Current and potentially novel antithrombotic treatment in acute ischemic stroke

Thrombosis Research 236 (2024) 74–84

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review Article

Current and potentially novel antithrombotic treatment in acute ischemic stroke

Angelique Ceulemans [a,b], Henri M.H. Spronk [b,c,e], Hugo ten Cate [b,d,e], Wim H. van Zwam [b,f], Robert J. van Oostenbrugge [a,b], Magdolna Nagy [b,c,e,*]

[a] Department of Neurology, Maastricht University Medical Center+, Maastricht, the Netherlands
[b] School for Cardiovascular Diseases (CARIM), Maastricht University, Maastricht, the Netherlands
[c] Department of Biochemistry, Maastricht University Medical Center+, Maastricht, the Netherlands
[d] Department of internal medicine, Maastricht University Medical Center+, Maastricht, the Netherlands
[e] Thrombosis Expertise Center, Heart & Vascular Center, Maastricht University Medical Center+, Maastricht, the Netherlands
[f] Department of Radiology and Nuclear Medicine, Maastricht University Medical Center+, Maastricht, the Netherlands

ARTICLE INFO

Keywords:
Acute ischemic stroke
Primary prevention
Secondary prevention
Platelets
Coagulation
Major bleeding

ABSTRACT

Acute ischemic stroke (AIS) is the most common type of stroke and requires immediate reperfusion. Current acute reperfusion therapies comprise the administration of intravenous thrombolysis and/or endovascular thrombectomy. Although these acute reperfusion therapies are increasingly successful, optimized secondary antithrombotic treatment remains warranted, specifically to reduce the risk of major bleeding complications. In the development of AIS, coagulation and platelet activation play crucial roles by driving occlusive clot formation. Recent studies implicated that the intrinsic route of coagulation plays a more prominent role in this development, however, this is not fully understood yet. Next to the acute treatments, antithrombotic therapy, consisting of anticoagulants and/or antiplatelet therapy, is successfully used for primary and secondary prevention of AIS but at the cost of increased bleeding complications. Therefore, better understanding the interplay between the different pathways involved in the pathophysiology of AIS might provide new insights that could lead to novel treatment strategies. This narrative review focuses on the processes of platelet activation and coagulation in AIS, and the most common antithrombotic agents in primary and secondary prevention of AIS. Furthermore, we provide an overview of promising novel antithrombotic agents that could be used to improve in both acute treatment and stroke prevention.

1. General introduction

Stroke is the second leading cause of death worldwide, affecting approximately 13,7 million people, whereof 5,8 million people die each year. When combined, stroke-related deaths and disabilities cause an annual loss of healthy life of 116 million years. Additionally, the incidence of recurrent strokes is estimated at 7–20% at 1 year post-stroke, and 16–35% at 5 years post-stroke, further increasing functional dependence and mortality [1,2]. Moreover, due to the demographic age shift, this number is expected to rise even more each year [3,4]. Therefore, it is not only warranted to improve stroke treatment in the acute setting, but to focus on secondary prevention as well.

Up to 80% of all strokes are of acute ischemic nature, the remainder is caused by intracranial hemorrhages (ICH), though actual proportions may differ depending on population and/or ethnicity [4]. Acute ischemic stroke (AIS) is caused by sudden occlusion of an artery supplying the brain, resulting in impairment or loss of neurological function given no timely reperfusion of that vascular territory [4,5]. AIS can result from either an embolic (approximately 20%) or non-embolic event, though most papers do not make this distinction [6]. Currently, the main approach for determining clot origin is based on clot histology [7].

There are three treatment options in the acute setting of AIS next to the initiation of antiplatelet therapy with e.g. acetylsalicylic acid (i.e. aspirin): 1) intravenous thrombolysis (IVT); 2) endovascular thrombectomy (EVT); 3) a combination of IVT and EVT. IVT comprises the timely administration of a thrombolytic agent, typically a recombinant tissue plasminogen activator (rtPA), to dissolve the clot and restore

* Corresponding author at: Universiteitssingel 50, 6229 ER Maastricht, the Netherlands.
E-mail address: m.nagy@maastrichtuniversity.nl (M. Nagy).

https://doi.org/10.1016/j.thromres.2024.02.009
Received 14 September 2023; Received in revised form 22 January 2024; Accepted 12 February 2024
Available online 15 February 2024

cerebral perfusion, whereas EVT utilizes mechanical removal of the clot via a catheter-based approach. With regards to current acute treatment options, the MR CLEAN NO-IV trial investigated the added benefit of IVT prior to EVT on clinical outcome in AIS patients, but found neither inferiority nor non-superiority compared to EVT alone [8]. Likewise, the MR CLEAN MED investigated the effect of periprocedural heparin, acetylsalicylic acid, neither, or both on clinical outcome in EVT patients. Due to the incidence of heparin-related bleedings the trial was prematurely terminated without providing a clear beneficial effect of acetylsalicylic acid or heparin on functional outcome [9].

Occlusive clot formation results from two closely intertwined processes, namely the activation of platelets and the activation of coagulation. Activated coagulation factors give rise to the formation of thrombin, which cleaves soluble fibrinogen into insoluble fibrin, but also, amongst others, promotes the activation of upstream coagulation factor XI (FXI) and the activation of platelets. In turn, the surface of activated platelets provides the main proteolytic site for coagulation factors, again promoting the formation of fibrin (Fig. 1) [10–12]. While this process is essential to arrest bleeding (hemostasis), excess reciprocal activation can result in thrombus formation (thrombosis). Literature regarding the initiation of thrombus formation in AIS remains up for debate. While some evidence suggests excess levels of circulating hyperreactive platelets expressing high levels of P-selectin as a possible driving factor [13,14], other recent evidence proposes local hypercoagulability to be a key trigger of clot formation [15,16]. The latter is supported by a systematic review indicating an association between increased levels of specific plasma biomarkers for hypercoagulability, i.e. vWF, FXIa and FXIIa, and increased risk for AIS [10].

Both scenarios may be valid, but likely depend on the etiology of AIS. While atrial fibrillation (AF)-related stroke may be dominated by hypercoagulability, atherothrombosis-related stroke may be initially influenced by platelet reactivity [17,18]. The latter is comparable with acute coronary artery disease. However, there may be vascular bed-specific differences in atherothrombosis where contact activation may be more prominent in AIS, compared to the coronary circulation, given that subjects with a factor XI deficiency appear to be protected against stroke, but not against myocardial infarction [19]. These considerations are important in the ongoing search for improved prognostic biomarkers for clinical outcome of AIS, but also for safer treatment options [20].

First, this review will focus on the key players involved in thrombus formation underlying AIS: 1) the role of platelets; 2) the role of the coagulation cascade. Second, this review will provide insights into: 1) current antithrombotic management for both primary and secondary prevention; 2) promising new antithrombotic agents for the prevention or treatment of AIS.

