet and antithrombotic agents, with or without PCI. Yet more important than the type of reperfusion regimen used is the urgent need to make the “symptom-to-needle” or the “symptom-to-PCI” time as short as possible and to ensure that all potentially eligible patients receive reperfusion (internationally at least one fourth do not).
14. ***Future progress.*** The major yield from a society perspective is to treat all eligible patients with STEMI as quickly as possible. If this is achieved, overall gain is far greater than the difference between reperfusion regimens. Unfortunately, many patients, including those at highest risk, receive no reperfusion therapy at all. It is here that the least amount of effort could provide the highest yield.

References

1.. Hoffman M, et al: A cell-based model of hemostasis. *Thromb Haemost* 2001; 85:958-965.

2.. Mackman N, et al: Role of the extrinsic pathway of blood coagulation in hemostasis and thrombosis. *Arterioscler Thromb Vasc Biol* 2007; 27:1687-1693.

3.. Steffel J, et al: Tissue factor in cardiovascular diseases. molecular mechanisms and clinical implications*Circulation* 2006; 113:722-731.

4.. Ruggeri ZM, et al: Adhesion mechanisms in platelet function. *Circ Res* 2007; 100:1673-1685.

5.. Offermanns S: Activation of platelet function through G protein-coupled receptors. *Circ Res* 2006; 99:1293-1304.

6.. Rao LV, et al: Tissue factor-factor VIIa signaling. *Arterioscler Thromb Vasc Biol* 2005; 25:47-56.

7.. Schneider DJ, et al: Conundrums in the combined use of anticoagulants and antiplatelet drugs. *Circulation* 2007; 116:305-315.

8.. Nieswandt B, et al: Platelet-collagen interaction. is GPVI the central receptor*Blood* 2003; 102:449-461.

9.. Denis CV, et al: Platelet adhesion receptors and their ligands in mouse models of thrombosis. *Arterioscler Thromb Vasc Biol* 2007; 27:728-739.

10.. Meadows TA, et al: Clinical aspects of platelet inhibitors and thrombus formation. *Circ Res* 2007; 100:1261-1275.

11.. Hankey GJ, et al: Aspirin resistance. *Lancet* 2006; 367:606-617.

12.. Yank V, et al: Systematic review. benefits and harms of in-hospital use of recombinant factor VIIa for off-label indications*Ann Intern Med* 2011; 154:529-540.

13.. Eerenberg ES, et al: Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate. a randomized, placebo-controlled, crossover study in healthy subjects*Circulation* 2011; 124:1573-1579.

14.. Zhou W, et al: Hemostatic therapy in experimental intracerebral hemorrhage associated with the direct thrombin inhibitor dabigatran. *Stroke* 2011; 42:3594-3599.

15.. CRASH-2 trial collaborators , Shakur H, et al: Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2). a randomised, placebo-controlled trial*Lancet* 2010; 376:23-32l.

16.. Prieto-Merino D, et al: The importance of early treatment with tranexamic acid in bleeding trauma patients. an exploratory analysis of the CRASH-2 randomised controlled trial*Lancet* 2011; 377:1096-1101.1101

17.. Antman EM, et al: Cyclooxygenase inhibition and cardiovascular risk. *Circulation* 2005; 112:759-770.

18.. UK-TIA Study Group. The United Kingdom Transient Ischaemic Attack (UK-TIA) Aspirin Trial. final results*J Neurol Neurosurg Psychiatry* 1991; 54:1044-1054.

19.. Hayden M, et al: Aspirin for the primary prevention of cardiovascular events. a summary of the evidence for the U.S. Preventive Services Task Force*Ann Intern Med* 2002; 136:161-172.

20.. Ridker PM, et al: Low-dose aspirin therapy for chronic stable angina. A randomized placebo-controlled

clinical trial. *Ann Int Med* 1991; 114:835-839.

21.. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction and stroke in high-risk patients. *Brit Med J* 2002; 324:71-86.

22.. Peters RJ, et al: Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes. observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study*Circulation* 2003; 108:1682-1687.

23.. Heras M, et al: Effects of thrombin inhibition on the development of acute platelet-thromubus deposition during angioplasty in pigs. *Circulation* 1989; 79:657-665.

24.. López-Farré A, et al: Effects of aspirin on platelet-neutrophil interactions. Role of nitric oxide and endothelin-1. *Circulation* 1995; 91:2080-2208.

25.. Ridker PM, et al: Inflammation, aspirin and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997; 336:973-979.

26.. Eikelboom JW, et al: Aspirin-resistant thromboxane biosynthesis and the risk of myocardial infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events. *Circulation* 2002; 105:1650-1655.

27.. Maree AO, et al: Variable platelet response to aspirin and clopidogrel in atherothrombotic disease. *Circulation* 2007; 115:2196-2207.

28.. Cotter G, et al: Lack of aspirin effect. aspirin resistance or resistance to taking aspirin*Am Heart J* 2004; 147:293-300.

29.. Gum PA, et al: A prospective, blinded determination of the natural history of aspirin resistance among stable patients with cardiovascular disease. *J Am Coll Cardiol* 2003; 41:961-965.

