Owing to the fact that the frequency of cerebrovascular diseases is increasing we report about recent developments in acute stroke treatment and in stroke prevention.

Foundation review: Current therapies in ischemic stroke. Part A. Recent developments in acute stroke treatment and in stroke prevention

Erasmia Broussalis[1], Monika Killer[1], Mark McCoy[2], Andrea Harrer[1], Eugen Trinka[1] and Jörg Kraus[1]

[1] Paracelus Medical University, Christian Doppler Klinik, Department of Neurology, Ignaz-Harrer Strasse 79, 5020 Salzburg, Austria
[2] Paracelus Medical University, Christian Doppler Klinik, Department of Radiology and MRT, Ignaz-Harrer Strasse 79, 5020 Salzburg, Austria

Stroke is the third leading cause of death with an increasing prevalence. In previous years many important achievements and new therapeutic strategies have been established. This article provides an overview on recent developments and is an update to the article of Green *et al.* that was published in 2004. As this article is a comprehensive review we divided it in two parts. In this Part A of our review, recent developments in acute stroke treatment and in stroke prevention are described. In Part B we will reflect on neuroprotection.

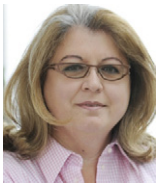
Stroke is the third leading cause of death and the main cause of long-term disability in western societies [1]. The frequency of cerebrovascular diseases is increasing, so that nowadays approximately 5.7 million people are estimated to die from acute ischemic stroke per year worldwide. Recurrent stroke risk after cerebrovascular diseases ranges from 5% to 20% per year [2]. It has been estimated that the lifetime risk of stroke is between 8% and 10% [3]. However, medical treatment has changed over the years both for primary and secondary stroke prevention and also for acute treatment. An overview of the actual primary and secondary stroke prevention is given in Box 1.

This article is an update of the article by Green *et al.* who has provided an overview on the therapeutic strategies of stroke treatment. Green *et al.* reported about new perfusion-enhancing compounds that had been in development and they also reviewed potential neuroprotective drugs [4].

We have collected data of current studies and trials by conducting an extensive search in the Pubmed database. Data from published trials were complemented by abstracts from innovative trials that have been presented at important congresses in the field.

Since 2006 the developments of new treatment options have increased enormously. In this article, we provide a comprehensive overview on stroke treatment. Part A describes recent developments in acute stroke treatment and in stroke prevention. In Part B we will provide an overview on newer drugs that have the potential to be implemented in stroke therapy in the future.

ERASMIA BROUSSALIS, MD received her doctorate in human medicine from the University of Graz in 2001. She is a clinical Neurologist working at the Department of Neurology at the Paracelsus Medical University (PMU). Her research interests include cerebrovascular diseases, predominantly stroke and neurointervention.



MONIKA KILLER, MD is a fully trained neurosurgeon who is specialized in neurointerventional therapy. Her clinical skills and scientific interests are focused on diagnosis and treatment of cerebrovascular diseases and spinal vascular malformations. Dr. Killer graduated in 1993 as MD from the University of Vienna, Medical School. She received her license as Specialist in Neurosurgery from the Austrian Medical Chamber in 1999 and her International Master (MSc) for Neurovascular Diseases in 2002 from Université Paris Sud-Faculté de Médecine de Bicêtre. Since 2004, Dr. Killer has been the attending Neurointerventionalist at Christian Doppler Clinic Salzburg. Since 2005 she is the Head of the Division Experimental Neurointervention of the Neuroscience Institute Salzburg and since 2009 Associate Professor of Neurointervention at Paracelsus Medical University. She is a peer reviewer for multiple international journals as Stroke, AJNR, Neuroradiology and Acta Neurochirurgica and author of more than 50 scientific articles.

JÖRG KRAUS, MD is a clinical Neurologist working at the Department of Neurology at the Paracelsus Medical University (PMU). He received 'Venia Legendi' at the PMU in 2007. He is currently the leading physician ("Leitender Oberarzt") of the Multiple Sclerosis outpatients' clinic and of the ward for Neuroimmunology and Neurooncology. Moreover, he is the head of the research group for Neuroimmunology and Multiple Sclerosis. His research work primarily focuses on biomarkers in multiple sclerosis and other neurologic diseases based upon neuroimmunologic changes at the blood–brain barrier. He is author of about 60 scientific publications in the field of multiple sclerosis and cerebrovascular diseases.

Corresponding author:. Broussalis, E. (e.broussalis@salk.at)

1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2011.11.005

BOX 1

Overview on primary and secondary stroke prevention [119,120].

Overview on primary stroke prevention

Over 75% of all strokes are first-ever strokes, so it is probably that effective prevention in persons with established risk factors who have not had a stroke (i.e. primary prevention) can have as great or an even greater impact on reducing the burden of the disease as compared with prevention of recurrent stroke. Primary stroke prevention includes:

- Blood pressure lowering
- Antiplatelet therapy
- Antithrombotic therapy for atrial fibrillation
- Lipid-lowering therapy
- Antidiabetic therapy
- Weight reduction
- Stopping cigarette smoking
- Stopping alcohol consumption

Overview on secondary stroke prevention

Survivors of a transient ischemic attack or stroke have an increased risk of a further stroke, which is a major source of increased mortality and morbidity.

- Blood pressure-lowering
- Lipid-lowering therapy
- Stopping alcohol consumption
- Antiplatelet medication or antiplatelet modification
- Endovascular or surgical treatment in extracranial or intracranial carotid or vertebral artery disease
- Antidiabetic therapy
- Stopping cigarette smoking
- Weight reduction
- Antithrombotic therapy in cardioembolic strokes caused by atrial fibrillation or persistent foramen ovale
- Therapeutic strategies in hypercoable states (inherited thrombophilias, antiphospholipid antibodies), sickle cell disease

Pathogenesis, pathophysiology, symptoms and the economic burden of stroke

Types of stroke

The highest mortality and disability rates beyond the stroke types have intracerebral hemorrhages (ICH) that are defined as spontaneous bleeding into the brain [5]. ICH constitutes 15% of all strokes in the USA and Europe and 20–30% in Asian populations [16]. Advancing age and hypertension are the most important risk factors for ICH. Degeneration and rupture of small arteries or arterioles because of sustained hypertension is the most common cause of ICH, accounting for more than 60% of cases [6,7] followed by cerebral amyloid angiopathy accounting for approximately 10% of cases [5,6].

The WHO places the global incidence of stroke at approximately 200 cases per 100,000 inhabitants [7], although data vary among countries. Highest rates were in Japan and the lowest in the UK, Germany and New Zealand. Moreover, the age-specific incidence of stroke increases progressively, and the range of stroke incidence in people aged 55 years or more was 420–650 per 100,000, except in Japan, Russia and Ukraine, where rates were even higher. When differences by gender were analyzed, the occurrence of stroke was elevated in males in all studies [8]. Life expectancy is increasing in most parts of the world, because of lower childhood mortality, but also owing to a decline in mortality in adults. By 2025 there will be more than 800 million people over the age of 65. With increasing age, the stroke incidence will also increase [9].

The three main mechanisms causing ischemic strokes are: thrombosis, embolism and global ischemia (hypotensive) stroke. Not all ischemic strokes fall into these categories and the list of entities responsible for unusual stroke syndromes is long. Some of rare causes of stroke are vasospasm, vasculitis, artery dissection or changes in blood coagubility, like thrombocythemia [10].

Thrombosis

Atherosclerosis is the most common pathological feature of vascular obstruction resulting in thrombotic stroke [11]. Vessel occlusion accounts for approximately 85% of all strokes [5]. Atherosclerotic plaques can undergo pathological changes, such as ulcerations, thrombosis, calcifications and intra-plaque hemorrhage. The susceptibility of the plaque to disrupt or ulcerate depends on the structure of the plaque, and its composition and consistency. Disruption of the endothelium initiates a complicated process that activates many destructive vasoactive enzymes resulting in platelet adherence and aggregation to the vascular wall, forming small nidi of platelets and fibrin [11–14].

In addition to atherosclerosis, other pathological conditions that cause thrombotic occlusion of a vessel include clot formation because of hypercoagulable state, fibromuscular dysplasia, arteritis (e.g. Giant cell or Takayasu) and dissection of a vessel wall. Lacunar infarcts occur as a result of occlusion of deep penetrating arteries that are 100–400 mm in diameter and originate from the larger cerebral arteries. The size of a lacunar infarct is less than 20 mm in diameter. The incidence of lacunar infarcts is 10–30% of all strokes depending on race and preexisting hypertension and diabetes mellitus. The small arterioles lengthen, become tortuous and develop subintimal dissections and micro-aneurysms rendering the arterioles susceptible to occlusion from micro-thrombi. This is mainly caused by chronic hypertension. Fibrin deposition resulting in lipohyalinosis is considered to be the underlying pathological mechanism [15,16].

Embolism

Embolic stroke can result from embolization of an artery in the central circulation from a variety of sources. Besides clot, fibrin and pieces of atheromatous plaque, materials known to embolize into the central circulation include fat, air, tumor or metastasis, bacterial clumps and foreign bodies. Superficial branches of cerebral and cerebellar arteries are the most frequent targets of emboli. Air embolisation can result from neurosurgical, otolaryngological and anesthesiological (central venous catheterization) interventions, and from injuries, like penetrating chest injuries or in case for divers like the barotrauma [17–20]. Most emboli lodge in the

middle cerebral artery distribution because 80% of the blood carried by the large neck arteries flow through the middle cerebral arteries [21]. The two most common sources of emboli are: the left ventricular cardioembolic emboli and large arterial emboli (e.g. 'artery to artery') that result from detachment of a thrombus from the internal carotid artery at the site of an ulcerated plaque [10,21].

Global – ischemic or hypotensive stroke

Stroke can be caused by hemodynamic changes especially in regions with marginal blood supply resulting from vessel stenosis or decrease in arterial blood pressure [10]. Global ischemia causes the greatest damage to areas between the territories of the major cerebral and cerebellar arteries known as the 'boundary zone' or 'watershed area'. The parietal-temporal-occipital triangle at the junction of the anterior, middle and posterior cerebral arteries is most commonly affected. Watershed infarcts make up approximately 10% of all ischemic strokes and almost 40% of these occur in patients with carotid stenosis or occlusion [21].