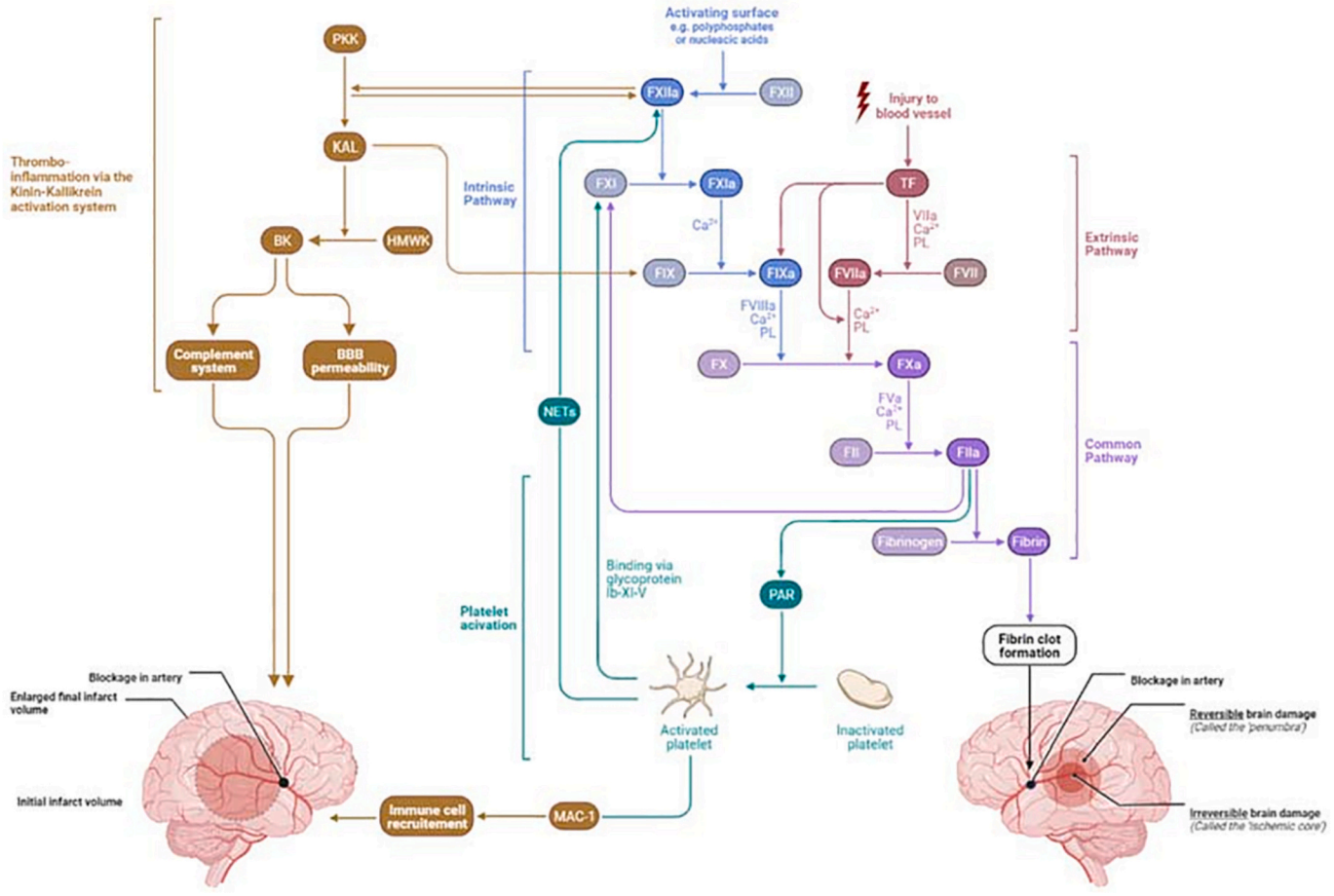

Fig. 1. Overview of coagulation and thrombo-inflammation. The extrinsic and intrinsic coagulation are activated by pathway specific events and converge into the common coagulation pathway to form thrombin for clot stabilization. Thrombin can form a direct positive feedback loop for the activation of the intrinsic coagulation by activating factor XI, and an indirect positive feedback loop by the activation of platelets that activate factor XII via neutrophil extracellular traps (NETs). Coagulation can be linked to inflammatory pathways via activation of the kinin-kallikrein system, leading to the formation of bradykinin, and subsequent activation of the complement system and breakdown of the BBB. F = Factor; a = activated form; TF = tissue factor, PAR = protease-activated receptors; NETs = neutrophil-extracellular traps; MAC-1 = Integrin αMβ2; PKK = prekallikrein; KAL = kallikrein; BK bradykinin; HMWK = high molecular-weight kininogen; BBB = blood-brain barrier; PL = Phospholipid; Ca2+ = Calcium. Of note, thrombo-inflammation is not included in this review. Created with Biorender.com.

2. Thrombus formation in the course of acute ischemic stroke

2.1. Role of platelets in acute ischemic stroke

Platelets are important in the onset of AIS due to their prominent role in wound healing and clot formation. Upon vascular damage, initial binding of platelets to the injured endothelium is mediated through interaction of the platelet glycoprotein Ib (GPIb) with subendothelial von Willebrand factor (vWF), leading to initial platelet tethering, platelet-vessel wall adhesion and primary hemostasis by formation of a platelet plug [11]. Consequent to initial platelet activation, platelet binding to subendothelial collagen via glycoprotein VI (GPVI) results in further platelet activation and firm platelet adhesion [21]. Additionally, GPVI binding to fibrin amplifies platelet activation and stimulates thrombus growth and stabilization [22,23]. The processes described above lead to activation of GPIIb/IIIa, resulting in platelet aggregation by binding fibrinogen or vWF between receptors [11,24].

Several preclinical and clinical studies addressed the role of specific platelet surface receptors in AIS development (Table 1). One study assessed the role of GPIb, GPVI and GPIIa/IIIb in AIS, by using a transient middle cerebral artery occlusion mouse model (tMCAO), lasting 1 hour. Complete blockage of these receptors was achieved by injection of specific monoclonal antibodies 1 hour before occlusion. Results showed that interfering with early platelet activation and platelet-vessel wall adhesion via GPIb depletion, decreased the ischemic infarct size by 60%. This also led to improved functional outcomes 24 hours post-AIS without increasing the risk for intracerebral hemorrhage. Moreover, blocking GPIb 1 hour after occlusion was as effective as prophylactic administration resulting in comparable reductions in ischemic infarct size. The beneficial effects of GPIb interference might be indicative of the essential platelet-vessel wall interaction under high shear forces, suggesting a central role of GPIb in stroke development [25]. These results were confirmed by other studies utilizing the same tMCAO mouse model with analogous infarct size assessment techniques, indicating that selectively blocking early stages of platelet activation and platelet-vessel wall interaction protected against AIS [11,26,27]. Similar to the depletion of GPIb, depleting GPVI resulted in decreased ischemic infarct sizes, though to a lesser extent [25]. Interestingly, using a GPVI-fusion protein which binds to collagen and other GPVI ligands and thereby prevents platelet binding to the surface led to reduced infarct size and improved functional outcome [28]. In addition, targeting the downstream signaling events of GPVI by either genetic or pharmacological deletion of spleen tyrosine kinase (Syk) showed a similar favorable effect in reducing ischemic stroke size and improved neurological outcome [29].

Despite the strong evidence for the importance of GPVI in AIS pathophysiology in animal models, its involvement in human AIS is not well understood. Using blood samples from AIS patients, studies showed higher GPVI expression levels on platelets and higher soluble GPVI (sGPVI) in plasma compared to healthy individuals [30–32]. On the contrary, Wurster et al. showed higher levels of surface expressed GPVI and a lower level of sGPVI in AIS patients compared to patients suffering from a transient ischemic attack (TIA) and patients with non-ischemic events [33]. These findings may support the notion that GPVI is an important contributor to AIS in both experimental models and humans. In contrast, blocking GPIIb/IIIa in both mice and AIS patients increased the occurrence of intracerebral hemorrhage and mortality in a dose-dependent manner, while not affecting the course of stroke [25,34].

Table 1
Summary of the main findings of all included original articles regarding changes of platelet activity or platelet inhibition in acute ischemic stroke.

Target	Model type	Study type	Intervention	Main findings
Glycoprotein Ib (GPIb)	Mice - tMCAO (60–90 min)	In vivo	Pharmacological inhibition	● Reduced AIS volumes [11,27] ● Improved neurological functional outcome [11,25,27] ● Protection against stroke without increasing bleeding complications [25–27]
			Genetic depletion	● Reduced infarct size and improved functional outcome [28]
Glycoprotein VI (GPVI)	Mice - tMCAO (60–90 min)	In vivo	Pharmacological inhibition	● Reduced AIS volumes [29] ● Improved neurological/ functional outcome [25,29] ● Protection against stroke without increasing bleeding complications [25,26,36]
	Humans	Case-control	n.a.	● Increased GPVI surface expression is significantly higher in AIS patients [33]
		Cohort	n.a.	● Increased GPVI surface expression levels are associated with increased stroke risk and poorer clinical outcome [31] ● Reduced soluble GPVI levels are associated with increased AIS risk [34]
Glycoprotein IIb/IIIa (GPIIb/IIIa)	Mice - tMCAO (60–90 min)	In vivo	Pharmacological inhibition	● No protection against AIS but increased bleeding complications [25,26]
	Humans	RCT	n.a.	● No definite protection against AIS but increased bleeding complications [35]

tMCAO = transient middle cerebral artery occlusion; RCT = randomized controlled trial; AIS = acute ischemic stroke; n.a. = not applicable.