30.. Lev EI, et al: Aspirin and clopidogrel drug response in patients undergoing percutaneous coronary intervention. the role of dual drug resistance*J Am Coll Cardiol* 2006; 47:27-33.

31.. Juul-Möller S, et al: For the Swedish Angina Pectoris Aspirin Trial (SAPAT) Group. Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. *Lancet* 1992; 340:1421-1425.

32.. Belch J, et al: The prevention of progression of arterial disease and diabetes (POPADAD) trial. factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease*Brit Med J* 2008; 337:a1840.

33.. De Berardis , et al: Association of aspirin use with major bleeding in patients with and without diabetes. *JAMA* 2012; 307:2286-2294.

34.. Goldstein LB, et al: Guidelines for the primary prevention of stroke. a guideline for healthcare professionals from the American Heart Association/American Stroke Association*Stroke* 2011; 42:517-584.Erratum in Stroke 2011;42:e26

35.. Rothwell PM, et al: Effect of daily aspirin on long-term risk of death due to cancer. analysis of individual patient data from randomised trials*Lancet* 2011; 377:31-41.

36.. Burn J, et al: for the CAPP2 Investigators. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer. an analysis from the CAPP2 randomised controlled trial*Lancet* 2011; 378:2081-2087.

37.. Rothwell PM, et al: Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death. analysis of the time course of risks and benefits in 51 randomised controlled trials*Lancet* 2012; 379:1602-1612.

38.. Rothwell PM, et al: Effect of daily aspirin on risk of cancer metastasis. a study of incident cancers

during randomised controlled trials*Lancet* 2012; 379:1591-1601.

39.. Opie LH: Aspirin and the prevention of cancer. *Lancet* 2011; 377:1651.

40.. Chan AT, et al: Editorial comment. Are we ready to recommend aspirin for cancer prevention. *Lancet* 2012; 379:1569-1571.

41.. Capodanno D, et al: Antithrombotic therapy in patients with chronic kidney disease. *Circulation* 2012; 125:2649-2661.

42.. Mehta SR, et al: CURRENT-OASIS 7 Investigators. *N Engl J Med* 2010; 363:930-942.Erratum in N Engl J Med 2010;363:1585

43.. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction. *Lancet* 1988; 2:349-360.

44.. Berger JS, et al: Initial aspirin dose and outcome among ST-elevation myocardial infarction patients treated with fibrinolytic therapy. *Circulation* 2008; 117:192-199.

45.. Mangano DT: Aspirin and mortality from coronary bypass surgery. *N Engl J Med* 2002; 347:1309-1317.

46.. Rothwell PM, et al: Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke (EXPRESS study): a prospective population-based sequential comparison. *Lancet* 2007; 370:1432-1442.

47.. Fuster V, et al: Aspirin as a therapeutic agent in cardiovascular disease. *Circulation* 1993; 87:659-675.

48.. Dutch TIA Trial Study Group. A comparison of two doses of aspirin (30 mg vs 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. *New Engl J Med* 1991; 325:1261-1266.

49.. Taylor D, et al: Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy. a randomised controlled trial*Lancet* 1999; 353:2179-2184.

50.. McQuaid KR, et al: Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. *Am J Med* 2006; 119:624-638.

51.. McNamara RL, et al: Management of atrial fibrillation. review of the evidence for the role of pharmacologic therapy, electrical cardioversion, and echocardiography*Ann Intern Med* 2003; 139:1018-1033.

52.. Segal R, et al: Early and late effects of low-dose aspirin on renal function in elderly patients. *Am J Med* 2002; 115:462-466.

53.. Awtry EH, et al: Aspirin. *Circulation* 2000; 101:1206-1218.

54.. MacDonald TM, et al: Effect of ibuprofen on cardioprotective effect of aspirin. *Lancet* 2003; 361:573-574.

55.. Teo KK, et al: Effects of long-term treatment with angiotensin-converting-enzyme inhibitors in the presence or absence of aspirin. a systematic review*Lancet* 2002; 360:1037-1043.

56.. Latini R, et al: Clinical effects of early angiotensin-converting enzyme inhibitor treatment for acute myocardial infarction are similar in the presence and absence of aspirin. systematic overview of individual data from 96,712 randomized patients. Angiotensin-converting Enzyme Inhibitor Myocardial Infarction Collaborative Group*J Am Coll Cardiol* 2000; 35:1801-1807.

57.. van Wijngaarden , et al: Effects of acetylsalicylic acid on peripheral hemodynamics in patients with chronic heart failure treated with angiotensin-converting enzyme inhibitors. *J Cardiovasc Pharmacol* 1994; 23:240-245.

58.. Chan FK, et al: Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. *N*

Engl J Med 2005; 352:238-244.

59.. Steinhubl SR, et al: Ticlopidine pretreatment before coronary stenting is associated with sustained decrease in adverse cardiac events. data from the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) Trial*Circulation* 2001; 103:1403-1409.