Clinical symptoms

Acute stroke symptoms are limb weakness, sensibility deficits, facial palsy, ataxia, dysphagia, speech problems (aphasia or dysphasia) or visual disturbances. The degree of affection is commonly measured by the modified Rankin scale and the National Institute of Health Stroke Scale (NIHHS). These scores are usually used in clinical trials for symptom description and as clinical outcome parameters.

Stroke pathogenesis

Ischemia is defined as a reduction in blood flow that is sufficient enough to alter normal cellular function [22]. Brain tissue is exquisitely sensitive to ischemia, so that even brief ischemic periods to neurons can initiate a complex sequence of events that ultimately might culminate in cellular death. Different brain regions have varying thresholds for ischemic cell damage, with white matter being more resistant than gray matter [23]. The brain does not store glucose, therefore brain ischemia causes anaerobic metabolism [24].

Normal cerebral blood flow (CBF) is approximately 50–60 ml/100 g brain tissue/min. In response to ischemia, the cerebral autoregulatory mechanisms cause a local vasodilatation to increase the extraction of oxygen and glucose from the blood. However, the reduction of CBF of less than 10 ml/100 g/min results in irreversible neuronal injury [24–26]. Brain ischemia induces activation of destructive vasoactive enzymes that are released by the endothelium, leucocytes, platelets and other neuronal cells [27]. This process is called 'excitotoxicity'. Glutamate, which is normally stored inside the synaptic terminals, is cleared from the extracellular space by an energy dependent process. Glutamate causes the opening of calcium channels [28,29]. Intracellular calcium activates a series of destructive enzymes, such as proteases, lipases and endonucleases that enable the release of cytokines and other mediators, resulting in the loss of cellular integrity [29]. This further results in the excretion of many different inflammatory mediators, oxygen free radicals and nitric acid. These mediators can cause brain edema and might result in space-occupying hemispheric infarctions in some patients (Fig. 3). An overview on space-occupying hemispheric infarctions is given in Box 2 and 3.

Ischemic penumbra

The concept of an existing penumbra means 'ischemic tissue that is potentially destined for infarction but not yet irreversibly injured and is the target of acute stroke therapies' [30].

The crucial time period during which this volume of brain tissue is at risk is referred to as the 'window of opportunity'

BOX 2

Overview over space-occupying hemispheric infarction [121].

- Total or subtotal middle cerebral artery or hemispheric infarctions account for approximately 10% of all ischemic strokes.
- Total or subtotal middle cerebral artery or hemispheric infarctions are associated with variable degrees of brain edema and a high mortality rate.
- Progressive brain edema leads to a tissue shift compressing the midline structures; it eventually leads to transtentorial and uncal herniation.
- Outcome is fatal in the majority of untreated patients with space-occupying hemispheric infarction, with a mortality of 80%.
- Conservative treatment for reducing brain edema and controlling elevated intracranial pressure are hyperventilation, osmotherapy, tromethamine and barbiturate administration.
- Early surgical decompression is effective in lowering mortality and improving neurological outcome.

BOX 3

Etiology of cerebral edema in space-occupying hemispheric infarction [121].

Two major types of edema generation in ischemic stroke, the intracellular (cytotoxic) and the extracellular (vasogenic) edema are known:

- Cytotoxic edema develops within minutes in the ischemic core and is mainly caused by energy failure and anoxic membrane depolarization with subsequent accumulation of intracellular Na^+, leading to an influx of water and cellular swelling.
- Vasogenic edema is because of a disruption of the blood–brain barrier, leading to increased permeability and movement of proteins and fluids from the intravascular space to the interstitial and intracellular compartments.

because the neurological deficits created by ischemia can be partly or completely reversed by reperfusing the ischemic yet viable brain tissue within a crucial time period [24,25,31]. The penumbra zone can be verified in magnetic resonance tomography (MRT) by the so-called mismatch of diffusion and perfusion weighted sequences. The determined volumes of the regions with abnormal perfusions are compared with the volumes of the acute diffusion weighted lesions. If the final infarct size as assessed by the diffusion weighted sequences is assumed to be larger than one third of the hypo diffused area in perfusion weighted images, a mismatch can be diagnosed, and thrombolytic treatment can be started [31].

Stroke classification

The Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria enables investigators to report responses to treatment among important subgroups of patients with ischemic stroke. The TOAST classification denotes five subtypes of ischemic stroke: (i) large-artery atherosclerosis, (ii) cardioembolism, (iii) small-vessel occlusion, (iv) stroke of other determined etiology and (v) stroke of undetermined etiology [32].

Economic burden

The majority of cost-related analyses have focused on short-term in-hospital care and early crucial care as the key drivers of acute ischemic stroke hospitalization costs. Moreover, long-term medical expenses resulting from nursing home and ambulatory care and indirect expenditure from reduced income and informal care represent the most significant burden on lifetime costs of stroke [33].

A recent US study identified 12,278 patients and revealed that the total mean annual direct medical costs for the entire sample cost US$18,953. With approximately 22 million US residents having prevalent cardiovascular diseases or stroke, this extrapolates to direct costs of more than US$400 billion. Inpatient costs accounted for 42.8% of total costs. The greatest differences in costs were found when comparing patients who did versus those who did not experience a secondary cardiovascular diseases hospitalization (US$62,755 vs US$13,509, $P = 0.001$). Other large differences were found in comparisons of patients with versus without diabetes (US$27,258 vs US$17,210), an estimated glomerular filtration rate of less than 60 ml/min/1.73 m(2) (US$29,498 vs US$16,326), depression (US$26,681 vs US$17,303) and death (US$28,689 vs US$17,779) ($P = 0.001$ for all) [34].

Acute stroke treatment

Intravenous tissue plasminogen activator

The intravenous recombinant tissue plasminogen activator (rt-PA) has been approved for stroke therapy because it was shown to improve the clinical outcome after acute ischemic stroke [35] and can reduce the effects of stroke and permanent disability [36].

Thrombolytic therapy began as early as 1933, since discovering that filtrates of broth cultures of certain strains of Streptococcus bacteria could dissolve a fibrin clot. In 1958, streptokinase was first used in patients with acute myocardial infarction (MI), and this changed the focus of treatment [37]. In 1996, the US Food and Drug Administration (US FDA) approved the use of intravenous thrombolysis with the more sophisticated rt-PA to treat ischemic stroke in the first three hours after the start of symptoms [38,39].

European Cooperative Acute Stroke Studies (ECASS) III demonstrated the efficacy and safety of intravenous thrombolysis for patients up to 4.5 hours after onset of acute stroke [40–44]. Treatment with thrombolysis even up to 4.5 hours from stroke onset enhances the chance of a favorable outcome. Serious hemorrhage rates are independent from the time after stroke onset, but mortality increases when thrombolysis starts after more than 4.5 hours. Early treatment provides the best outcome, therefore results from ECASS III should not be an excuse to start thrombolytic treatment later [39] (Fig. 1). The phrase 'Time is brain' documents the importance of rapid treatment because it has been estimated that every minute 1.9 million neurons are dying after stroke [45]. The Simplified Management of Acute Stroke Using Revised Treatment (SMART) criteria study is ongoing, including all stroke patients for thrombolysis in a time window up to 4.5 hours, the only exclusion criterion is intracranial hemorrhage [45]. Another interesting ongoing study is the Building Radiological support for Intra-arterial Delivery in acute stroke by Gaining Efficiency (the BRIDGE study), that showed that creating an in-hospital, endovascular team over 24 hours each day results in a significant reduction of time until thrombolysis procedure initiation so that time could be saved in stroke patients [46].

Endovascular stroke therapy

The benefit of thrombolysis after acute ischemic stroke depends on the size of the occluded vessel. The intra-arterial route, using a

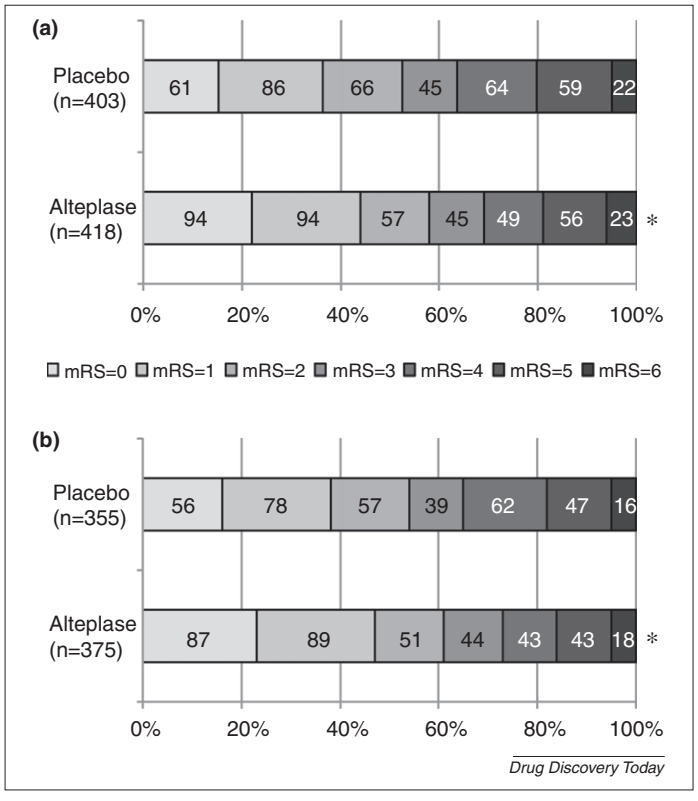


FIGURE 1

In European Cooperative Acute Stroke Studies (ECASS) III, a double-blind, multicentre study, patients with acute ischaemic stroke were randomly assigned to intravenous alteplase or placebo. Distribution of modified Rankin scale scores (mRS) at day 30 for the intention-to-treat **(a)** and per-protocol **(b)** populations according to Hacke *et al.* [41].

microcatheter delivery system, offers several advantages, compared to intravenous administration. These include higher concentrations of fibrinolytic agent at the clot site and reduced systemic exposure to thrombolytics. The use of intra-arterial thrombolysis or combining intravenous administration of rt-PA has been established for large vessels occlusion. Although intra-arterial fibrinolysis has been used for decades [47,48], it is not a therapy approved by the US FDA. Trials have shown beneficial effects compared with intravenous thrombolysis in acute ischemic stroke with hyperdense middle cerebral artery sign (MCA). The Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial showed in 66% of patients a satisfactory partial recanalization rate compared with 18% in the control group [49], with no increasing mortality. The complete recanalization rate was 19% in the treatment group as compared with 18% in the control group [50]. Combined intra-arterial and intravenous thrombolysis showed only a modest trend towards an improved clinical outcome [49].