2.2. In vivo platelet activity

Upon platelet activation, platelets release autocrine mediators (e.g. ADP and thromboxane A2) leading to further (autocrine) platelet activation via activation of specific G-protein coupled receptors (GCPRs), possibly affecting clinical outcome after AIS [24]. Sustained platelet activation leads to the release of their granular content into the circulation, increased copy number of the surface expressed receptors as well as shedding of surface expressed receptors which is a proxy measure of their in vivo activity [12].

Studies in AIS patients show hyperreactivity of platelets in the (sub)

acute or even recovery phase of AIS, through assessment of platelet activation markers [12]. Induruwa et al. found elevated P-selectin (CD62P) and GPVI expression on resting platelets within 8 hours of stroke onset compared to healthy controls, indicating a higher platelet activation state in stroke patients. The level of GPVI dimers further increased after 3-months follow-up, whereas no difference was seen in P-selectin levels [32]. These results were confirmed by Marquardt et al., showing that patients with AIS had an excess of platelets expressing CD62P and CD63 on day 1 after the stroke event. Interestingly, CD62P expression rapidly declined during the first days/weeks after stroke, presumably due to shedding, while CD63 expression remained elevated for at least 90 days after stroke [13]. Given that the average lifespan of platelets ranges from 7 to 10 days, such long periods of elevated CD63 expression might indicate prolonged platelet activation. Therefore, CD63 expression might be a suitable biomarker for the occurrence of secondary thrombotic events, though further research is warranted [13].

3. Thrombus formation through activation of the coagulation system

Under physiological circumstances, vascular trauma results in the activation of primary hemostasis, enabling the aggregation of platelets, followed by the formation of a platelet plug that binds to subendothelial collagen. Next, secondary hemostasis facilitates platelet plug stabilization by propagating fibrin formation, initiated by two distinct pathways: the extrinsic and intrinsic coagulation. Both pathways converge into a common coagulation pathway, ultimately leading to the formation of a fibrin mesh [35].

Both pathways are characterized by pathway-specific plasma coagulation factors, i.e. serine proteases, and act through cleavage of downstream substrates in an avalanche-like manner. This process, from vascular trauma to stabilized clot formation, arises from highly coordinated protein-protein interactions (Fig. 1). Disturbances in these processes may give rise to pathological hypercoagulable conditions. In AIS patients, cardioembolism or unstable plaque erosion/rupture are the main initiators for these thromboembolic events. Understanding the specific coagulation processes involved in AIS development, could lead to improved targeted therapies, and better clinical outcomes [36,37].

3.1. The extrinsic coagulation pathway

Under pathological conditions, such as atherosclerotic plaque rupture, tissue factor (TF), an integral membrane protein, gets exposed to the circulation, thereby increasing its blood- borne concentrations, and promoting secondary hemostasis. In addition, inflammatory cytokines can stimulate TF expression in monocytes and macrophages leading to further exacerbation of the extrinsic coagulation. Exposed TF can bind to coagulation factor VII (FVII) causing FVII activation (FVIIa). The TF-FVIIa complex cleaves FIX and FX, resulting in thrombin and subsequent fibrin generation [38,39] (Fig. 1). The TF:FVIIa complex is inhibited by either tissue factor pathway inhibitor (TFPI) via formation of a tetramolecular complex (TF:FVIIa:TFPI:FXa) or by antithrombin (AT) through formation of FVIIa:AT complex [40]. Several preclinical and clinical studies addressed the role of the extrinsic coagulation in AIS

Table 2
Summary of the main findings of all included original articles regarding changes of coagulation activity or inhibition of coagulation in acute ischemic stroke.

Target	Model type	Study type	Intervention	Main findings
Tissue factor (TF)	Humans	Cohort and case-control	n.a.	● Increased levels of circulating TF are potential risk factors for AIS [47] ● Reduced TF levels and increased tissue factor-bearing microparticle levels at onset of AIS [49] ● Increased TF activity and antigen levels at onset of AIS [76]
Factor VII (FVII)	Humans	Case-control	n.a.	● Reduced FVII antigen levels in AIS [49] ● Reduced FVIIa-AT levels in AIS [49] ● Increased FVIIa-AT levels in AIS [53] ● Increased FVIIa levels in AIS [53]
		RCT	Administration of IVT	● No IVT treatment: reduced FVII/FVIIa levels post-AIS [51,76] ● IVT treatment: reduced FVIIa and increased FVII levels in post-AIS [51,76]
Factor XII (FXII)	Mice/rats - tMCAO (60 min - permanent)	Experimental	Pharmacological inhibition	● Reduced AIS volume without increased in infarct-associated hemorrhage [57,59,60,72] ● Unaltered infarct size [63]
			Genetic depletion	● Reduced AIS volume without increased infarct-associated hemorrhage [57,59,60]
	Humans	Case-control/ prospective cohort	n.a.	● No association between FXII antigen levels and AIS risk or clinical outcome after AIS [65,66] ● No changes of FXII antigen levels between baseline and 3 days post-AIS [67] ● Increased FXIIa:C1-esterase-inhibitor complex levels are associated with increase AIS risk in young women [68]
Plasma kallikrein (PK)	Mice - tMCAO (60 min - permanent)	Experimental	Pharmacological inhibition	● Reduced infarct size, edema and improved neurological Behavior increasing infarct-associated hemorrhages [70,72] Without
			Genetic depletion	● Reduced infarct size, edema and improved neurological Behavior increasing infarct-associated hemorrhages [70] Without
	Humans	Case-control	n.a.	● No association between PK antigen levels and increased risk of AIS [65] ● Increased PK:C1-esterase-inhibitor complex levels are associated with increase AIS risk in young women [68]
Factor XI (FXI)	Mice/rabbits - tMCAO (60 min - permanent)	Experimental	Pharmacological inhibition Genetic depletion	● Reduced cerebral microembolic signals and prolonged bleeding time [73] ● FXIIa-mediated FXI activation plays a crucial role in AIS development [64] ● Reduced ischemic brain injury and improved neurological behavior without increased infarct-associated hemorrhages [57]
	Humans	Cohort and case-control	n.a.	● Increased FXI antigen and activity levels are associated with increased AIS risk [65,66,74] ● No association between FXI antigen levels and AIS risk [75] ● No changes of FXI antigen levels between baseline and 3 days post-AIS [67] ● Increased FXIa:C1-esterase-inhibitor and FXIa:Antithrombin complex levels are associated with increase AIS risk in young women [68]

tMCAO = transient middle cerebral artery occlusion; RCT = randomized controlled trial; FVIIa = Activated factor FVII; FVIIa-AT = Factor VIIa-antithrombin complex; AIS = acute ischemic stroke.

development (Table 2).

The importance of TF and FVII in normal hemostasis is supported by studies demonstrating an increased likelihood of spontaneous hemorrhages in humans with severe FVII-deficiencies [41]. As described elsewhere, humans and mice lacking FVII and/or TF are not viable and die in the embryonic or perinatal phase [38,41,42]. On the other hand, elevated levels of circulating and monocyte-expressed TF are associated with an increased risk for the development of venous and arterial thrombosis [43,44]. Changes in the extrinsic pathway have been shown to play a role in AIS pathogenesis as well [45].

Early studies reported decreased FVIIa:AT complex (i.e. proxy for in vivo FVII activation), FVIIa:ag and elevated TF-bearing microparticle plasma levels in the acute phase of first-ever AIS, compared to healthy controls [48,49]. In contrast, patients with prior AIS showed increased FVIIa:AT complex plasma levels, compared to healthy controls [40,46]. In addition, a subgroup of patients who received thrombolysis showed significantly lower levels of FVII at day 7 compared with the patients who did not receive thrombolysis [47]. Likewise, Welch et al. showed a significant decrease in FVIIa at 48 hours after thrombolysis with alteplase, though this patient population was extremely small ($n = 2$), and hence meaningful conclusions cannot be drawn [48].

Furthermore, studies identified several single nucleotide polymorphisms in the FVII gene associated with increased FVII:ag, as risk factors for AIS development, however data are conflicting [49,50]. Interestingly, a prospective population-based study showed an association between increased FVIIa and AIS, while FVIIa-AT was not significantly associated after adjustment for risk factors and FVII clotting activity showed no association at all [50].

The differences seen in the association between FVII and AIS could originate from the different stroke etiology or underlying mechanisms by which these complexes are generated or incorporated in the clot during the acute phase of stroke. For instance, AIS patients with AF showed lower FVII:ag compared to non-AF AIS patients [47,51]. Importantly, the increased FVII:ag levels appeared to be associated with overall AIS after adjustment for warfarin treatment [51]. To unravel the relevance of FVII:ag levels, more studies should be performed.