60.. Bhatt DL, et al: Meta-analysis of randomized and registry comparisons of ticlopidine with clopidogrel after stenting. *J Am Coll Cardiol* 2002; 39:9-14.

61.. Wallentin L, et al: For the PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; 361:1045-1057.

62.. Hochholzer W, et al: Impact of the degree of peri-interventional platelet inhibition after loading with clopidogrel on early clinical outcome of elective coronary stent placement. *J Am Coll Cardiol* 2006; 48:1742-1750.

63.. Bassand JP, et al: Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. The Task Force for the Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of the European Society of Cardiology. *Eur Heart J* 2007; 28:1598-1660.

64.. Müller I, et al: Effect of a high loading dose of clopidogrel on platelet function in patients undergoing coronary stent placement. *Heart* 2001; 85:92-93.

65.. Mehta SR, et al: CURRENT-OASIS 7 trial investigators. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7). a randomised factorial trial*Lancet* 2010; 376:1233-1243.

66.. Roberts JD, et al: Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE). a prospective, randomised, proof-of-concept trial*Lancet* 2012; 379:1705-1711.

67.. Bates ER, et al: Clopidogrel-drug interactions. *J Am Coll Cardiol* 2011; 57:1251-1263.

68.. Saw J, et al: CHARISMA Investigators. Lack of evidence of a clopidogrel-statin interaction in the CHARISMA trial. *J Am Coll Cardiol* 2007; 50:291-295.

69.. Sibbing D, et al: Impact of proton pump inhibitors on the antiplatelet effects of clopidogrel. *Thromb Haemost* 2009; 101:714-719.

70.. Bhatt DL, et al: Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med* 2010; 363:1909-1917.

71.. Brar SS, et al: Impact of platelet reactivity on clinical outcomes after percutaneous coronary intervention a collaborative meta-analysis of individual participant data. *J Am Coll Cardiol* 2011; 58:1945-1954.

72.. Price MJ, et al: Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention. the GRAVITAS randomized trial*JAMA* 2011; 305:1097-1105.Erratum JAMA 2011;305;2174

73.. Hamm CW, et al: ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. the Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)*Eur Heart J* 2011; 32:2999-3054.

74.. Wallentin L, et al: For the PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; 361:1045-1057.

75.. Trenk D, et al: Results of the TRIGGER-PCI (Testing Platelet Reactivity In Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) Study. *J Am Coll Cardiol* 2012; 59:2159-2164.

76.. Grines CL, et al: Prevention of premature discontinuation of dual antiplatelet therapy in patients with

coronary artery stents. a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians*Circulation* 2007; 115:813-818.

77.. Ho PM, et al: Incidence of death and acute myocardial infarction associated with stopping clopidogrel after acute coronary syndrome. *JAMA* 2008; 299:532-539.

78.. CAPRIE Steering Committee. A randomized, blinded trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). *Lancet* 1996; 348:1329-1339.

79.. ESPIRIT Study Group , Halkes PH, et al: Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT). randomised controlled trial*Lancet* 2006; 367:1665-1673.

80.. Penny W, et al: Antithrombotic therapy for patients with cardiac disease. *Curr Probl Cardiol* 1988; 13:433-513.

81.. Pfeffer MA, et al: The charisma of subgroups and the subgroups of CHARISMA. *N Engl J Med* 2006; 354:1744-1746.

82.. Chen ZM, et al: Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction. randomised placebo-controlled trial*Lancet* 2005; 366:1607-1621.

83.. Bhatt DL, et al: Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. *J Am Coll Cardiol* 2007; 49:1982-1988.

84.. Wright RS, et al: 2011 ACCF/AHA Focused update of the guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 Guideline). a report of the ACC Foundation/AHA Task Force on Practice Guidelines*Circulation* 2011; 123:2022-2060.

85.. Steinhubl SR, et al: Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention. a randomized controlled trial*JAMA* 2002; 288:2411-2420.

86.. Gilard M, et al: Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin. The Randomized Double-Blind OCLA (Omeprazole CLopidogrel Aspirin) Study*J Am Col Cardiol* 2008; 51:256-260.

87.. Diener HC, et al: Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH). randomised, double-blind, placebo-controlled trial*Lancet* 2004; 364:331-337.

88.. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; 345:494-502.

89.. Cuisset T, et al: Benefit of a 600-mg loading dose of clopidogrel on platelet reactivity and clinical outcomes in patients with non-ST-segment elevation acute coronary syndrome undergoing coronary stenting. *J Am Coll Cardiol* 2006; 48:1339-1345.

90.. Kastrati A, et al: Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment. the ISAR-REACT 2 randomized trial*JAMA* 2006; 295:1531-1538.

91.. Wiviott SD, et al: Randomized comparison of prasugrel (CS-747, LY640315), a novel thienopyridine P2Y12 antagonist, with clopidogrel in percutaneous coronary intervention. results of the Joint Utilization of Medications to Block Platelets Optimally (JUMBO)-TIMI 26 trial*Circulation* 2005; 111:3366-3373.

92.. Wiviott SD, et al: Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007; 357:2001-2015.