Several clot retrieval devices that physically grasp cerebral thrombi and pull them out of the cerebral circulation and suction thrombectomy devices that aspirate occlusive material from the vessel are known [49]. These devices have been reported to increase recanalization rate and patient outcome. Several retrievers are in clinical use, like Microsnare, Neuronet, the Merci retriever [51–53] and the TREVO device (ClinicalTrials.gov: http://clinicaltrials.gov/ct2/show/NCT01088672). The Merci retriever was tested in the multicenter Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial, with the result of achieving in 54% partial or complete recanalization with a good clinical outcome [52].

Symptomatic hemorrhage occurred in 5% of patients treated with the device alone and in 24% treated with additional an intra-arterial thrombolysis. Further studies reported a better outcome for thrombectomy following intravenous thrombolysis [54]. Emergency carotid artery stent placement was performed in a small study group with good clinical outcomes [55]. For a comprehensive overview on endovascular stroke therapy and about new promising pharmacological and mechanical treatment options refer to the recent review by Killer *et al.* [56].

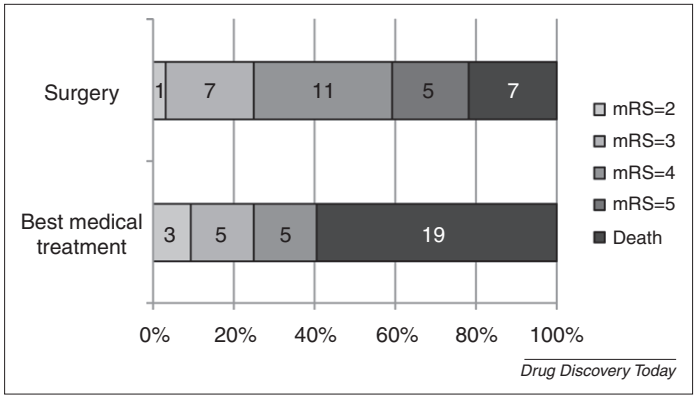


FIGURE 2

In the Hemicraniectomy After Middle cerebral artery infarction with Life-threatening Edema Trial (HAMLET) trial 64 patients were randomly assigned to surgical decompression or best medical treatment. This illustration shows the distribution of scores on the modified Rankin Scale for the two treatment groups after one year [57]. For the primary measure of outcome, an mRS score of 4–6, the absolute risk reduction was 0%, 95% CI-21 to 21. Poor outcome, defined as an mRS score of 5 or 6, was slightly lower after surgical decompression, but this was not significant (absolute risk reduction of 19%, −5 to −43; $P = 0.13$). Only risk of death was significantly lower in the patients who were treated surgically (absolute risk reduction of 38%; $P = 0.002$).

Surgical decompression for space-occupying cerebral infarction

Decompressive surgery has been performed for decades. However, clear evidence was obtained only in 2009 when the Hemicraniectomy After Middle cerebral artery infarction with Life-threatening Edema Trial (HAMLET) was published [57]. Patients with space-occupying hemispheric infarctions have a poor prognosis, with case fatality rates of up to 80%. HAMLET assessed that surgical decompression reduces case fatality and poor outcome in patients with space-occupying infarctions who are treated within 48 hours of stroke onset (Figs 2,3). There is no evidence that this operation improves functional outcome when it is delayed for up to 96 hours after stroke onset [57].

Clotbust

A multicenter collaborative group prospectively implemented a protocol for transcranial Doppler (TCD) assessment of intracranial recanalization with rt-PA treatment on the basis of the (Combined Lysis of Thrombus in Brain ischemia using transcranial Ultrasound and Systemic tPA Trial) (CLOTBUST-PRO) clinical trial for early recanalization [58]. In stroke patients treated with intravenous rt-PA, continuous TCD monitoring of intracranial occlusion was safe. rt-PA induced arterial recanalization showed a trend to more patients recovering from stroke [59]. The aim of Phase II CLOTBUST trial was to determine the rates of early complete recanalization and dramatic/early clinical recovery in r-tPA and TCD and rt-PA groups. It showed that the combination of alteplase plus two hours of continuous TCD increases recanalization rates [59].

Primary and secondary stroke prevention

An overview of the American Heart Association/American Stroke Association (AHA/ASA) Guidelines for antithrombotic therapy for prevention of stroke in patients with non-cardioembolic and cardioembolic cerebrovascular events is given in Box 4 and 5.

Antiplatelet drugs

Acetylsalicylic acid

For secondary prevention of vascular events, including stroke and MI the benefits of acetylsalicylic acid (ASA) are well established. This has been summarized by data from the Antithrombotic Trialists' collaboration showing further that ASA does not significantly increase hemorrhagic stroke rate [60]. ASA is a broadly used antiplatelet agent and inhibits irreversible platelet aggregation by blocking the enzyme cyclooxygenase [61]. The normal dosage supplied ranges from 75 mg to 150 mg. Higher doses have been tested, and it was demonstrated that it doesn't cause a greater ischemic risk reduction, but causes a higher hemorrhage complication rate [62].

ASA resistant patients, as measured by current laboratory tests, suffer from cerebrovascular events more frequently. Possible causes of ASA resistance include poor compliance, inadequate dose and drug interactions, genetic polymorphisms of cyclooxygenase-1, increased platelet turnover and upregulation of nonplatelet pathways of thromboxane production. However, standardized approaches to the diagnosis and the treatment for ASA resistance have not been outlined [53].

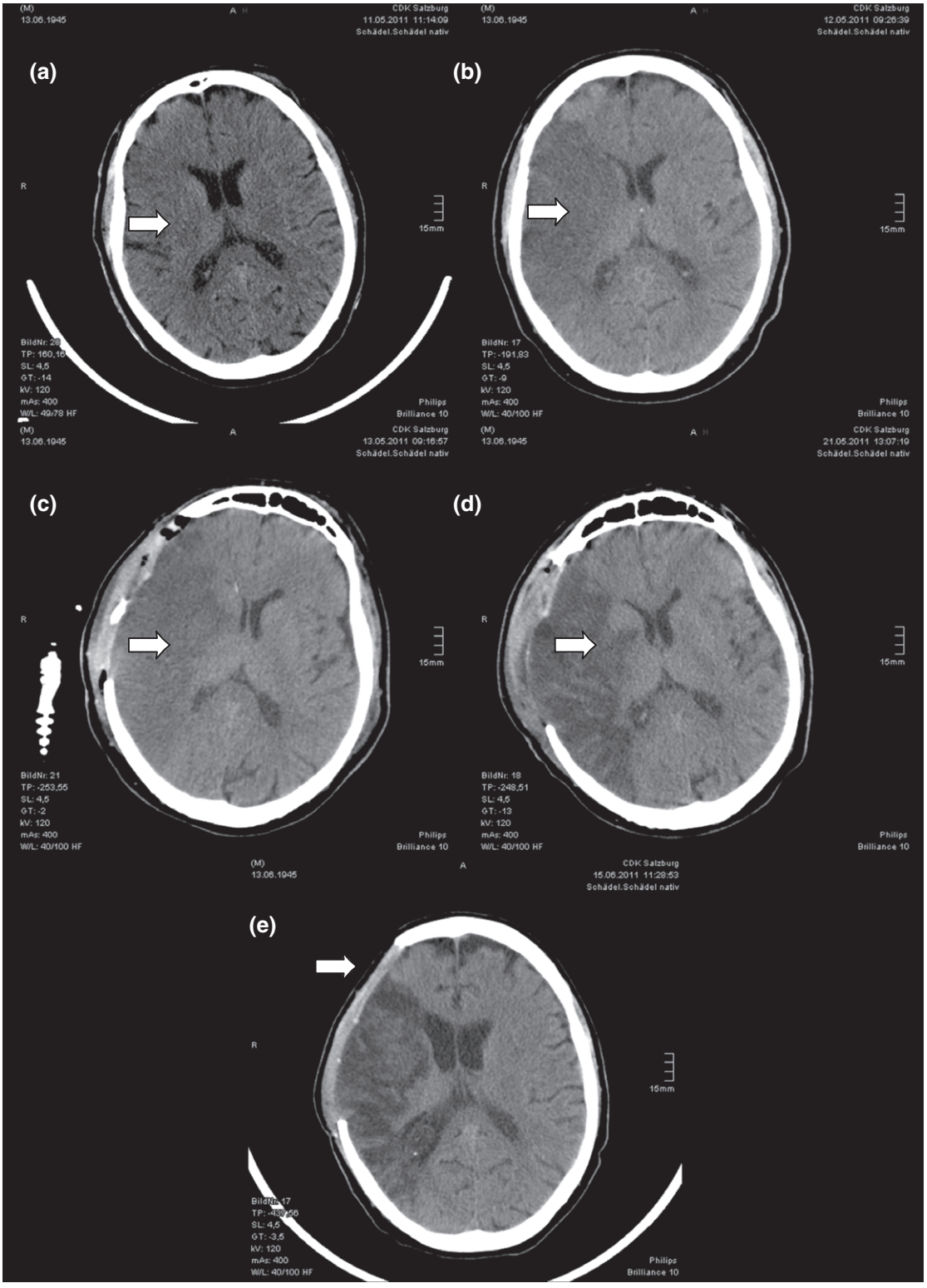


FIGURE 3

(a) Axial computed tomography (CT) scan shows acute cerebral infarction on the right – early infarct signs (arrow) can hardly be seen. **(b)** Axial CT scan (one day later), the subacute cerebral infarct in the right middle cerebral artery (MCA) distribution shows a slight mass effect by compression of the right lateral ventricle and a slight midline shift. **(c)** One day after decompressive surgery CT scan shows still discernible edema, with even more mass effect on the right lateral ventricle. **(d)** Reduced mass effect, because of decompressive surgery, the infarct shows gyriform areas of increased attenuation indicating slight hemorrhagic transformation. **(e)** Axial CT scan (five weeks later) the mass effect has resolved.