3.2. The intrinsic coagulation pathway

While the extrinsic coagulation pathway has been associated with the development of AIS, the involvement of the intrinsic coagulation pathway in AIS pathophysiology remains elusive. Therefore, precise mechanisms of activation of the intrinsic coagulation are gaining more awareness. Recent histological studies showed the presence of neutrophil extracellular traps within AIS thrombi, which could be an important player in the FXII mediated intrinsic coagulation [52,53]. Consequently to FXII activation, FXIIa is formed and converts FXI into FXIa, promoting the cleavage of FIX into FIXa. Eventually, FIXa gives rise to the formation of FXa, leading to thrombin generation via the common coagulation pathway (Fig. 1). Several preclinical and clinical studies addressed the role of the intrinsic coagulation in AIS development (Table 2).

Data from FXII deficient individuals and animal studies utilizing FXII deficient mice models show that FXII is not essential for normal hemostasis, since its deletion or blockage does not increase bleeding risk [54]. Epidemiologically, however, there is no data showing protection against AIS in FXII deficient subjects, while for FXI deficiency such protective effect has been observed [19,55]. Renné et al. and Kleinschnitz et al. demonstrated improved reperfusion after experimental stroke using mice with genetic deletion or pharmacological inhibition of FXII [54,56]. Pharmacological blockage of FXII by rHA-infestin-4, in a mouse and rat tMCOA model, resulted in decreased infarct sizes [57–59]. Notably, one study in mice showed no reduction in ischemic infarct size after pharmacological selective inhibition of FXII by COU254 [60]. However, the pharmacodynamics- and kinetics of COU254 in animals is lacking, therefore, the lack of effect might be due to insufficient dosage [60]. In addition, inhibition of the signaling cascade downstream of FXII by either genetically depleting FXI or by selectively inhibiting FXII-mediated FXI activation, while leaving FXI activation by thrombin intact, increased cerebral reperfusion, and led to improved neurological outcomes in mice [54,61]. This evidence supports a role of FXII (and FXII-mediated FXI activation) in AIS pathophysiology, although the role of this protein in humans remains controversial. A population based case-control study and a retrospective cohort study showed that increased FXII:ag in humans is not associated with an increased risk for AIS [62,63], while another study showed no significant changes of FXII:ag between baseline and 3 days post-AIS [64]. Siegerink et al. showed that increased FXIIa activity measured by FXIIa:C1-esterase-inhibitor complexes were significantly associated with increased risk for AIS in young females on oral contraceptives [65].

Importantly, FXIIa can also trigger inflammation by cleaving plasma prekallikrein (PKK) to kallikrein (PK), leading to the formation of bradykinin (BK) [66]. When uninhibited, such as in patients with congenital angioedema, this results in inflammation and edema formation, and might enlarge the infarcted area in case of stroke. In accordance with findings regarding FXII deletion or blockage, PK deletion or blockage with DX-88 in mice resulted in smaller cerebral infarct volumes and reduced neurological deficits [67,68]. Similarly, blocking PK and FXIIa by Sylvestin was protective against experimental stroke in mice [69]. As is the case for deficiencies in FXII, deficiencies in PK are not associated with spontaneous hemorrhages. Moreover, increased PK:ag was neither associated with an increased risk for AIS, nor was there a significant association between increased PK:ag and PK activity [62,67]. While PK antigen levels showed no association with increased AIS risk, increased PKa:C1-esterase-inhibitor complexes - indicating in vivo PK activity - demonstrated significant association with AIS in young women on oral contraceptives [65].

FXI deficiency is associated with a relatively mild bleeding disorder, and reduced risk of AIS and venous thromboembolisms in humans [62]. The cerebral protective effect was confirmed by experiments in rabbits, revealing a negative dose-dependent relationship between FXI inhibition and cerebral microembolic signals [70,71]. Additionally, increased FXI:ag and activity were associated with an increased AIS risk and unfavorable clinical outcome in AIS patients [62,63]. Furthermore, the risk of arterial thrombosis in relation to oral contraceptives study showed an association between elevated levels of FXIa:C1-esterase-inhibitor and FXIa:AT complexes and AIS in young females [65]. Interestingly, a good association was revealed between FXI:ag and activity, while this association was not seen for FXII:ag and PK:ag and their respective activity [62]. Interestingly, Rohmann et al. showed that increased FXIa activity after first-ever stroke (either ischemic stroke, hemorrhage or venous sinus thrombosis, based on WHO-criteria) was associated with worse vascular outcomes, defined as a combination of secondary AIS, MI or death due to any cause during the follow-up period [63]. In contrast, other studies neither found differences between FXI:ag levels at baseline and 3 days post-AIS, nor between FXI:ag levels and increased risk for AIS [64,72]. Notably, results of the latter study need to be regarded with caution as the plasma samples used for analysis were approximately 20 years old. These controversial findings point towards the urgent need for new studies to clarify the relative contribution of the intrinsic pathway factors in AIS development.

4. Antithrombotic management

4.1. Current antithrombotic agents

Antithrombotic therapy is applied to reduce the risk for primary or secondary AIS, and consists of antiplatelet or anticoagulant therapy (Fig. 2). Current guidelines strongly recommend anticoagulant therapy for primary stroke prevention in AF patients who have an increased risk for stroke development [73]. However, the use of these anticoagulants is accompanied with an increased risk of major bleeding, also including intracranial hemorrhage (ICH) [74]. Currently, several oral

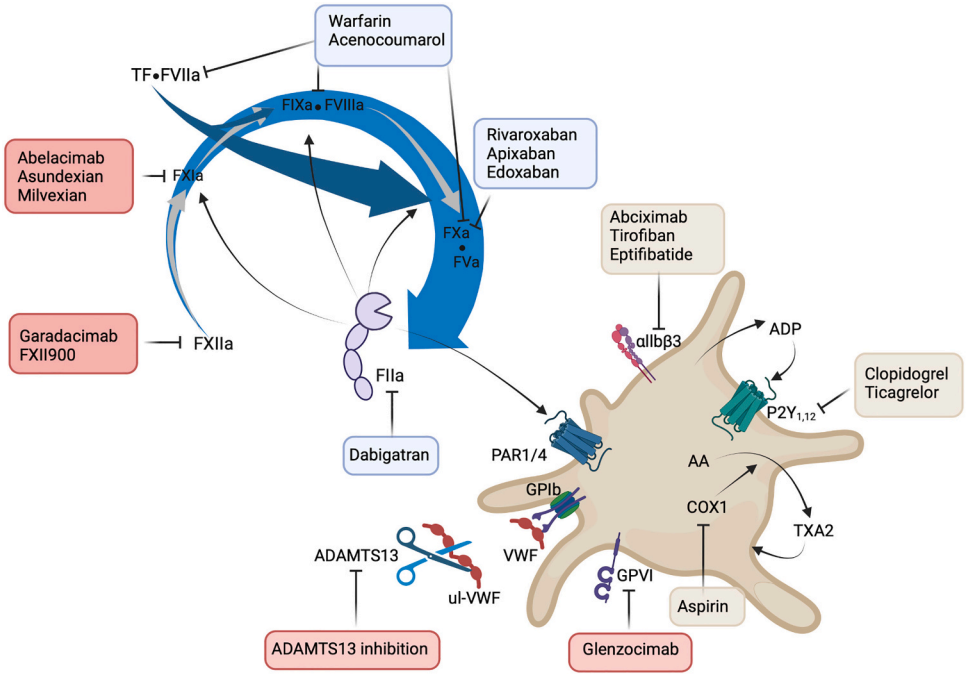

Fig. 2. Overview of current and novel antithrombotic agents in stroke treatment. Mechanisms of action of current and novel antiplatelet and anticoagulant agents are depicted by indicating the major pathways. Current treatments are indicated with beige and light blue textboxes and novel targets are indicated in red textboxes. For further details, see paragraph 4. F = Factor; FXIIa = Activated FXII; TF = Tissue factor; FVIIa = Activated factor VII; FIXa = Activated factor IX; FVIIIa = activated factor VIII; FXa = Activated factor X; FVa = Activated factor V; FIIa = Thrombin; PAR1/4 = Protease-activated receptor 1/4; ADAMTS13 = A Disintegrin and metalloproteinase with a thrombospondin type 1 motif member 13; (ul)VWF = (ultra large) Von Willebrand factor; GPIb = Glycoprotein Ib; GPVI = Glycoprotein VI; GPIIb/IIIa = Glycoprotein IIb/IIIa; ADP = Adenosine triphosphate; P2Y1,12 = ADP-based chemoreceptor; AA = Arachidonic acid; TXA2 = Thromboxane A2; COX1 = Cyclooxygenase 1. Created with Biorender.com. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

anticoagulants are used for the primary prevention of stroke in patients suffering from e.g. AF: 1) vitamin-K antagonists (VKAs; e.g. warfarin, acenocoumarol); 2) direct oral anticoagulants (DOACs); (e.g. dabigatran directed against FIIa or rivaroxaban, apixaban and edoxaban directed against FXa).