93.. Serebruany VL: Timing of thienopyridine loading and outcomes in the TRITON trial. the FDA Prasugrel Action Package outlook*Cardiovasc Revasc Med* 2011; 12:94-98.

94.. Hochholzer W, et al: Predictors of bleeding and time dependence of association of bleeding with mortality. insights from the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel—Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38)*Circulation* 2011; 123:2681-2689.

95.. Cannon C, et al: for the PLATelet inhibition and patient Outcomes (PLATO) investigators. Ticagrelor compared with clopidogrel in acute coronary syndromes patients with a planned invasive strategy (PLATO). a randomized double-blind study*Lancet* 2010; 375:283-293.

96.. White HD, et al: Reduced immediate ischemic events with cangrelor in PCI. a post-hoc pooled analysis of the CHAMPION trials using the Universal Definition of Myocardial Infarction*Am Heart J* 2012; 163:182-190.

97.. Angiolillo DJ, et al: Bridging antiplatelet therapy with cangrelor in patients undergoing cardiac surgery. A randomized controlled trial. *JAMA* 2012; 307:265-274.

98.. Tricoci P, et al: for the TRACER Investigators Thrombin-receptor antagonist vorapaxar in acute coronary syndromes. *N Engl J Med* 2012; 366:20-33.

99.. Morrow DA, et al: TRA 2P–TIMI 50 Steering Committee and Investigators. Vorapaxar in the secondary prevention of atherothrombotic events. *N Engl J Med* 2012; 366:1404-1413.

100.. White HD: Oral antiplatelet therapy for atherothrombotic disease. current evidence and new directions*Am Heart J* 2011; 161:450-461.Erratum in Am Heart J 2011;162:569.

101.. Caixeta A, et al: Incidence and clinical consequences of acquired thrombocytopenia after antithrombotic therapies in patients with acute coronary syndromes. results from the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial*Am Heart J* 2011; 161:298-306.

102.. Stone GW, et al: Routine upstream initiation vs deferred selective use of glycoprotein IIb/IIIa inhibitors in acute coronary syndromes. the ACUITY Timing trial*JAMA* 2007; 297:591-602.

103.. Friedland S, et al: Meta-analysis of randomized controlled trials of intracoronary versus intravenous administration of glycoprotein IIb/IIIa inhibitors during percutaneous coronary intervention for acute coronary syndrome. *Am J Cardiol* 2011; 108:1244-1251.

104.. Ohlmann P, et al: Prehospital Abciximab in ST-Segment Elevation Myocardial Infarction. Results of the Randomized, Double-Blind MISTRAL Study*Circ Cardiovasc Interv* 2012; 5:69-76.

105.. EPILOG Investigators. Platelet glycoprotein IIb-IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med* 1997; 336:1689-1696.

106.. Kastrati A, et al: A clinical trial of abciximab in elective percutaneous coronary intervention after pretreatment with clopidogrel. *N Engl J Med* 2004; 350:232-238.

107.. Tcheng J, et al: Readministration of abciximab is as effective as first time administration with similar risks. results from the ReoPro Readministration Registry (R^3) [abstract]*J Am Coll Cardiol* 1999; 33(Suppl. A):14A-15A.

108.. Topol EJ, et al: TARGET Investigators. Do Tirofiban and ReoPro Give Similar Efficacy Trial. Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *N Engl J Med* 2001; 344:1888-1894.

109.. Mukherjee D, et al: Mortality at 1 year for the direct comparison of tirofiban and abciximab during percutaneous coronary revascularization. do tirofiban and ReoPro give similar efficacy outcomes at trial 1-year follow-up*Eur Heart J* 2005; 26:2524-2528.

110.. Valgimigli M, et al: Tirofiban as adjunctive therapy for acute coronary syndromes and percutaneous coronary intervention. a meta-analysis of randomized trials*Eur Heart J* 2010; 31:35-49.

111.. ten Berg JM, et al: On-TIME 2 Study Group. Effect of early, pre-hospital initiation of high bolus dose tirofiban in patients with ST-segment elevation myocardial infarction on short- and long-term clinical

outcome.. *J Am Coll Cardiol* 2010; 55:2446-2455.

112.. PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med* 1998; 339:433-443.

113.. Hirsh J, et al: American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. *J Am Coll Cardiol* 2003; 41:1633-1652.

114.. Huhtakangas J, et al: Effect of increased warfarin use on warfarin-related cerebral hemorrhage. a longitudinal population-based study*Stroke* 2011; 42:2431-2435.

115.. Kamel H, et al: Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in patients with atrial fibrillation and prior stroke or transient ischemic attack. *Stroke* 2012; 43:881-883.

116.. Millican EA, et al: Genetic-based dosing in orthopedic patients beginning warfarin therapy. *Blood* 2007; 110:1511-1515.

117.. Shen AY, et al: Racial/ethnic differences in the risk of intracranial hemorrhage among patients with atrial fibrillation. *J Am Coll Cardiol* 2007; 50:309-315.