BOX 4

American Heart Association/American Stroke Association guidelines for antithrombotic therapy for prevention of stroke in patients with noncardioembolic stroke or transient ischemic attack [122].

Agent	Type	Recommendation
Aspirin	Antiplatelet, US FDA approved for secondary ischemic stroke prevention	• Recommended as an acceptable option for initial therapy at doses of 50–325 mg/day • For patients who experience ischemic stroke while on aspirin, no evidence supports increasing the aspirin dose, and no other antiplatelet agent or combination has been well studied under these circumstances
Ticlopidine	Antiplatelet, US FDA approved for secondary ischemic stroke prevention	• No specific recommendations for use as initial antiplatelet therapy
Clopidogrel (monotherapy)	Antiplatelet, US FDA approved for secondary ischemic stroke prevention	• Recommended as an acceptable option for initial therapy • Might be considered instead of aspirin monotherapy, in particular for patients who cannot tolerate aspirin
Aspirin plus ER dipyridamole	Antiplatelet combination, US FDA approved for secondary ischemic stroke prevention	• Recommeded as an acceptable option for initial therapy • Combination of aspirin plus ER dipyridamole is recommended instead of aspirin alone
Aspirin plus clopidogrel	Antiplatelet combination	• Not routinely recommended for ischemic stroke and transient ischemic attack patients because of the increased risk of hemorrhage, unless a specific indication for this therapy exists (e.g. carotid artery stenting)
Warfarin	Oral anticoagulant	• Not recommended because of increased risk of bleeding complications and costs of monitoring

TIA: transient ischemic attack.

BOX 5

American Heart Association/American Stroke Association guidelines for antithrombotic therapy for prevention of stroke in patients with cardioembolism [123].

Risk factor	Recommendation
Atrial fibrillation	• Ischemic stroke or transient ischemic attack patients with atrial fibrillation should receive oral anticoagulants • Warfarin targeted to INR intensity 2.5 (range 2.0–3.0) is recommended
Acute myocardial infarction and left ventricular thrombus	• If ischemic stroke/transient ischemic attack is caused by acute myocardial infarction and left ventricular mural thrombus is identified oral anticoagulants are reasonable • Target INR should be 2.0–3.0 and treatment should be continued for three months to one year
Cardiomyopathy	• Either warfarin or antiplatelet therapy might be considered in patients with dilatative cardiomyopathy
Rheumatic mitral valve disease	• Long-term oral anticoagulation is recommended in ischemic stroke/transient ischemic attack patients with rheumatic mitral valve disease whether atrial fibrillation is present or not • Target INR 2.5 (range 2.0–3.0) is recommended • Adding aspirin is suggested if recurrent embolisms occurs while receiving warfarin
Mitral valve prolapse	• Long-term antiplatelet therapy is recommended in patients who have ischemic stroke/transient ischemic attack
Mitral annular calcification	• Antiplatelet therapy might be considered in patients with ischemic stroke/transient ischemic attack and mitral annular calcification • Either antiplatelet drugs or warfarin might be considered in patients with mitral regurgitation resulting from mitral annular calcification without atrial fibrillation
Aortic valve disease	• Antiplatelet therapy might be considered in patients with ischemic stroke/transient ischemic attack and aortic valve disease in the absence of atrial fibrillation
Prosthetic heart valves	• Oral anticoagulants are recommended • Target INR 2.5 (range 2.0–3.0) is recommended • If ischemic stroke or systemic embolism occurs despite adequate oral anticoagulant therapy it is reasonable to add aspirin 75–325 mg/daily while maintaining target INR 3.0 (range 2.5–3.5) • For ischemic stroke patients with bioprosthetiv heart valves and no other source of thromboembolism warfarin to INR 2.0–3.0 might be considered

Clopidogrel

Clopidogrel, a thienopyridine compound, is an antiplatelet agent and is marginally more effective than ASA. The Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial is the largest study that has compared clopidogrel 75 mg with ASA 325 mg. The CAPRIE study revealed a relative risk reduction of 7.3% with clopidogrel among a stroke subgroup of 6431 patients [63]. The study also revealed that clopidogrel causes less gastrointestinal bleedings and it is the agent of choice in patients with contraindications to or adverse effects of ASA or in cases of ASA failure [64]. As an inactive prodrug it requires generation of its active compound, the hepatic cytochrome P450 system [65]. Concomitant administration of a proton-pump inhibitor attenuates clopidogrel's antiplatelet action because of a drug interaction at the level of the P450 cytochrome system [65]. However, costs of clopidogrel are greater than that of ASA [65]. Several studies reported that clopidogrel resistance causes a poorer clinical outcome. Tests measuring clopidogrel activity are under investigation [65].

Ticlopidine

Ticlopidine is also an adenosine diphosphate (ADP) receptor inhibitor. The Ticlopidine Aspirin Stroke Study (TASS) compared ticlopidine with ASA and showed a 12% risk reduction with ticlopidine in the three-year event rate for non-fatal stroke or death. Moreover, it revealed a 21% risk reduction of the rates of fatal and non-fatal stroke at three years with ticlopidine [66]. The Canadian American Ticlopidine Study (CATS) assessed the effect of ticlopidine (250 mg twice daily) in reducing the rate of subsequent occurrence of stroke, MI, or vascular death in patients with a recent thromboembolic stroke. Adverse events were reversible, and included neutropenia (severe in about 1%), skin rash and diarrhea (severe in 2% each) [67].

The African American Antiplatelet Stroke Study (AAASPS), however, failed to show any benefit of ticlopidine compared with ASA in a high-risk population [68].

ASA plus extended release (ER) dipyridamole

Dipyridamole is a pyrimidopyridine derivative with antiplatelet and vasodilator properties [69]. Owing to its costs ASA plus ER dipyridamole has a limited use and to its side effects. The European Stroke Prevention Study 2 (ESPS-2) demonstrated a significant risk reduction (37%) of recurrent stroke in patients with a recent cerebrovascular event who were treated with the combination of ASA plus ER dipyridamole compared with ASA and dipyridamole monotherapy (18% and 16%, respectively) [70]. In the European/Australasian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) an advantage of ASA and dipyridamole over ASA monotherapy after cerebrovascular events was seen with a documented 20% risk reduction in ischemic events. A total of 70% of patients receiving the combination therapy discontinued mostly because of the side effects, mainly headache, compared with 2% in the ASA treated group. However, dipyridamole induced headache occurs typically during treatment initiation and is in most cases transient [71].

Oral anticoagulation

Warfarin

The use of oral anticoagulation with vitamin K antagonists to maintain an international normalized ratio (INR) of 2.0–3.0 has been the cornerstone of antithrombotic therapy for more than 20 years [72]. Warfarin's limitations include the substantially bleeding risk increasing with the intensity of anticoagulation, several drug interactions, and variable intakes of dietary vitamin K that can create significant fluctuations in the anticoagulation effects despite the same dose of warfarin [73]. Warfarin has been demonstrated to be effective in the prevention of cardioembolic strokes as demonstrated by the European Atrial Fibrillation Trial showing a reduced risk of recurrent cerebrovascular events from 12% to 4%, compared with placebo [74]. The Warfarin Aspirin Recurrent Stroke Study (WARSS) compared warfarin and ASA efficacy in non-cardioembolic strokes, however, the study did not demonstrate a significant difference in clinical outcome and also in the hemorrhage rates [75].

A more recent trial with intensive warfarin monitoring suggested a remarkable reduction of stroke recurrences without more adverse events, but because of the risk of bleeding during warfarin therapy, antiplatelet drugs are still the treatment of choice for the prevention of stroke after non-cardioembolic stroke [74]. Further oral anticoagulants that are predominantly used in Europe are acenocoumarol and phenprocoumon, they have the same proven efficacy by reducing stroke risk by 68% against placebo [76].

Combination therapies

In patients with contraindication for anticoagulant treatment the combination of ASA and clopidogrel is not as effective as warfarin in case of atrial fibrillation [77]. A further analysis showed that patients with paroxysmal atrial fibrillation who were treated with ASA and clopidogrel or oral anticoagulation had a similar risk for thromboembolic events [78]. ASA has been investigated to be the most commonly used alternative to warfarin, as it reduces the risk of stroke and other major vascular events in patients with atrial fibrillation by approximately 17% compared with control [65].

Patients who have had MI in addition to stroke are still more probably to have a stroke before a second MI. ASA is in this setting efficacious but according to the ESPS-2 and ESPRIT [79,80] trials not as much as ASA in combination with dipyridamole. The CAPRIE [63] trial suggested clopidogrel to be more effective than the others. In patients with coronary disease, treatment with clopidogrel and ASA should be considered in accordance to the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE), the Clopidogrel as Adjunctive Reperfusion Therapy – Thrombolysis in Myocardial Infarction 28 (CLARITY-TIMI-28) and COMMIT ClOpidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) trials [81–83].

In the Management of Atherothrombosis with Clopidogrel in High-risk (MATCH) trial for patients with recent cerebrovascular event, the addition of ASA to clopidogrel showed no significant benefit in reduction of major vascular events (relative risk reduction of 6.4%). The reason for this finding was a higher absolute risk of life-threatening bleeding on dual antiplatelets compared with clopidogrel monotherapy [75,84]. Dual antiplatelet therapy using ASA and clopidogrel is recommended after stent placement [85]. Moreover, the Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence (FASTER) trial investigating patients with acute cerebrovascular events, revealed that the combination of ASA and clopidogrel might be more effective than

ASA alone if administered immediately and for only the first few months. The rationale is that the risk of recurrent stroke is highest in the first months and the patients are not exposed to the long-term risks of bleeding associated with the dual therapy compared with aspirin or clopidogrel alone. Clopidogrel was given with 300 mg as a loading dose then 75 mg daily in combination with ASA 100 mg daily [86].