The effectiveness of the VKA warfarin, for the prevention of stroke in AF patients, has been well established [75,76], but DOACs, including dabigatran, apixaban, rivaroxaban, and edoxaban, are increasingly recommended over VKAs by guidelines. Several meta-analyses demonstrated no superiority or non-inferiority of DOACs over warfarin for the prevention of stroke, while others showed superiority of DOACs (studies summarized in Table 3). Regarding the risk of major bleeding and ICHs, DOACs have a better safety profile compared to warfarin (Table 3). The major bleeding risk in AF patients treated with warfarin was 0.71–9.47%, and for DOACs treatment this risk ranged from 0.39 to 5.26% risk. Both for warfarin and DOACs treatment the risk for ICH and hemorrhagic stroke was much lower than for major bleeding, however, warfarin-treated patients represented a higher risk of ICH in comparison to DOACs-treated patients (0.9–1.77% vs. 0.44–0.69%, respectively).

In addition, the use of DOACs in secondary stroke prevention after embolic stroke of undetermined source (ESUS), a subset of cryptogenic stroke, has also been studied [77,78]. A large systematic review and meta-analysis assessed the efficacy and safety of DOACs compared with aspirin in ESUS patients. DOACs showed no superiority to aspirin for the prevention of recurrent stroke in ESUS patients (Table 3). The ATTICUS trial, investigating the efficacy and safety of apixaban compared to aspirin in ESUS patients, was stopped prematurely due to futility [78]. The major bleeding risk was 2.20% for DOACs versus 1.38% for aspirin, and the clinically relevant non-major bleeding risk was 2.98% for DOACS versus 1.91% for aspirin. Lastly, hemorrhagic stroke occurred in 0.30% in DOAC-treated patients and in 0.14% in aspirin-treated patients [77].

Despite that the differential effect between DOACs and warfarin has been widely studied, there are no studies available directly comparing the various DOACs with each other. A recent systematic review and meta-analysis comparing the efficacy of each DOAC showed the highest efficacy for apixaban in reducing stroke, whereas the highest risk for ICH was associated with rivaroxaban [79].

While oral anticoagulants are indicated for both primary and secondary stroke prevention in AF patients, antiplatelet therapy is used for the initial and long-term secondary prevention of stroke in patients with history of noncardioembolic ischemic stroke, atherothrombotic stroke, lacunar or cryptogenic stroke. The primary choice of treatments consists of aspirin and clopidogrel for the first 21–90 days after AIS followed by either aspirin or clopidogrel [80]. In addition, ticagrelor is used less frequently, while prasugrel is contraindicated due to significantly increased risk in major and/or fatal bleedings [94].

Similar to the anticoagulant therapies, antiplatelet therapy is also associated with increased bleeding risk. This has also been supported by the fact that the wide-spread use of (low-dose) aspirin for cardiovascular prophylaxis increases the major bleeding risks (relative risk = 1.71; 95% confidence interval [CI], 1.41–2.08)) [81]. Noteworthy, the increase in absolute risk was only modest, as only one major bleeding (both intracranial and gastro-intestinal) occurred in 769 patients treated with low-dose aspirin [81]. Interestingly, a meta-analysis indicated prophylactic use of aspirin resulted in a lower risk of AIS in apparently healthy adults, whereas it had no protective effect against AIS in patients with cardiovascular diseases [82].

P2Y12 inhibitors, such as clopidogrel and ticagrelor, are also associated with increased bleeding risk. In case of clopidogrel, a previous study showed increased risk of upper and lower gastrointestinal bleedings [83]. Furthermore, despite the greater and faster platelet inhibition of ticagrelor compared to clopidogrel, a meta-analysis showed non-superiority of ticagrelor over clopidogrel in major adverse cardiac

Table 3
Summary of meta-analyses investigating medication associated bleeding risks.

	Patient population	Medication type	Bleeding type	Calculated risk (HR, RR, OR or ARR)	Bleeding risk (%)
Primary stroke prevention					
Dahal et al. [82]	AF patients with/without HD	Warfarin vs control	Major bleeding	HR = 1,15; 95 % CI: 0.88 to 1.49 (CKD without HD) HR = 1.30; [95 % CI: 1.08 to 1.56] (CKD with HD)	n.a.
Randhawa et al. [83]	AF patients with CKD	Warfarin vs control	Hemorrhagic stroke	HR = 1.46; [95 % CI: 1.05 to 2.04]	1.77% vs 1.47%
			Major bleeding	HR = 1.20; [95 % CI: 0.99 to 1.47]	9.47% vs 10.45%
Ruff et al. [84]	AF patients	DOACs vs warfarin	Hemorrhagic stroke	RR = 0.49; [95 % CI: 0.38 to 0.64]	0.44% vs 0.9%
			ICH	RR = 0.48; [95 % CI: 0.39 to 0.59]	0.69% vs 1.45%
			Major bleeding	RR = 1.25; [95%CI: 1.01 to 1.55]	5.26% vs 6.16%
Carnicelli et al. [85]	AF patients	DOACs vs warfarin	ICH	HR = 0.45 [95%CI 0.37 to 0.56]	0.63% vs 1.4%
			Major bleeding	HR = 0.86 [95%CI 0.74 to 1.01]	5.05% vs 5.94%
Liew et al. [86]	AF patients	DOACs vs warfarin	ICH	RR = 0.42 [95%CI: 0.34 to 0.53]	0.6% vs 1.45%
			Bleeding related mortality	RR = 0.54 [95%CI: 0.44 to 0.67]	0.39% vs 0.71%
Sun et al. [87]	ACS patients	Clopidogrel vs ticagrelor	Major bleeding	OR = 1.22; [95%CI: 0.93 to 1.61]	n.a.
Lei et al. [88]	Individuals with or without cardiovascular disease	Aspirin vs placebo	Hemorrhagic stroke	OR = 1.32; [95%CI: 1.04 to 1.68]	1.67% vs 0.17%
			Major bleeding	OR = 1.62; [95%CI: 1.31 to 2.00]	0.66% vs 0.41%
Secondary stroke prevention					
Liu et al. [89]	Non-valvular AF patients after first ICH	DOACs vs warfarin	ICH	DOACs vs no DOACs: RR = 0.91; [95%CI: 0.53 to 1.55] Warfarin vs no warfarin: RR = 1.00; [95%CI: 0.45 to 2.22] DOACs vs warfarin: RR = 0.68; [95%CI: 0.54 to 0.86]	n.a.
			Major bleeding	DOACs vs no DOACs: RR = 1.50; [95%CI: 0.94 to 2.40] DOACs vs warfarin: RR = 0.54; [95%CI: 0.26 to 1.10]	
Paciaroni et al. [90]	Patients with recent AIS	Clopidogrel vs aspirin	AIS or ICH	RR = 0.72; [95%CI: 0.55 to 0.94]	4.5% vs 10.2%
			Major bleeding	RR = 0.57; [95%CI: 0.45 to 0.74][$]	3.39% vs 2.19%
McQuaid et al. [91]	Individuals for primary or secondary prophylaxis of cardiovascular diseases	Aspirin vs placebo	ICH	RR = 1.65; [95%CI: 1.12 to 2.44]	n.a.
			Major bleeding	RR = 1.71; [95 % CI: 1.41 to 2.08]	n.a.
		Aspirin vs clopidogrel	ICH	RR = 1.38; [95%CI: 0.89 to 2.15][$]	0.49% vs 0.35%
			Major bleeding	RR = 1.13; [95%CI: 0.90 to 1.43][$]	1.55% vs 1.38%
		DAPT vs aspirin	ICH	RR = 0.71; [95%CI: 0.23 to 2.23][#]	0.11% vs 0.08%
			Major bleeding	RR = 0.73; [95%CI: 0.60 to 0.88][#]	3.69% vs 2.68%
		DAPT vs clopidogrel	ICH	RR = 0.62; [95%CI: 0.38 to 1.03][$]	1.05% vs 0.66%
			Major bleeding	RR = 0.42 [95%CI: 0.32 to 0.55][$]	4.45% vs 1.87%
Bhatia et al. [92]	Patients with previous stroke or TIA	DAPT vs aspirin	Hemorrhagic stroke	RR = 1.82; [95%CI: 0.83 to 3.98][#]	0.23% vs 0.12%
			Major bleeding	RR = 2.22; [95%CI: 1.41 to 4.34][#]	0.66% vs 0.27%