118.. Loebstein R, et al: A coding VKORC1 Asp36Tyr polymorphism predisposes to warfarin resistance. *Blood* 2007; 109:2477-2480.

119.. Anderson JL, et al: Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. *Circulation* 2007; 116:2563-2570.

120.. Vink R, et al: The optimal intensity of vitamin K antagonists in patients with mechanical heart valves. a meta-analysis*J Am Coll Cardiol* 2003; 42:2042-2048.

121.. Heneghan C, et al: Self-monitoring of oral anticoagulation. a systematic review and meta-analysis*Lancet* 2006; 367:404-411.

122.. Johnson JA: Warfarin pharmacogenetics. a rising tide for its clinical value*Circulation* 2012; 125:1964-1966.

123.. Flaherty ML, et al: The increasing incidence of anticoagulant-associated intracerebral hemorrhage. *Neurology* 2007; 68:116-121.

124.. Huhtakangas J, et al: Effect of increased warfarin use on warfarin-related cerebral hemorrhage. a longitudinal population-based study*Stroke* 2011; 42:2431-2435.

125.. Gage BF, et al: Risk of osteoporotic fracture in elderly patients taking warfarin. results from the National Registry of Atrial Fibrillation 2*Arch Intern Med* 2006; 166:241-246.

126.. Hylek EM, et al: Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation* 2007; 115:2689-2696.

127.. Yiu KH, et al: Comparison of the efficacy and safety profiles of intravenous vitamin K and fresh frozen plasma as treatment of warfarin-related over-anticoagulation in patients with mechanical heart valves. *Am J Cardiol* 2006; 97:409-411.

128.. Mohler 3rd ER: Atherothrombosis—wave goodbye to combined anticoagulation and antiplatelet therapy. *N Engl J Med* 2007; 357:293-296.

129.. Homma S, et al: WARCEF Investigators. Warfarin and aspirin in patients with heart failure and sinus rhythm. *N Engl J Med* 2012; 366:1859-1869.

130.. Ridker PM, et al: Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. *N Engl J Med* 2003; 348:1425-1434.

131.. Gage BF, et al: Validation of clinical classification schemes for predicting stroke. results from the National Registry of Atrial Fibrillation*JAMA* 2001; 285:2864-2870.

132.. Lip GY, et al: Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach. the Euro heart survey on atrial fibrillation*Chest* 2010; 137:263-272.

133.. Pisters R, et al: 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; 138:1093-1100.

134.. Fang MC, et al: A new risk scheme to predict warfarin-associated hemorrhage. The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study*J Am Coll Cardiol* 2011; 58:395-401.

135.. AFFIRM Investigators. First Antiarrhythmic Drug Substudy. Maintenance of sinus rhythm in patients with atrial fibrillation. *J Am Coll Cardiol* 2003; 42:20-29.

136.. Hart RG, et al: Stroke with intermittent atrial fibrillation. incidence and predictors during aspirin therapy. Stroke Prevention in Atrial Fibrillation Investigators*J Am Coll Cardiol* 2000; 35:183-187.

137.. Mant J, et al: Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA). a randomised controlled trial*Lancet* 2007; 370:493-503.

138.. De Caterina R, et al: Anticoagulants in heart disease. current status and perspectives*Eur Heart J* 2007; 28:880-913.

139.. Kennedy J, et al: Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER). a randomised controlled pilot trial*Lancet Neurol* 2007; 6:961-969.

140.. Reddy VY, et al: Safety of percutaneous left atrial appendage closure. results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry*Circulation* 2011; 123:417-424.

141.. Viles-Gonzalez JF, et al: The clinical impact of incomplete left atrial appendage closure with the Watchman Device in patients with atrial fibrillation. a PROTECT AF substudy*J Am Coll Cardiol* 2012; 59:923-929.

142.. Hirsh J, et al: Guide to anticoagulant therapy. Part 1. Heparin*Circulation* 1994; 89:1449-1468.

142a.. Kleinow ME, et al: Effect of chronic kidney disease on warfarin management in a pharmacist-managed anticoagulation clinic. *J Manag Care Pharm* 2011; 17:523-530.

143.. Hart RG, et al: Warfarin in atrial fibrillation patients with moderate chronic kidney disease. *Clin J Am Soc Nephrol* 2011; 6:2599-2604.

144.. Brodsky SV: Warfarin-related nephropathy occurs in patients with and without chronic kidney disease and is associated with an increased mortality rate. *Kidney Int* 2011; 80:181-189.

145.. Chimowitz MI, et al: Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med* 2005; 352:1305-1316.

146.. Kearon C, et al: Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. *N Engl J Med* 2003; 349:631-639.

147.. Büller HR, et al: for the EINSTEIN–PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012; 366:1287-1289.

148.. Katsnelson M, et al: Progress for stroke prevention with atrial fibrillation. emergence of alternative oral anticoagulants*Circulation* 2012; 125:1577-1583.

149.. Nainggolan L: *New analysis extends dabigatran MI signal to other thrombin inhibitors*. [accessed 05.10.2012] http://www.theheart.org/article/1380075.do

150.. Hankey GJ, et al: Dabigatran etexilate. a new oral thrombin inhibitor*Circulation* 2011; 123:1436-1450.