The Prevention Regimen for Effectively Avoiding Second Strokes (PROFESSs) trial compared ER-dipyridamole plus ASA versus clopidogrel [87]. From a total of 20,332 enrolled patients no statistical differences were found in either arm for the primary outcome of fatal or non-fatal stroke. ER-dipyridamole plus ASA were also associated with an increase in hemorrhagic events but there was no evidence to suggest a statistically significant increase in combined rates of stroke recurrence. It is important to note that the comparison to ASA was not the goal of PROFESS, and the results of this study should only be used to compare clopidogrel and ASA-ER-dipyridamole regimens [87].

Combination therapy of warfarin and ASA is indicated only in rare conditions, such as patients with atrial fibrillation who have coexisting atherosclerotic vascular disease, for prevention of thrombus formation in the left atrium and in arteries. Warfarin prevents formation of fibrin-rich thrombi and ASA prevents platelet-rich thrombi associated with arterial vascular disease [65,79]. The indications for triple antithrombotic therapy, including warfarin, ASA and clopidogrel, are rare and only used in patients with special conditions [85]. In summary, combination therapy should therefore be considered only in very special cases because it leads to increased bleeding complications.

Further antithrombotic regimes

GPIIb/IIIa blockade represents a significant advance in interventional cardiology and treatment of acute ischemic syndromes. GPIIb/IIIa blockers target the unique platelet GPIIb/IIIa receptor for the adhesive proteins, fibrinogen and von Willebrand Factor. GPIIb/IIIa receptor blockers bind through their arginine-glycine-aspartic acid recognition site. A larger recognition sequence is specific for the gamma chain of fibrinogen. Except for some tumor cells, the GPIIb/IIIa receptor is confined to cells of the megakaryocyte/platelet lineage [88].

Platelet GPIIb/IIIa blockers administered intravenously have proven efficacy in mitigating arterial thrombosis in acute coronary syndromes and percutaneous coronary interventions. At present, orally-active platelet GPIIb/IIIa blockers are being developed to provide additional benefits for primary and secondary prevention of thrombosis as chronic treatment, in particular in high-risk patients [88].

Abciximab

Abciximab, a human murine chimeric antibody to the GPIIb/IIIa receptor, in combination with ASA and adjusted-dose heparin, is approved for the prevention of ischemic complications in patients undergoing percutaneous coronary interventions. Abciximab immediately induces an 80% blockade of GPIIb/IIIa receptors, a reduction of ADP-induced platelet aggregation to 15% of pre-treatment levels, and prolongation of the bleeding time to 30 min. Hemostatic effects persist for four to six hours after termination of the intravenous infusion, and platelet function gradually recovers over the next 24–48 hours. Abciximab appeared to be safe when administered up to 24 hours after stroke onset, and it was shown to improve functional outcome [89].

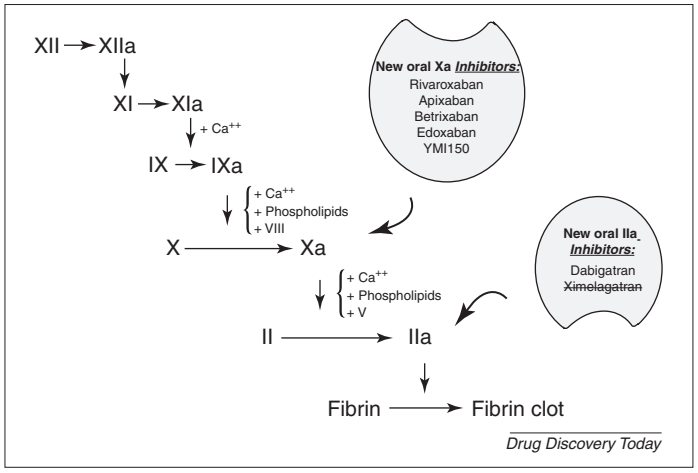


FIGURE 4

Coagulation cascade illustrating the targets of new oral anticoagulants under development. Cancelling of ximelagatran symbolizes withdrawal of this oral IIa inhibitor from development.

However, these positive data could not be confirmed in the Abciximab in Emergent Stroke Treatment Trial – II (AbESTT-II) that showed an increased rate of symptomatic or fatal intracranial hemorrhages in primary and wake-up stroke patients [90]. Furthermore, Abciximab was not more effective than ASA [65].

Iotrafiban, Terutroban and Ximelagatran

Ximelagatran was the first orally available direct thrombin inhibitor [91]. In Stroke Prevention using ORal Thrombin Inhibitor in atrial Fibrillation (SPORTIF) III and V the efficacy of warfarin and ximelagatran were similar for prevention of cardioembolic and non-cardioembolic strokes. However, it has been withdrawn from the market because of severe hepatic injury, but similar compounds are presently being studied [65,92,93] (Fig. 4).

Iotrafiban is a member of the latest generation of orally-active platelet GPIIb/IIIa blockers undergoing Phase III clinical trials to test the relative effectiveness versus other oral platelet inhibitors [88]. Preliminary results of the clinical trial Anti Platelet Useful Dose Trial (APLAUD) showed that iotrafiban is clinically safe and well-tolerated in patients with recent MI, unstable angina, transient ischemic attack, or stroke when added to ASA therapy [88].

A worldwide large-scale Phase III clinical trial [blockage of the GPIIb/IIIa receptor to avoid vascular occlusion = (BRAVO)] found that a combination of ASA and GPIIb/IIIa blockers is not superior to ASA monotherapy but showed a higher bleeding risk [64].

Terutroban, a specific antagonist of the thromboxane A2 receptor on platelets and the vessel wall has been shown to be more effective than ASA in the prevention of recurrent stroke and other major vascular events [65]. The prevention of cerebrovascular and cardiovascular events of ischemic origin with terutroban treatment in patients with a history of ischemic stroke or transient ischemic attack (PERFORM) trial was an international, multicenter, randomized, double-blind, parallel-group study in patients aged 55 and older who have suffered ischemic strokes (below three months) or transient ischemic attacks (below eight days) [93].

However, the trial has recently been halted because of non-promising interim analyses [65].

Phosphodiesterase inhibitor

Cilostazol

An alternative to ASA is cilostazol, a phosphodiesterase 3 inhibitor [94]. It has demonstrated antiplatelet and vasodilator effects with low rates of bleeding complications [95]. In a trial 720 patients were enrolled who had had an ischemic stroke. Cilostazol was compared with ASA with no significant differences in the rate of recurrence of stroke. The lower rates of ischemic and hemorrhagic stroke in the cilostazol group suggest that cilostazol might be a safe alternative to ASA. However, a larger Phase III trial is required to confirm this [95]. Another trial compared the effects of cilostazol versus ASA on cerebral arteries and cerebrovascular blood flow in secondary prevention of ischemic stroke. It was concluded that cilostazol is as effective as ASA [96].

Promising future anticoagulants – direct thrombin inhibitors

Dabigatran

Dabigatran etexilate is a prodrug of the direct thrombin inhibitor dabigatran, a direct, reversible, potent inhibitor of thrombin. Dabigatran does not interact with food, and is associated with few known drug interactions. In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial dabigatran, at dosages of 110 and 150 mg twice daily, was shown to be non-inferior to warfarin with regards to the incidence of stroke or systemic embolisms in a wide spectrum of patients with atrial fibrillation [97]. Moreover, the higher dosage was associated with significantly greater efficacy compared with warfarin. Dabigatran was only associated with a higher rate of dyspepsia than warfarin. Major bleedings were as common in recipients of the higher dosage as with warfarin and less common in recipients of the lower dosage of dabigatran. Intracranial bleedings, life-threatening major bleedings and total bleedings were less common in recipients of dabigatran than in warfarin recipients. The incidence of hepatotoxicity did not significantly differ across treatment groups. In conclusion, dabigatran 150 mg twice daily is more effective than warfarin for the prevention of stroke and systemic embolisms in patients with atrial fibrillation [97] (Fig. 4). One concerning contrast to warfarin is that there is currently no available antidote and available monitoring is not standardized [98].

Oral, direct factor Xa inhibitors

Factor Xa (FXa) is a trypsin-like serine protease that has a key role in the blood coagulation cascade. FXa inhibitors selectively impair the central protease common to both the intrinsic and extrinsic pathways. FXa converts the prothrombin zymogen to its active form, thrombin. FXa is the primary and rate-limiting source of amplification in the coagulation cascade [99].

LY517717

LY517717 (Lilly) has an elimination half-life of approximately 25 hours in healthy subjects [96]. LY517717 has not yet been studied for stroke prevention in patients with atrial fibrillation, and only venous thromboembolism prevention data are currently available. In a randomized, double-blind, dose-escalation study in patients undergoing total knee or hip replacement, LY517717 demonstrated dose dependent efficacy with a similar incidence of bleeding like enoxaparin for the prevention of venous thromboembolism. No information is currently available regarding future studies with LY517717 [100].

YM150

YM150 (Astellas) is a direct FXa inhibitor with a potent antithrombotic effect. Bleeding complications are less frequent than with warfarin [101]. Studies in patients with total hip replacement showed a significant dose–response with relationship to the primary efficacy endpoint, none of the 174 patients had bleeding complications. An ongoing Phase II study is evaluating YM150 for stroke prevention in patients with atrial fibrillation in comparison with warfarin, and enrolled more than 1200 patients [101; ClinicalTrials.gov: http://clinicaltrials.gov/ct2/show/NCT00938730?term=YM150&rank=8].