(*continued on next page*)

Table 3 (*continued*)

	Patient population	Medication type	Bleeding type	Calculated risk (HR, RR, OR or ARR)	Bleeding risk (%)
Hariharan et al. [77]	Patients with embolic stroke of undetermined source	DOACs vs aspirin	Hemorrhagic stroke	RR = 2.21; [95%CI: 0.29 to 16.69]	0.30% vs 0.14%
			Clinically relevant non-major bleeding	RR = 1.56; [95%CI: 1.25 to 1.96]	2.98% vs 1.91%
			Major bleeding	RR = 1.77; [95%CI: 0.80 to 3.89]	2.20% vs 1.38%

Abbreviations: AF = Atrial fibrillation; HD = Hemodialysis; CKD = Chronic kidney disease; ACS = Acute coronary syndrome; VTE = Venous thromboembolism; ICH = Intracranial hemorrhage; AIS = Acute ischemic stroke; TIA = Transient ischemic attack; DOACs = Direct oral anticoagulants; DAPT = Dual antiplatelet therapy (aspirin+P2Y12 inhibitor); RRR = Relative risk reduction; RR = Risk ratio; OR = Odds ratio; HR = Hazard ratio; ARR = Absolute risk reduction; n.a = Not applicable; CI = Confident interval.

events (MACE) and in secondary stroke development [84]. Additionally, ticagrelor was associated with a higher bleeding risk in patients with acute coronary syndrome [84].

A large retrospective study comparing the safety and efficacy of aspirin versus clopidogrel monotherapy for secondary AIS prevention showed non-superiority of clopidogrel over aspirin. However, clopidogrel use was significantly associated with increased mortality, but the mechanism of this observation remains uncertain [85]. This finding was not in line with the CAPRIE trial that showed that monotherapy of clopidogrel was superior to aspirin in terms of major bleeding and recurrent stroke in AIS patients [86]. These results were confirmed in a meta-analysis including 5 large studies with over 29.000 patients in total receiving either clopidogrel or aspirin as monotherapy. This meta-analysis revealed that clopidogrel treatment resulted in a significantly lower risk for MACE, recurrent stroke and bleeding compared with aspirin, without difference in all-cause mortality [87].

The reduction in recurrent stroke and/or MACE upon aspirin monotherapy can be further attenuated by combining aspirin with one of the P2Y12 inhibitors (i.e. utilizing DAPT). When comparing aspirin monotherapy with DAPT in a meta-analysis including 4 major trials, the reduction in both recurrent stroke and MACE was apparent in the DAPT group, but at the expense of increased bleeding risk [88]. The PRINCE study showed that, in patients with minor stroke or TIA, DAPT with ticagrelor and aspirin resulted in decreased platelet activity compared to dual antiplatelet therapy with clopidogrel and aspirin, in particular in patients with CYP2C19 loss-of-function allele carriers. However, patients who received ticagrelor plus aspirin had more bleeding events compared to the clopidogrel plus aspirin group [89].

According to the guidelines of the American Heart Association and American Stroke Association, short term DAPT is only recommended in high risk patients and long term DAPT is not recommended for secondary prevention [80].

From the above discussion it appears that there remains room for improvement of current antithrombotic medication in AIS management, to further reduce thrombotic risk as well as the major bleeding complications, in the acute phase and during secondary prevention.

4.2. Potential new antithrombotic agents

Current therapeutic strategies mainly focus on the acute aspect of stroke pathophysiology: restoring blood flow to the infarcted brain tissue by dissolving/removing the occluding thrombus and preventing re-occlusion. While effective, current invasive interventions, i.e. IVT and/or EVT, can still cause potential life-threatening complications such as vessel perforation, dissection or hyperperfusion injury including hemorrhagic transformation of infarcted brain tissue [90]. Therefore, here is a need for new agents that either support current therapies or that target novel pathways. Below we discuss 5 potential new therapies that can interfere with coagulation and platelet activation with possibly less impact on hemostasis [91].

4.2.1. ADAMTS13

ADAMTS13 is a protease that cleaves vWF, decreasing coagulation activity, and therefore, a potential target to improve functional outcome in AIS patients. A previous study showed that lower levels of ADAMTS13 were associated with a higher risk for AIS [92]. Similar results were found in a recent study with 43 AIS patients showing a significant association between the lowest quartile of ADAMTS13 at baseline and worse clinical improvement assessed via NIHSS-score after 24 hours. Additionally, patients in the lowest ADAMTS13 quartile showed significant increases in inflammatory markers between baseline and 90 days post-stroke. However, further research is needed to determine if pre-stroke inflammatory biomarkers are associated with low levels of ADAMTS13 and post-stroke clinical outcome [93].

Denorme et al. showed that ADAMTS13 was able to dissolve rtPA-resistant, vWF-rich clots in a middle cerebral artery occlusion (MCAO) model in mice. Furthermore, ADAMTS13 is suggested to improve recanalization in wild type mice (77.6% ± 18.0%, 50 minutes after occlusion), compared to ADAMTS13$^{-/-}$ mice (32.9% ± 9.6%, 50 minutes after occlusion) [94]. Additioally, a recent animal study with constitutively active ADAMTS13 (caADAMTS13; Ala1144Val ADAMTS13) showed a 5-fold enhanced activity against fluorescence resonance energy transfer substrate von Willebrand factor 73 (FRETS-VWF73) compared to wildtype ADAMTS13 (wtADAMTS13) in both a distal FeCl3 middle cerebral artery occlusion and tMCAO model. Furthermore, animals treated with caADAMTS13 showed significant restoration of regional cerebral blood flow (rCBF) and reduced lesion volume compared to animals treated with wtADAMTS13 [95]. Phase I human studies [96] and a recent proof of principle study in a patient with severe hereditary thrombotic thrombocytopenic purpura, showed the safety and potential efficacy of recombinant ADAMTS13 administration [97].

4.2.2. FXII inhibition

FXII(a) inhibition is of interest due to its minimal role in hemostasis. Inhibition of FXIIa by the macrocyclic peptide inhibitor FXII900 resulted in reduced thrombosis in a mouse, rabbit and pig FeCl3 MCAO model, and decreased clotting in an extracorporeal membrane oxygenation setting in rabbits [98]. However, the efficacy has yet to be established in a patient population.

In addition, the monoclonal antibody Garadacimab, directed against the catalytic domain of FXIIa, showed good tolerance at different doses in animal cynomolgus monkeys. Consequently, optimal doses for first-in-human phase I trials were selected: 0.1, 0.3, 1, 3 and 10 mg/kg for intravenous administration and 1, 3 and 10 mg/kg for subcutaneous administration [99]. In a subsequent phase II study, Garadacimab was well tolerated and reduced the number of monthly attacks in patients suffering hereditary angioedema that results from dysregulation in the FXII-kallikrein-kinin system [100].

4.2.3. FXI inhibition

FXI(a) inhibition has gained a lot of attention lately due to its postulated low bleeding risk, yet potent anticoagulation potential [101].

Abelacimab, a monoclonal antibody against FXI and FXIa was safe and effective when compared to low molecular weight heparin (LMWH) in preventing postoperative venous thromboembolism [102]. Currently, it is being tested as primary prevention in AF patients in the AZALEA-TIMI71 phase II study comparing its effect on bleeding with rivaroxaban in patients with moderate-to-high risk of stroke (NCT04755283).