151.. Wallentin L, et al: Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation. an analysis of the RE-LY trial*Lancet* 2010; 376:975-983.

152.. Connolly SJ, et al: Dabigatran versus warfarin in patients with atrial fibrillation. RE-LY Study. *N Engl J Med* 2009; 361:1139-1151.

153.. Eikelboom JW, et al: Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation. an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial*Circulation* 2011; 123:2363-2372.

154.. Hohnloser SH, et al: Myocardial ischemic events in patients with atrial fibrillation treated with dabigatran or warfarin in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial. *Circulation* 2012; 125:669-676.

155.. *Label update for dabigatran*. [accessed 05.10.12] http://www.theheart.org/article/1411191.do

156.. *FDA label*. FDA website[accessed 07.06.12] www.fda.gov/

157.. *Dabigatran fatal bleeding less than in clinical trials*. [accessed 05.10.12] http://www.theheart.org

158.. Patel MR, et al: ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; 365:883-891.

159.. Fox KAA, et al: Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. *Eur Heart J* 2011; 32:2387-2394.

160.. Mega JL, et al: for the ATLAS ACS 2–TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012; 366:9-19.

161.. Granger CB, et al: for the ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; 365:981-992.

162.. Connolly SJ, et al: for the AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011; 364:806-817.

163.. Goldhaber SZ, et al: for the ADOPT Trial Investigators. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. *N Engl J Med* 2011; 365:2167-2177.

164.. Alexander JH, et al: for the APPRAISE-2 Investigators Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med* 2011; 365:699-708.

164a.. Camm AJ, et al: 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC Guidelines for the management of atrial fibrillation. *Europace* 2012; 14:1385-1413.HYPERLINK

165.. Hirsh J, et al: Beyond unfractionated heparin and warfarin. current and future advances*Circulation* 2007; 116:552-560.

166.. Anderson JL, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction. a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine*J Am Coll Cardiol* 2007; 50:652-726.

167.. Antman EM, et al: 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction. a report of the American College of Cardiology/American

Heart Association Task Force on Practice Guidelines: developed in collaboration With the Canadian Cardiovascular Society endorsed by the American Academy of Family Physicians: 2007 Writing Group to Review New Evidence and Update the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction, Writing on Behalf of the 2004 Writing Committee*Circulation* 2008; 117:296-329.

168.. Davoren A, et al: Heparin-induced thrombocytopenia and thrombosis. *Am J Hematol* 2006; 81:36-44.

169.. Lo GK, et al: Evaluation of the pretest clinical score (4T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *J Thromb Haem* 2006; 4:759-765.

170.. Cruz-Gonzalez I, et al: Efficacy and safety of argatroban with or without glycoprotein IIb/IIIa inhibitor in patients with heparin induced thrombocytopenia undergoing percutaneous coronary intervention for acute coronary syndrome. *J Thromb Thrombolysis* 2007; 25:214-218.

171.. Spinler SA: New concepts in heparin-induced thrombocytopenia. diagnosis and management*J Thromb Thrombolysis* 2006; 21:17-21.

172.. Wester JP, et al: Low-dose fondaparinux in suspected heparin-induced thrombocytopenia in the critically ill. *Neth J Med* 2007; 65:101-108.

173.. Koster A, et al: Bivalirudin during cardiopulmonary bypass in patients with previous or acute heparin-induced thrombocytopenia and heparin antibodies. results of the CHOOSE-ON trial*Ann Thorac Surg* 2007; 83:572-577.

174.. Keeling D, et al: The management of heparin-induced thrombocytopenia. *Br J Haematol* 2006; 133:259-269.

175.. Schulz S, et al: Intracoronary Stenting and Antithrombotic Regimen. Rapid Early Action for Coronary Treatment (ISAR-REACT) 3A Trial Investigators. ISAR-REACT 3Aa study of reduced dose of unfractionated heparin in biomarker negative patients undergoing percutaneous coronary intervention*Eur Heart J* 2010; 31:2482-2489.

176.. Hirsh J, et al: Guide to anticoagulant therapy. Part 2. Oral anticoagulants*Circulation* 1994; 89:1469-1480.Erratum in Circulation 1995;91:A55–A56

177.. Murphy SA, et al: Efficacy and safety of the low-molecular weight heparin enoxaparin compared with unfractionated heparin across the acute coronary syndrome spectrum. a meta-analysis*Eur Heart J* 2007; 28:2077-2086.

178.. Bhatt DL, et al: Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006; 354:1706-1717.

179.. White H, et al: The use of intravenous enoxaparin in elective percutaneous coronary intervention in patients with renal impairment. results from the STEEPLE trial*Am Heart J* 2006; 157:125-131.

180.. FRISC Study Group. Fragmin During Instability in Coronary Artery Disease (FRISC). Low molecular-weight heparin during instability in coronary artery disease. *Lancet* 1996; 347:561-568.