Edoxaban: DU-176b

DU-176b (Daiichi Sankyo) inhibits FXa, and is 10,000-fold more selective for FXa than thrombin. In rat models, DU-176b inhibited both arterial and venous thrombosis in the same concentration range, whereas a 100-fold higher dose of fondaparinux (FXa inhibitor)[1] was required to inhibit arterial thrombosis than venous thrombosis. In a Phase I study in healthy male subjects, a single 60 mg dose of DU-176b inhibited FXa activity, prolonged clotting parameters and reduced thrombus formation in a Badimon chamber for up to five hours after administration. Results from a Phase IIa study of DU-176b for venous thromboembolism prevention after total hip replacement demonstrated proof-of-principle, but have yet to be published. Phase IIb studies with DU-176b in venous thromboembolism prevention, stroke prevention in patients with atrial fibrillation and prevention of thromboembolic events in patients with acute coronary syndrome are planned or have been initiated [57,99,102], ClinicalTrials.gov: http://clinicaltrials.gov/ct2/show/NCT00781391].

Apixaban

Apixaban is a direct, selective FXa inhibitor [103]. It has a half-life of approximately 12 hours and is eliminated predominantly through non-renal mechanisms. Apixaban has no known food–drug interactions, a minimal potential for drug–drug interactions and a low likelihood of QT-interval prolongation. Prolonged QT-interval indicates a risk for arrhythmia. It also did not show organ specific toxicity [104,105]. The Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE) 1 and 2 trials [101] showed in patients undergoing knee replacement that the primary outcome event rates in each treatment groups were similar to enoxaparin [106]. Also, they demonstrated a trend toward less clinically relevant bleeding [106]. The Apixaban for Stroke Prevention in Atrial Fibrillation (ARISTOTLE) trial will determine apixaban's efficacy by contrast to warfarin in preventing stroke and systemic embolism and its benefits and side effects in the warfarin-naive population [107].

[1] Weitz, J.I. *et al.* (2008) Randomized, parallel group, multicenter, multinational study evaluating safety of DU-176b compared with warfarin in subjects with non-valvular atrial fibrillation. *ASH Annual Meeting*, Vol. 112 (Abstract 33) (http://www.hematology.org/media/bloodclots.pd).

The Apixaban Versus Acetylsalicylic acid to Prevent Stroke in Atrial Fibrillation Patients who have Failed or are Unsuitable for Vitamin K Antagonist Treatment trial (AVVEROES) will determine whether apixaban is more effective than ASA in preventing cardioembolic strokes [ClinicalTrial.gov: http://clinicaltrials.gov/ct2/show/NCT00496769].

Betrixaban

Betrixaban is a small molecule, direct FXa inhibitor that reversibly inhibits FXa. It has an effective half-life of 20 hours and is excreted without modification in bile. The EXPERT trial [Evaluation of the FXa inhibitor, PRT054021 (PRT021), against enoxaparin is a randomized trial for the prevention of venous thromboembolic events after total knee replacement] randomized 215 patients undergoing elective total knee replacement to receive post-operative oral betrixaban 15 mg or 40 mg or enoxaparin 30 mg. Venous thromboembolism incidence was 20% for betrixaban 15 mg, 15% for betrixaban 40 mg and 10% for enoxaparin. No bleeding was reported with betrixaban 15 mg, 2.4% clinically significant non-major bleeds with betrixaban 40 mg, and 2.3% major and 4.6% clinically significant non-major bleedings with enoxaparin [108]. The EXPLORE-Xa trial (Phase II study of the safety, tolerability and pilot efficacy of oral FXa inhibitor betrixaban compared with warfarin) evaluated betrixaban for stroke prevention in 508 patients with atrial fibrillation. Betrixaban dosage was blinded for 40 mg, 60 mg and 80 mg daily. The most common side effects were diarrhea and nausea, the 40 mg dosage was associated with a lower bleeding rate than warfarin, whereas the 60 mg and 80 mg dosage had bleeding rates comparable with warfarin [99].

Rivaroxaban

Rivaroxaban is a small-molecule direct FXa inhibitor that is under investigation for the prevention and treatment of venous and arterial thrombosis. Rivaroxaban does not show hepatotoxicity. Furthermore, there is no considerable drug–drug interaction [99,109].

The Phase II ATLAS ACS TIMI 46 (Anti Xa therapy to lower cardiovascular events in addition to acetylsalicylic acid with/without thienopyridine therapy in subjects with acute coronary syndrome) tested 16,000 patients with an acute coronary syndrome treated with rivaroxaban and diagnosed a 31% relative risk reduction in the risk of death, MI or stroke. However, a dose dependent increased bleeding rate was seen [110]. The Phase III ROCKET AF study (Rivaroxaban once daily oral direct FXa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation) will determine in detail the efficacy and safety of rivaroxaban [109].

Indirect FXa inhibitors

Idraparinux is a subcutaneous, indirect FXa inhibitor. It is a hypermethylated, long-acting pentasaccharide, enabling once-weekly dosing. In a randomized treatment study, idraparinux had similar efficacy to warfarin and demonstrated dose-dependent increases in major bleedings. The AMADEUS (Evaluating the use of SR34006 compared with warfarin or acenocoumarol in patients with atrial fibrillation) trial revealed that in patients with atrial fibrillation at risk of thromboembolism, long-term treatment with idraparinux was not inferior to vitamin K antagonists in terms of efficacy, but caused significantly more bleedings [111]. A bioequipotency study of biotinylated idraparinux versus idraparinux for the treatment of deep venous thrombosis is currently ongoing [clinical study assessing SSR126517E injections once-weekly in pulmonary embolism therapeutic approach (CASSIOPEA) study of biotinylated idraparinux vs warfarin for the treatment of pulmonary embolism] [112–114].

Novel vitamin K antagonists

Tecarfarin is an orally administered vitamin K epoxide reductase antagonist that has mechanisms of action identical to those of warfarin, but is metabolised by carboxylesterases. This fact could improve maintenance of the INR in the therapeutic range. A preliminary open label study showed that compared with warfarin patients had a 10% improvement in time within the therapeutic INR range [65]. However, further studies are mandatory to investigate the efficacy.

Novel thienopyridine derivatives

Novel ADP P2Y (12) antagonists, including prasugrel, ticagrelor, cangrelor and elinogrel, are in various phases of clinical development. These ADP P2Y (12) antagonists have advantages over clopidogrel ranging from faster onset to greater and less variable inhibition of platelet function. They are under investigation to determine whether their use can result in improved antiplatelet activity, faster onset of action and/or greater antithrombotic effects than clopidogrel, without an unacceptable increase in bleeding or other side effects [115]. Prasugrel has a more potent antiplatelet activity, faster onset of action and less interpatient variability as compared with clopidogrel [116]. These pharmacodynamic properties led to the fact that prasugrel was more effective in preventing ischemic events in patients undergoing acute percutaneous coronary intervention of the recent TRITON-TIMI 38 (trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel–thrombolysis in myocardial infarction) study [117]. However, the greater protective effects were partially counterbalanced by an increased risk of bleeding.

Another candidate is ticagrelor that is not a prodrug and exhibits a more rapid onset of action than the thienopyridine prodrugs. Clinical trials showed that ticagrelor was a potent inhibitor of ADP-induced platelet aggregation and demonstrated effects and a bleeding profile that were comparable to clopidogrel. However, an increased incidence of dyspnea was observed. The platelet inhibition and patient outcomes (PLATO) trial enrolled 18,624 patients with acute coronary syndrome to receive ticagrelor or clopidogrel, and ASA. At 12 months a composite of death from cerebrovascular or cardiovascular causes had occurred in 9.8% of patients receiving ticagrelor as compared with 11.7% of those taking clopidogrel. There was no significant difference in the risk of stroke between the two groups [118]. However, considering the side effects and the apparent non-superiority, if is not yet clear whether ticagrelor has a benefit in stroke patients [118].

Concluding remarks

Acute stroke therapy has improved significantly in recent years and further new treatments will be developed in future. The most important future directions for acute stroke therapy are to extend the therapeutic time window. Further drugs that are currently under investigation might have the potential to be applied. In accordance with primary and secondary stroke prevention many

medical therapies have been developed and new drugs are on the horizon. The 'polypill' containing 75 mg ASA, 20 mg simvastatin, 10 mg lisinopril and 12.5 mg hydrochlorothiazide is under investigation. A new aspect of antiplatelet drugs is the decreasing response in patients to ASA or clopidogrel that is correlated independently with an increased risk of cardiovascular events. However, there is still no evidence from randomized trials referring about ASA or clopidogrel resistance. Another goal in the treatment of cardioembolic strokes that will potentially be solved soon by the upcoming oral anticoagulants is a better or comparable efficacy compared with warfarin with a lower bleeding complication rate.

Combination therapies will probably become prevalent for acute ischemic stroke, like the combination of intravenous thrombolysis as bridging therapy for thrombectomy, or combination of thrombectomy with intra-arterial thrombolysis or even the combination of all three of them. Moreover, the concomitant treatment of thrombectomy with abciximab or tirofibane is becoming an effective treatment option.

Novel approaches will include extending penumbral survival for the later use of reperfusion therapy, reducing reperfusion injury after successful reperfusion and using drugs with both neuroprotective and recovery enhancing effects. Part B of our review will therefore focus on new experimental therapies that have the potential of further improving stroke outcome. Some of these substances will be implemented in clinical routine in approximately 5–10 years.