In addition, the PACIFIC-STROKE phase II clinical trial in AF patients compared different doses of the small molecule asundexian, and found doses of 20 mg and 50 mg, once daily, to be associated with decreased, mostly minor, bleeding complications, compared with standard dosing of apixaban. Moreover, 50 mg asundexian reached near-complete free FXIa inhibition in AF patients [103]. The PACIFIC-STROKE phase IIb trial studied asundexian in patients with non-cardioembolic AIS for secondary prevention and showed no reduction in AIS, and associated bleedings were not increased compared to placebo [104]. The OCEANIC-AF phase III trial aimed to evaluate the efficacy (decrease in AIS risk) and safety (major bleeding events) of asundexian in AF patients compared to apixaban (NCT05643573). The trial was stopped prematurely due to inferior efficacy, as shown by the study's independent data monitoring committee [105]. In addition, the ongoing OCEANIC-STROKE phase III trial is investigating the efficacy and safety of asundexian on top of standard-of-care antiplatelet therapy compared to placebo for prevention of AIS in patients who suffered AIS of non-cardioembolic origin or patients at high risk of a TIA (NCT05686070) [105]. Lastly, the OCEANIC-AFINA phase III trial will investigate the efficacy and safety of asundexian compared to placebo in AF patients who are at risk for AIS or systemic emboli and are ineligible for regular oral anticoagulant treatment. The OCEANIC-AFINA trial has yet to start recruiting.

Milvexian, an oral FXIa inhibitor, was effective as compared to LMWH in prevention against venous thromboembolism in patients undergoing knee arthroplasty [106]. The AXIOMATIC-SSP phase II clinical trial (NCT03766581) investigated Milvexian as secondary prevention on top of standard-of-care DAPT for 3 weeks followed by SAPT after AIS or TIA. Within the 90 days follow-up period, the reduction in the rate of AIS was accompanied by nonsignificant increase in bleeding events [107]. Currently, the LIBREXIA-AF phase III clinical trial is investigating the effect of Milvexian in the secondary prevention of recurrent stroke in patients after AIS or TIA on top of standard-of-care antiplatelet therapy with 4 years of follow-up period (NCT05702034).

4.2.4. GPVI inhibition

Glenzocimab is a humanized monoclonal antibody, directed against the platelet GPVI receptor with favorable antithrombotic effect while having limited impact on hemostasis. Inhibiting GPVI showed a great potential in reducing infarct volume in an in vivo ischemic stroke model [108]. Currently, the first clinical trials testing novel GPVI inhibitors are ongoing. A recent phase I study showed a good safety and tolerability profile in healthy volunteers [109,110]. The phase Ib/IIa clinical study administering Glenzocimab on top of the standard of care stroke treatment (intravenous tPA and mechanical thrombectomy) showed a lower rate of ICH compared to patients only receiving the standard care treatment, in an unpublished interim safety analysis [111]. Given these surprising and promising results of the phase Ib/IIa clinical trial, Glenzocimab has entered the phase II/III trial as an add-on therapy in AIS patients (NCT05070260). While most novel drugs aim to improve primary or secondary prevention of AIS, the GREEN phase II/III trial aims to evaluate the efficacy of Glenzocimab in addition to EVT compared to EVT plus placebo in acute treatment (NCT05559398).

5. Conclusion

Approximately half of the surviving stroke patients suffer from permanent disabilities caused by the first stroke event, and up to 35% suffer from recurrent stroke within 5 years after the initial event. To date, AIS therapies comprise IVT and/or EVT followed by antiplatelet therapy as secondary prevention. In vulnerable patients (e.g. patients with AF), anticoagulants are used as primary prevention. These current antithrombotic therapies, however, are associated with an increased risk for major bleedings (up to 10%) and hemorrhagic stroke (up to 2%). Therefore, potentially safer antithrombotic agents are warranted. Based on preclinical and early clinical studies, several novel antithrombotics (e.g. GPVI inhibitor glenzocimab, FXII and FXI(a) inhibitors) emerged suggesting benefits in preventing AIS as primary or secondary prevention without impacting hemostasis. Most of these therapies are currently in clinical trials.

Sources of funding

The authors did not receive funding for writing this review.

CRediT authorship contribution statement

Angelique Ceulemans: Investigation, Writing – original draft, Writing – review & editing. **Henri M.H. Spronk:** Supervision, Writing – review & editing. **Hugo ten Cate:** Supervision, Writing – review & editing. **Wim H. van Zwam:** Supervision, Writing – review & editing. **Robert J. van Oostenbrugge:** Supervision, Writing – review & editing. **Magdolna Nagy:** Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

H.t.C. has received consultancy fees from Aleveron, AstraZeneca, Galapagos and Novostia and research funding from Bayer; all revenues are deposited at the CARIM Institute and labelled for research. H.t.C. and H.M.H.S. are shareholders of Coagulation Profile, a spinoff diagnostic company of Maastricht University. The other authors declared no conflict of interest.

Acknowledgements

All authors thank the CONTRAST consortium for full support. The CONTRAST consortium acknowledges support from the Netherlands Cardiovascular Research Initiative, an initiative of the Dutch Heart Foundation (CVON2015-01: CONTRAST). This work was supported by the Dutch Heart Foundation (03-006-2022-0052 to M. Nagy) and the Netherlands Brain Foundation (HA2015.01.06).

References

[1] A.N. Khanevski, A.T. Bjerkreim, V. Novotny, H. Naess, L. Thomassen, N. Logallo, et al., Recurrent ischemic stroke: incidence, predictors, and impact on mortality, Acta Neurol. Scand. 140 (1) (2019 Jul) 3–8.
[2] V.L. Feigin, M. Brainin, B. Norrving, S. Martins, R.L. Sacco, W. Hacke, et al., World Stroke Organization (WSO): global stroke fact sheet 2022, Int. J. Stroke 17 (1) (2022 Jan) 18–29.
[3] M.S. Phipps, C.A. Cronin, Management of acute ischemic stroke, BMJ 13 (368) (2020 Feb) l6983.
[4] E.S. Donkor, Stroke in the 21st century: a snapshot of the burden, epidemiology, and quality of life, Stroke Res Treat. 27 (2018) (2018 Nov) 3238165.
[5] S.S. Virani, A. Alonso, H.J. Aparicio, E.J. Benjamin, M.S. Bittencourt, C. W. Callaway, et al., Heart disease and stroke statistics-2021 update: a report from the American Heart Association, Circulation 143 (8) (2021 Feb 23) e254–e743.
[6] A. Arboix, J. Alió, Cardioembolic stroke: clinical features, specific cardiac disorders and prognosis, Curr. Cardiol. Rev. 6 (3) (2010 Aug) 150–161.
[7] F.C. Roessler, N. Kalms, F. Jann, A. Kemmling, J. Ribbat-Idel, F. Stellmacher, et al., First approach to distinguish between cardiac and arteriosclerotic emboli of individual stroke patients applying the histological THROMBEX-classification rule, Sci. Rep. 11 (1) (2021 Apr 19) 8433.
[8] N.E. LeCouffe, M. Kappelhof, K.M. Treurniet, L.A. Rinkel, A.E. Bruggeman, O. A. Berkhemer, et al., A randomized trial of intravenous alteplase before endovascular treatment for stroke, N. Engl. J. Med. 385 (20) (2021 Nov 11) 1833–1844.
[9] W. van der Steen, R.A. van de Graaf, V. Chalos, H.F. Lingsma, P.J. van Doormaal, J.M. Coutinho, et al., Safety and efficacy of aspirin, unfractionated heparin, both,