181.. Eikelboom JW, et al: Unfractionated and low-molecular-weight heparin as adjuncts to thrombolysis in aspirin-treated patients with ST-elevation acute myocardial infarction. a meta-analysis of the randomized trials*Circulation* 2005; 112:3855-3867.

182.. Reed MD, et al: Clinical pharmacology of bivalirudin. *Pharmacotherapy* 2002; 22:105S-111S.

183.. Hanna EB, et al: Characteristics and in-hospital outcomes of patients with non-ST-segment elevation myocardial infarction and chronic kidney disease undergoing percutaneous coronary intervention. *JACC Cardiovasc Interv* 2011; 4:1002-1008.

184.. Lincoff AM, et al: Long-term efficacy of bivalirudin and provisional glycoprotein IIb/IIIa blockade vs heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary revascularization. REPLACE-2 randomized trial*JAMA* 2004; 292:696-703.

185.. Stone GW, et al: Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006; 355:2203-2216.

186.. Stone GW, et al: Bivalirudin in patients with acute coronary syndromes undergoing percutaneous coronary intervention. a subgroup analysis from the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial*Lancet* 2007; 369:907-919.

187.. Waksman R: ACUITY-PCI. one drug does not fit all*Lancet* 2007; 369:881-882.

188.. Yusuf S, et al: Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med* 2006; 354:1464-1476.

189.. Mehran R, et al: HORIZONS-AMI Trial Investigators. Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI). 1-year results of a randomised controlled trial*Lancet* 2009; 374:1149-1159.

190.. Hanna EB, et al: Antiplatelet and anticoagulant therapies in acute coronary syndromes. *Cardiovasc Drugs Ther* 2010; 24:6.

191.. Stone GW, et al: HORIZONS-AMI Trial Investigators. Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI). final 3-year results from a multicentre, randomised controlled trial*Lancet* 2011; 377:2193-2204.

192.. Bangalore S, et al: EVENT Registry Investigators, Bleeding risk comparing targeted low-dose heparin with bivalirudin in patients undergoing percutaneous coronary intervention. results from a propensity score-matched analysis of the Evaluation of Drug-Eluting Stents and Ischemic Events (EVENT) registry*Circ Cardiovasc Interv* 2011; 4:463-473.

193.. Silvain J, et al: Efficacy and safety of enoxaparin versus unfractionated heparin during percutaneous coronary intervention. systematic review and meta-analysis*Brit Med J* 2012 Feb 3; 344:e553.

194.. Lassen MR, et al: RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 2008; 358:2776-2786.

195.. Eriksson BI, et al: RE-NOVATE II Study Group Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II*). A randomised, double-blind, non-inferiority trial. *Thromb Haemost* 2001; 105:721-729.

196.. Mehta SR, et al: Efficacy and safety of Fondaparinux versus Enoxaparin in patients with acute coronary syndromes undergoing percutaneous coronary intervention. Results from the OASIS-5 Trial. *JACC* 2007; 50:1742-1751.

197.. Yusuf S, et al: Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction. the OASIS-6 randomized trial*JAMA* 2006; 295:1519-1530.

198.. Steg PG, et al: FUTURA/OASIS-8 Trial Group. Low-dose vs standard-dose unfractionated heparin for percutaneous coronary intervention in acute coronary syndromes treated with fondaparinux. the FUTURA/OASIS-8 randomized trial*JAMA* 2010; 304:1339-1349.

199.. Fay WP, et al: Vascular functions of the plasminogen activation system. *Arterioscler Thromb Vasc Biol* 2007; 27:1231-1237.

200.. Alessi MC, et al: Plasminogen activator inhibitor-1, adipose tissue and insulin resistance. *Curr Opin Lipidol* 2007; 18:240-245.

201.. Gersh BJ, et al: Thrombolysis and myocardial salvage. results of clinical trials and the animal paradigm—paradoxic or predictable*Circulation* 1993; 88:296-306.

202.. White H, et al: Clinical cardiology. new frontiersthrombolysis for acute myocardial infarction*Circulation* 1998; 97:1632-1646.

203.. Steg PG, et al: Impact of time to treatment on mortality after prehospital fibrinolysis or primary angioplasty. data from the CAPTIM randomized clinical trial*Circulation* 2003; 108:2851-2856.

204.. Weaver WD, et al: For the Myocardial Infarction Triage and Intervention Trial. Prehospital-initiated vs hospital-initiated thrombolytic therapy. *J Am Med Assoc* 1993; 270:1211-1216.

205.. Van de Werf FJ: Fine-tuning the selection of a reperfusion strategy. *Circulation* 2006; 114:2002-2003.

206.. Fibrinolytic Therapy Trial (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction; collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994; 343:311-322.

207.. Taher T, et al: Aborted myocardial infarction in patients with ST-segment elevation. insights from the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen-3 Trial Electrocardiographic Substudy*J Am Coll Cardiol* 2004; 44:38-43.

208.. Giugliano RP, et al: Selecting the best reperfusion strategy in ST-elevation myocardial infarction. it's all a matter of time*Circulation* 2003; 108:2828-2830.