References

1 Lopez, A.D. *et al.* (2001) Global, regional burden of disease, disk factors, 2001: systematic analysis of population health data. *Lancet* 367, 1747–1757
2 Bravata, D.M. *et al.* (2007) Readmission and death after hospitalization for acute ischemic stroke: 5-year follow-up in the medicare population. *Stroke* 38, 1899–1904
3 Beal, C.C. (2010) Gender and stroke symptoms: a review of the current literature. *J. Neurosci. Nurs.* 42, 80–87
4 Green, A.R. and Shuaib, A. (2006) Therapeutic strategies for the treatment of stroke. *Drug Discov. Today* 11, 681–693
5 Mayer, S.A. (2003) Ultra-early hemostatic therapy for intracerebral hemorrhage. *Stroke* 34, 224–229
6 Bonita, R. (1992) Epidemiology of stroke. *Lancet* 339, 342–344
7 Soler, E.P. and Ruiz, V.C. (2010) Epidemiology and risk factors of cerebral ischemia and ischemic heart diseases: similarities and differences. *Curr. Cardiol. Rev.* 6, 138–149
8 Truelsen, T. *et al.* (2001) Surveillance of stroke: a global perspective. *Int. J. Epidemiol.* 30, 11–16
9 Paulson, O.B. (1971) Cerebral apoplexy (stroke): pathogenesis, pathophysiology and therapy as illustrated by regional blood flow measurements in the brain. *Stroke* 2, 327–360
10 Jovićević, M. *et al.* (2010) Non-atherosclerotic arteriopathy as the cause of ischemic stroke among young adults. *Med. Pregl.* 63, 324–332
11 Elkind, M.S. (2010) Inflammatory mechanisms of stroke. *Stroke* 41, 3–8
12 Fuster, V. *et al.* (1990) Atherosclerotic plaque rupture and thrombosis: evolving concepts. *Circulation* 82, 47–59
13 Glaglov, S. and Zarins, C.B. (1989) What are the determinants of plaque instability and its consequences? *J. Vasc. Surg.* 9, 389–390
14 Pullicino, P.M. (1993) Pathogenesis of lacunar infarcts and small deep infarcts. *Adv. Neurol.* 62, 125–140
15 Yu, R. *et al.* (1995) Risk factors for lacunar infarction syndromes. *Neurology* 45, 1483–1487
16 Salgado, A.V. *et al.* (1996) Long-term prognosis of first-ever lacunar strokes. A hospital-based study. *Stroke* 27, 661–666
17 Dudney, T.M. and Elliott, C.G. (1994) Pulmonary embolism from amniotic fluid, fat, and air. *Prog. Cardiovasc. Dis.* 36, 447–474
18 Estrera, A.S. *et al.* (1990) Systemic arterial air embolism in penetrating lung injury. *Ann. Thorac. Surg.* 50, 257–261
19 James, P.M. and Myers, R.T. (1972) Central venous pressure monitoring: misinterpretation, abuses, indications and a new technic. *Ann. Surg.* 175, 693–701
20 King, M.B. and Harmon, K.R. (1994) Unusual forms of pulmonary embolism. *Clin. Chest Med.* 15, 561–580
21 Demaerschalk, B.M. *et al.* (2010) US cost burden of ischemic stroke: a systematic literature review. *Am. J. Manage. Care* 16, 525–533
22 Woodruff, T.M. *et al.* (2011) Pathophysiology, treatment, and animal and cellular models of human ischemic stroke. *Mol. Neurodegener.* 6, 11
23 Mattson, M.P. *et al.* (2001) Neurodegenerative disorders and ischemic brain diseases. *Apoptosis* 6, 69–81
24 Jones, T.H. *et al.* (1981) Thresholds of focal cerebral ischemia in awake monkeys. *J. Neurosurg.* 54, 773–782
25 Pulsinelli, W.A. *et al.* (1995) The ischemic penumbra in stroke. *Sci. Med.* 1, 16–25
26 Hakim, A.M. (1998) Ischemic penumbra, the therapeutic window. *Neurology* 51, 44–46
27 Garcia, J.H. *et al.* (1994) Brain microvessels: factors altering their patency after the occlusion of a middle cerebral artery (Wistar rat). *Am. J. Pathol.* 145, 728–740
28 Del Zoppo, G.J. *et al.* (1991) Polymorphonuclear leukocytes occlude capillaries following middle cerebral artery occlusion and reperfusion. *Stroke* 22, 1276–1283
29 DeGraba, T.J. (1998) The role of inflammation after acute stroke, utility of pursuing anti-adhesion molecule therapy. *Neurology* 3, 62–68
30 Ma, L. *et al.* (2011) Effect of baseline magnetic resonance imaging (MRI) apparent diffusion coefficient lesion volume on functional outcome in ischemic stroke. *Neurol. Res.* 33, 494–502
31 Garcia, J.H. *et al.* (1993) Progression from ischemic injury to infarct following middle cerebral artery occlusion in the rat. *Am. J. Pathol.* 142, 623–635
32 Adams, H.P. *et al.* (1993) Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 24, 35–41
33 Nichols, G.A. *et al.* (2010) Medical care costs among patients with established cardiovascular disease. *Am. J. Manage. Care* 16, 86–93
34 Wolfe, T. *et al.* (2008) Comparison of combined venous and arterial thrombolysis with primary arterial therapy using recombinant tissue plasminogen activator in acute ischemic stroke. *J. Stroke Cerebrovasc. Dis.* 17, 121–128
35 Stemer, A. and Lyden, P. (2010) Evolution of the thrombolytic treatment window for acute ischemic stroke. *Curr. Neurol. Neurosci. Rep.* 10, 29–33
36 (1995) The National Institute of Neurolgical Disorders and Stroke rt-Pa Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N. Engl. J. Med.* 333, 1581–1587
37 Lees, K.R. *et al.* (2010) Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet* 375, 1695–1703
38 Diener, H.C. *et al.* (2001) Treatment of acute ischemic stroke with the low-molecular-weight heparin certoparin: results of the TOPAS trial. *Stroke* 32, 22–29
39 Hacke, W. *et al.* (1995) Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: the European Cooperative Acute Stroke Study (ECASS). *J. Am. Med. Assoc.* 274, 1017–1025
40 Nakahima, T. and Minematsu, K. (2009) Prospects of thrombolytic therapy for acute ischemic stroke. *Brain Nerve* 61, 1003–1012
41 Hacke, W. *et al.* (2008) Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N. Engl. J. Med.* 359, 1317–1329
42 Ahmed, N. *et al.* (2010) Implementation and outcome of thrombolysis with alteplase 3–4.5 h after an acute stroke: an updated analysis from SITS-ISTR. *Lancet* 9, 866–874
43 Zeumer, H. *et al.* (1983) Local intra-arterial thrombolysis in vertebrobasilar thromboembolic disease. *AJNR Am. J. Neuroradiol.* 4, 401–404
44 Saver, J.L. (2006) Time is brain – quantified. *Stroke* 37, 263–266
45 Tong, D.C. *et al.* (2011) Increasing IV rt-PA use using modern eligibility criteria. The Simplified Management of Acute Stroke Using Revised Treatment (SMART) criteria study: feasibility, safety and efficacy. *Neurology* WNL.0b013e31821ccd60
46 Barreto, A.D. (2002) Building radiological support for intra-arterial delivery in acute stroke by gaining efficiency – the BRIDGE study. *Neurology* IN9
47 Molina, C. and Saver, J.L. (2005) Extending reperfusion therapy for acute ischemic stroke. Emerging pharmacological, mechanical, and imaging strategies. *Stroke* 36, 2311–2320
48 Berger, C. *et al.* (2001) Hemorrhagic transformation of ischemic brain tissue: asymptomatic or symptomatic? *Stroke* 32, 1330–1335

49 Lee, M. *et al.* (2010) Efficacy of intra-arterial fibrinolysis for acute ischemic stroke. Meta-analysis of randomized controlled trials. *Stroke* 41, 932–937
50 Mayer, T.E. *et al.* (2002) Treatment of basilar artery embolism with a mechanical extraction device: necessity of flow reversal. *Stroke* 33, 2232–2235
51 Starkmann, S. *et al.* (2004) Results of the combined MERCI I-II (Mechanical Embolus Removal in Cerebral Ischemia) trials. *Stroke* 35, A240
52 Shi, Z.S. *et al.* (2010) Clinical outcomes in middle cerebral artery trunk occlusions versus secondary divisions occlusions after mechanical thromectomy. Pooled analysis of the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and Multi MERCI Trial. *Stroke* 41, 953–960
53 Lansberg, M.G. *et al.* (2005) Mechanical thrombectomy following intravenous thrombolysis in the treatment of acute stroke. *Arch. Neurol.* 62, 1763–1765
54 Pfefferkorn, T. *et al.* (2010) Drip, ship, and retrieve: cooperative recanalization therapy in acute basilar artery occlusion. *Stroke* 41, 722–726
55 Lee, H.O. *et al.* (2010) Emergency carotid artery stent insertion for acute ischemic stroke. *J. Korean Neurosurg. Soc.* 47, 428–432
56 Killer, M. *et al.* (2010) Current endovascular treatment of acute stroke and future aspects. *Drug Discov. Today* 15, 640–647
57 Hofmeijer, J. *et al.* (2009) Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): a multicentre, open, randomised trial. *Lancet Neurol.* 8, 326–333
58 Saqqur, M. *et al.* (2008) Design of a PROspective multi-national CLOTBUST collaboration on reperfusion therapies for stroke (CLOTBUST-PRO). *Int. J. Stroke* 3, 66–72
59 Alexandrov, A.V. *et al.* (2004) CLOTBUST: design of a randomized trial of ultrasound-enhanced thrombolysis for acute ischemic stroke. *J. Neuroimaging* 14, 108–112
60 (2002) Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *Br. Med. J.* 324, 71–86
61 Catella-Lawson, F. *et al.* (2001) Cyclooxygenase inhibitors and the antiplatelt effects of aspirin. *N. Engl. J. Med.* 345, 1809–1817
62 Srivastava, P. (2010) Optimization of antiplatelet/antithrombotic therapy for secondary stroke prevention. *Ann. Indian Acad. Neurol.* 13, 6–13
63 CAPRIE Committee, (1996) A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). *Lancet* 348, 1329–1339
64 Hankey, G.J. and Eikelboom, J.W. (2010) Antithrombotic drugs for patients with ischemic stroke and transient ischemic attack to prevent recurrent major vascular events. *Lancet Neurol.* 9, 273–284
65 Maruyama, H. *et al.* (2011) Evaluation of clopidogrel resistance in ischemic stroke patients. *Intern. Med.* 50, 31–35
66 Pryse-Phillips, W. (1993) Ticlopidine aspirin stroke study: outcome by vascular distribution of the qualifying event. *J. Stroke Cerebrovasc. Dis.* 3, 49–56
67 Gent, M. *et al.* (1988) The Canadian American Ticlopidine Study (CATS) in thromboembolic stroke. Design, organization, and baseline results. *Stroke* 19, 1203–1210
68 Gorelick, P.B. *et al.* (2003) Aspirin and ticlopidine for prevention of recurrent stroke in black patients: a randomized trial. *J. Am. Med. Assoc.* 289, 2947–2957
69 Sudlow, C. (2005) What is the role of dipyridamole in long-term secondary prevention after an ischemic stroke or transient ischemic attack? *Can. Med. Assoc. J.* 173, 1024–1026
70 Diener, H. *et al.* (1996) European Stroke Prevention Study. 2. Dipirydamole and acetylsalicylic acid in the secondary prevention of stroke. *J. Neurol. Sci.* 143, 1–13
71 Fillippi, A. (2006) ESPRIT trial. *Lancet* 368, 447–448
72 Hart, R.G. *et al.* (2007) Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann. Int. Med.* 146, 857–867
73 Pete, J.L. (2005) Reviewing the reality: why we need to change. *Eur. Heart J. Suppl.* 7, 15–20
74 Paciaroni, M. and Bogousslavsky, J. (2010) Primary and secondary prevention of ischemic stroke. *Eur. Neurol.* 63, 267–278
75 Hankey, G.J. (2002) Warfarin-aspirin Recurrent Stroke Study (WARSS) trial: is warfarin really a reasonable therapeutic alternative to aspirin for preventing recurrent noncardioembolic stroke? *Stroke* 33, 1723–1726
76 Umer, U. *et al.* (2008) Advancement in antithrombotics for stroke prevention in atrial fibrillation. *J. Interv. Card. Electrophysiol.* 22, 129–137
77 (2006) ACTIVE Writing Group. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 367, 1903–1912
78 Hohnloser, S.H. *et al.* (2007) Incidence of stroke in paroxysmal versus sustained atrial fibrillation in patients taking oral anticoagulation or combined antiplatelet therapy: an ACTIVE W Substudy. *J. Am. Coll. Cardiol.* 50, 2156–2161
79 Ariesen, M.F. *et al.* (2006) Antiplatelet drugs in the secondary prevention after stroke: differential efficacy in large versus small vessel disease? A subgroup analysis from ESPS-2. *Stroke* 37, 134–138
80 Halkes, P.H. *et al.* (2007) Aspirin plus dipyridamole versus aspirin alone after cerebral ischemia of arterial origin (ESPRIT): randomized controlled trial. *Lancet* 367, 1665–1673
81 Yusuf, S. *et al.* (2001) Clopidogrel in unstable angina to prevent recurrent events (CURE) trial investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N. Engl. J. Med.* 245, 494–502
82 Sabatine, M.S. *et al.* (2005) Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N. Engl. J. Med.* 352, 1179–1189
83 Chen, Z.M. *et al.* (2005) Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomized placebo-controlled trial. *Lancet* 366, 1607–1621
84 Diener, H.C. *et al.* (2004) Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blinded, placebo-controlled trial. *Lancet* 364, 331–337
85 Hermosillo, A.J. *et al.* (2008) Aspirin, Clopidogrel, and Warfarin: is the combination appropriate and effective or inappropriate and too dangerous? *Ann. Pharmacother.* 42, 790–805
86 Kennedy, J. *et al.* (2007) Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial. *Lancet Neurol.* 6, 961–969
87 Philip, M.W. *et al.* (2010) Effect of combined aspirin and extended-realease Dipyridamole versus Clopidogrel on functional outcome and recurrence in acute ischemic stroke. PRoFESS Subgroup Analysis. *Stroke* 41, 732–738
88 Liu, F. *et al.* (2000) Lotrafiban: an oral platelet glycoprotein IIb/IIIa blocker. *Expert Opin. Investig. Drugs* 9, 2673–2687
89 (2000) The Abciximab in Ischemic Stroke Investigators. Abciximab in acute ischemic stroke: a randomized, double-blind, placebo-controlled, dose-escalation study. *Stroke* 31, 601–609
90 Adams, H.P. *et al.* (2008) Treating patients with 'wake-up' stroke: the experience of the AbESTT-II trial. *Stroke* 39, 87–99
91 Keisu, M. and Andersson, T.B. (2010) Drug-induced liver injury in humans: the case of ximelagatran. *Handb. Exp. Pharmacol.* 196, 407–418
92 Diener, H.C. *et al.* (2006) Stroke prevention using the oral direct thrombin inhibitor ximelagatran in patients with non valvular atrial fibrillation. Pooled analysis from the SPORTIF III and V studies. *Cerebrovasc. Dis.* 21, 279–293
93 Hennerici, M.G. *et al.* (2009) Rationale and design of the prevention of cerebrovascular and vardiovscuar events of ischemic origin with terutroban in patients with a history of ischemic stroke or transient ischemic attack (PERFORM) study. *Cerebrovasc. Dis.* 3, 28–32
94 Huang, Y. *et al.* (2008) Cliostazol as an alternative to aspirin after ischemic stroke: a randomised, double-blind, pilot study. *Lancet Neurol.* 7, 494–499
95 Sallustio, F. *et al.* (2010) Cliostazol in the management of atherosclerosis. *Curr. Vasc. Harmacol.* 8, 363–372
96 Guo, J.J. *et al.* (2009) Effect of cliostazol on cerebral arteries in secondary prevention of ischemic stroke. *Neurosci. Bull.* 25, 383–390
97 Conolly, S.J. *et al.* (2009) Dabigatran versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.* 361, 1139–1151
98 Maegdefessel, L. *et al.* (2010) New options with dabigatran etexilate in anticoagulant therapy. *Vasc. Health Risk Manage.* 6, 339–349
99 Piccini, J.P. *et al.* (2010) Oral factor Xa inhibitors for the prevention of stroke in atrial fibrillation. *Curr. Opin. Cardiol.* 25, 312–320
100 Agnelli, G. *et al.* (2007) A phase II study of the oral factor Xa inhibitor LY517717 for the prevention of venous thromboembolism after hip or knee replacement. *J. Thromb. Haemost.* 5, 746–753
101 Eriksson, B.I. *et al.* (2007) A dose escalation study of YM150, an oral direct factor Xa inhibitor, in the prevention of venous thromboembolism in elective primary hip replacement surgery. *J. Thromb. Haemost.* 5, 1660–1665
102 van Doormaal, F.F. *et al.* (2008) Development in anticoagulant therapy. *Crit. Rev. Oncol. Hematol.* 66, 145–154
103 Turpie, A.G. (2007) Oral direct factor Xa inhibitors in development for the prevention and treatment of thromboembolic diseases. *Arteriorscler. Thromb. Vasc. Biol.* 27, 1238–1247
104 Wong, P.C. *et al.* (2008) Apixaban, an oral, direct and highly selective factor Xa inhibitor: *in vitro*, antithrombotic and anthihemostatic studies. *J. Thromb. Haemost.* 6, 820–829
105 (2009) APRAISE Steering Committee and Investigators. Apixaban, an oral direct selective factor Xa inhibitor in combination with antiplatelet therapy after acute coronary syndrome. Results of the Apixaban for Prevention of Acute ischemic and safety events (APRAISE) Trial. *Circulation* 119, 2877–2885

106 Lassen, M.R. *et al.* (2010) Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomized double-blind trial. *Lancet* 375, 807–815
107 Lopes, R.D. *et al.* (2010) Apixaban for Reduction in stroke and other ThromboembоLic events in atrial fibrillation (ARISTOTLE) trial: design and rationale. *Am. Heart J.* 159, 331–339
108 Turpie, A.G. *et al.* (2009) A randomized evaluation of betrixaban, an oral factor Xa inhibitor, for prevention of thromboembolic events after total knee replacement (EXPERT). *Thromb. Haemost.* 101, 68–76
109 (2010) The Executive Steering Committee on behalf of the ROCKET AF Study Investigators. Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation: rationale and design of the ROCKET AF study. *Am. Heart J.* 159, 247–340
110 Mega, J.L. *et al.* (2009) Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. *Lancet* 374, 29–38
111 Bousser, M.G. *et al.* (2008) Comparison of idraparinux with vitamin K antagonists for prevention of thrombembolism in patients with atrial fibrillation: a randomised, open-label non-inferiority trial. *Lancet* 371, 315–321
112 Harenberg, J. (2009) Development of idraparinux and idraiotaparinux for anticoagulant therapy. *Thromb. Haemost.* 102, 811–815
113 Sobieraj-Teague, M. *et al.* (2009) New anticoagulants for atrial fibrillation. *Semin. Thromb. Hemost.* 35, 515–524
114 Weitz, J.I. (2010) Potential of new anticoagulants in patients with cancer. *Thromb. Res.* 125, 30–35
115 Mousa, S.A. *et al.* (2010) Antiplatelet therapy prasugrel: a novel platelet ADP P2Y12 receptor antagonist. *Clin. Appl. Thromb. Hemost.* 16, 170–176
116 Abbate, R. *et al.* (2010) Extent of platelet aggregation inhibition and clinical events: new evidence with prasugrel. *G. Ital. Caardiol.* 11, 127–137
117 Wiviott, S.D. *et al.* (2007) Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N. Engl. J. Med.* 357, 2001–2015
118 Scirica, B.M. *et al.* (2011) The incidence of bradyarrhythmias and clinical bradyarrhythmic events in patients with acute coronary syndromes treated with ticagrelor or clopidogrel in the PLATO (Platelet Inhibition and Patient Outcomes) Trial results of the continuous electrocardiographic assessment substudy. *J. Am. Coll. Cardiol.* 57, 1908–1916
119 Goldstein, L.B. and Rothwell, P.M. (2009) Advances in primary prevention and health services delivery. *Stroke* 40, 295–297
120 Sacco, R.L. *et al.* (2011) Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack a statement for healthcare professionals from the American Heart Association/American stroke association council on stroke co-sponsored by the council on cardiovascular radiology and intervention. The American Academy of Neurology affirms the value of this guideline. *Stroke* 42, 227–276
121 Bardutzky, J. and Schwab, S. (2007) Antiedema therapy in ischemic stroke. *Stroke* 38, 3084
122 Adams, R.J. *et al.* (2008) Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack. *Stroke* 39, 1647–1652
123 Sacco, R.L. *et al.* (2006) Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Circulation* 113, 409–449