209.. White HD: Optimal treatment of patients with acute coronary syndromes and non-ST-elevation myocardial infarction. *Am Heart J* 1999; 138:S105-114.

210.. Gersh BJ, et al: Pharmacological facilitation of primary percutaneous coronary intervention for acute myocardial infarction. is the slope of the curve the shape of the future*JAMA* 2005; 293:979-986.

211.. GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *New Engl J Med* 1993; 329:673-682.

212.. Parsons M, et al: A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. *N Engl J Med* 2012; 366:1099-1107.

213.. ASSENT-2 Investigators. Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction. the ASSENT-2 double-blinded randomised trial*Lancet* 1999; 354:716-722.

214.. ISIS-3 Study Group. (Third International Study of Infarct Survival) Collaborative Group. ISIS-3. a randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction*Lancet* 1992; 339:753-770.

215.. Hermentin P, et al: Comparative analysis of the activity and content of different streptokinase preparations. *Eur Heart J* 2005; 26:933-940.

216.. Collins R, et al: Clinical effects of anticoagulant therapy in suspected acute myocardial infarction. systematic overview of randomised trials*Brit Med J* 1996; 313:652-659.

217.. Tardiff BE, et al: Long term results from the Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO-I) Trial. sustained benefit of fibrin-specific therapy (Abstract)*Circulation* 1999; 100(18):I-498-I-499.

218.. Deswal A, et al: Cytokines and cytokine receptors in advanced heart failure. an analysis of the cytokine database from the Vesnarinone Trial (VEST)*Circulation* 2001; 103:2055-2059.

219.. Minners J, et al: Diazoxide-induced respiratory inhibition—a putative mitochondrial K(ATP) channel independent mechanism of pharmacological preconditioning. *Mol Cell Biochem* 2007; 294:11-18.

220.. Staat P, et al: Postconditioning the human heart. *Circulation* 2005.2143-2148.

221.. Keeley E, et al: Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction. a quantitative review of 23 randomised trials*Lancet* 2003; 361:13-20.

222.. Ellis S: *ESC Congress, Vienna*. [accessed 05.10.12] http://www.escardio.org

223.. ASSENT-4 PCI. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI). randomised trial*Lancet* 2006; 367:569-578.

224.. Armstrong PW: A comparison of pharmacologic therapy with/without timely coronary intervention vs. primary percutaneous intervention early after ST-elevation myocardial infarction. the WEST (Which Early ST-elevation myocardial infarction Therapy) study*Eur Heart J* 2006; 27:1530-1538.

225.. Larson DM, et al: Safety and efficacy of a pharmaco-invasive reperfusion strategy in rural ST-elevation myocardial infarction patients with expected delays due to long-distance transfers. *Eur Heart J* 2012; 33:1232-1240.

226.. Bonnefoy E, et al: Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction. a randomised study*Lancet* 2002; 360:825-829.

227.. Gershlick AH, et al: Rescue angioplasty after failed thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 2005; 353:2758-2768.

228.. Fernandez-Aviles F, et al: Routine invasive strategy within 24 hours of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1). a randomised controlled trial*Lancet* 2004; 364:1045-1053.

229.. Widimsky P, et al: On behalf of the PRAGUE Study Group Investigators. Long distance support for primary angioplasty vs immediate thombolysis in acute myocardial infarction. *Eur Heart J* 2002; 2003:94-104.

230.. Schomig A, et al: Therapy-dependent influence of time-to-treatment interval on myocardial salvage in patients with acute myocardial infarction treated with coronary artery stenting or thrombolysis. *Circulation* 2003; 108:1084-1088.

231.. Nallamothu BK, et al: Time to treatment in primary percutaneous coronary intervention. *N Engl J Med* 2007; 357:1631-1638.

232.. Kalla K, et al: Implementation of guidelines improves the standard of care. the Viennese registry on reperfusion strategies in ST-elevation myocardial infarction (Vienna STEMI registry)*Circulation* 2006; 113:2398-2405.

233.. Ting HH, et al: Regional systems of care to optimize timeliness of reperfusion therapy for ST-elevation myocardial infarction. the Mayo Clinic STEMI Protocol*Circulation* 2007; 116:729-736.

234.. Xavier D, et al: Treatment and outcomes of acute coronary syndromes in India (CREATE). a prospective analysis of registry data*Lancet* 2008; 371:1435-1442.

235.. Cantor WJ, et al: Routine early angioplasty after fibrinolysis for acute myocardial infarction. *N Engl J Med* 2009; 360:2705-2718.

236.. Chen H, et al: Functional properties of a novel mutant of staphylokinase with platelet-targeted fibrinolysis and antiplatelet aggregation activities. *Eur J Pharmacol* 2007; 566:137-144.

237.. Lefkovits J, et al: Direct thrombin inhibitors in cardiovascular medicine. *Circulation* 1994; 90:1522-1536.

238.. Simoons ML, et al: Individual risk assessment for intracranial haemorrhage during thrombolytic therapy. *Lancet* 1993; 342:1523-1528.