or neither during endovascular stroke treatment (MR CLEAN-MED): an open-label, multicentre, randomised controlled trial, Lancet 399 (10329) (2022 Mar 12) 1059–1069.
[10] A. Maino, F.R. Rosendaal, A. Algra, F. Peyvandi, B. Siegerink, Hypercoagulability is a stronger risk factor for ischaemic stroke than for myocardial infarction: a systematic review, PloS One 10 (8) (2015 Aug 7) e0133523.
[11] M.K. Schuhmann, J. Guthmann, G. Stoll, B. Nieswandt, P. Kraft, C. Kleinschnitz, Blocking of platelet glycoprotein receptor Ib reduces "thrombo-inflammation" in mice with acute ischemic stroke, J. Neuroinflammation 14 (1) (2017 Jan 21) 18.
[12] G. Baidildinova, M. Nagy, K. Jurk, P.S. Wild, H. Ten Cate, P.E.J. van der Meijden, Soluble platelet release factors as biomarkers for cardiovascular disease, Front Cardiovasc Med. 21 (8) (2021 Jun) 684920.
[13] L. Marquardt, A. Ruf, U. Mansmann, R. Winter, M. Schuler, F. Buggle, et al., Course of platelet activation markers after ischemic stroke, Stroke 33 (11) (2002 Nov) 2570–2574.
[14] S. Fateh-Moghadam, P. Htun, B. Tomandl, D. Sander, K. Stellos, T. Geisler, et al., Hyperresponsiveness of platelets in ischemic stroke, Thromb. Haemost. 97 (6) (2007 Jun) 974–978.
[15] L.M. de Lau, F.W. Leebeek, M.P. de Maat, P.J. Koudstaal, D.W. Dippel, Screening for coagulation disorders in patients with ischemic stroke, Expert Rev. Neurother. 10 (8) (2010 Aug) 1321–1329.
[16] M.D. Sfredel, E. Burada, B. Cătălin, V. Dinescu, G. Târtea, M. Iancău, et al., Blood coagulation following an acute ischemic stroke, Curr. Health Sci. J. 44 (2) (2018 Mar 27) 118–121.
[17] G.Y. Lip, Does atrial fibrillation confer a hypercoagulable state? Lancet 346 (8986) (1995 Nov 18) 1313–1314.
[18] H.M.H. Spronk, T. Padro, J.E. Siland, J.H. Prochaska, J. Winters, A.C. van der Wal, et al., Atherothrombosis and thromboembolism: position paper from the second Maastricht consensus conference on thrombosis, Thromb. Haemost. 118 (2) (2018 Feb) 229–250.
[19] O. Salomon, D.M. Steinberg, N. Koren-Morag, D. Tanne, U. Seligsohn, Reduced incidence of ischemic stroke in patients with severe factor XI deficiency, Blood 111 (8) (2008 Apr 15) 4113–4117.
[20] S.J. Donkel, B. Benaddi, D.W.J. Dippel, H. Ten Cate, M.P.M. de Maat, Prognostic hemostasis biomarkers in acute ischemic stroke, Arterioscler. Thromb. Vasc. Biol. 39 (3) (2019 Mar) 360–372.
[21] I. Induruwa, S.M. Jung, E.A. Warburton, Beyond antiplatelets: the role of glycoprotein VI in ischemic stroke, Int. J. Stroke 11 (6) (2016 Aug) 618–625.
[22] J.S. Gauer, C. Duval, R.G. Xu, F.L. Macrae, H.R. McPherson, C. Tiede, et al., Fibrin-glycoprotein VI interaction increases platelet procoagulant activity and impacts clot structure, J Thromb Haemost [Internet] (2022 Dec 22), https://doi.org/10.1016/j.jtha.2022.09.004. Available from.
[23] R.G. Xu, J.S. Gauer, S.R. Baker, A. Slater, E.M. Martin, H.R. McPherson, et al., GPVI (glycoprotein VI) interaction with fibrinogen is mediated by avidity and the fibrinogen αC-region, Arterioscler. Thromb. Vasc. Biol. 41 (3) (2021 Mar) 1092–1104.
[24] S.H. Yun, E.H. Sim, R.Y. Goh, J.I. Park, J.Y. Han, Platelet activation: the mechanisms and potential biomarkers, Biomed. Res. Int. 15 (2016) (2016 Jun) 9060143.
[25] C. Kleinschnitz, M. Pozgajova, M. Pham, M. Bendszus, B. Nieswandt, G. Stoll, Targeting platelets in acute experimental stroke: impact of glycoprotein Ib, VI, and IIb/IIIa blockade on infarct size, functional outcome, and intracranial bleeding, Circulation 115 (17) (2007 May 1) 2323–2330.
[26] P. Kraft, M.K. Schuhmann, F. Fluri, K. Lorenz, A. Zernecke, G. Stoll, et al., Efficacy and safety of platelet glycoprotein receptor blockade in aged and comorbid mice with acute experimental stroke, Stroke 46 (12) (2015 Dec) 3502–3506.
[27] T.T. Li, M.L. Fan, S.X. Hou, X.Y. Li, D.M. Barry, H. Jin, et al., A novel snake venom-derived GPIb antagonist, anfibatide, protects mice from acute experimental ischaemic stroke and reperfusion injury, Br. J. Pharmacol. 172 (15) (2015 Aug) 3904–3916.
[28] S. Goebel, Z. Li, J. Vogelmann, H.P. Holthoff, H. Degen, D.M. Hermann, et al., The GPVI-Fc fusion protein Revacept improves cerebral infarct volume and functional outcome in stroke, PloS One 8 (7) (2013 Jul 23) e66960.
[29] J.M.M. van Eeuwijk, D. Stegner, D.J. Lamb, P. Kraft, S. Beck, I. Thielmann, et al., The novel oral syk inhibitor, Bl1002494, protects mice from arterial thrombosis and thrombo-inflammatory brain infarction, Arterioscler. Thromb. Vasc. Biol. 36 (6) (2016 Jun) 1247–1253.
[30] B. Bigalke, K. Stellos, T. Geisler, S. Lindemann, A.E. May, M. Gawaz, Glycoprotein VI as a prognostic biomarker for cardiovascular death in patients with symptomatic coronary artery disease, Clin. Res. Cardiol. 99 (4) (2010 Apr) 227–233.
[31] B. Bigalke, K. Stellos, T. Geisler, E. Kremmer, P. Seizer, A.E. May, et al., Expression of platelet glycoprotein VI is associated with transient ischemic attack and stroke, Eur. J. Neurol. 17 (1) (2010 Jan) 111–117.
[32] I. Induruwa, H. McKinney, C. Kempster, P. Thomas, J. Batista, J.D. Malcor, et al., Platelet surface receptor glycoprotein VI-dimer is overexpressed in stroke: the glycoprotein VI in stroke (GYPSIE) study results, PloS One 17 (1) (2022 Jan 18) e0262695.
[33] T. Wurster, O. Poetz, K. Stellos, E. Kremmer, A. Melms, A. Schuster, et al., Plasma levels of soluble glycoprotein VI (sGPVI) are associated with ischemic stroke, Platelets 24 (7) (2013) 560–565.
[34] A. Ciccone, I. Abraha, I. Santilli, Glycoprotein IIb-IIIa inhibitors for acute ischaemic stroke, Cochrane Database Syst. Rev. (4) (2006 Oct 18) CD005208.
[35] R. Chaudhry, S.M. Usama, H.M. Babiker, Physiology, coagulation pathways, in: StatPearls. Treasure Island, StatPearls Publishing, FL, 2022.
[36] P.M. Rothwell, Atherothrombosis and ischaemic stroke, BMJ 334 (7590) (2007 Feb 24) 379–380.
[37] M. He, Z. Wen, X. He, S. Xiong, F. Liu, J. Xu, et al., Observation on tissue factor pathway and some other coagulation parameters during the onset of acute cerebrocardiac thrombotic diseases, Thromb. Res. 107 (5) (2002 Sep 1) 223–228.
[38] N. Mackman, R.E. Tilley, N.S. Key, Role of the extrinsic pathway of blood coagulation in hemostasis and thrombosis, Arterioscler. Thromb. Vasc. Biol. 27 (8) (2007 Aug) 1687–1693.
[39] S. Butenas, T. Orfeo, K.G. Mann, Tissue factor in coagulation: which? where? when? Arterioscler. Thromb. Vasc. Biol. 29 (12) (2009 Dec) 1989–1996.
[40] L. Spiezia, E. Campello, F.D. Valle, B. Woodhams, P. Simioni, Factor VIIa-antithrombin complex: a possible new biomarker for activated coagulation, Clin. Chem. Lab. Med. 55 (4) (2017 Mar 1) 484–488.
[41] M. Napolitano, S. Siragusa, G. Mariani, Factor VII deficiency: clinical phenotype, genotype and therapy, J Clin Med Res [Internet] 6 (4) (2017 Mar 28), https://doi.org/10.3390/jcm6040038. Available from.
[42] N. Mackman, Role of tissue factor in hemostasis, thrombosis, and vascular development, Arterioscler. Thromb. Vasc. Biol. 24 (6) (2004 Jun) 1015–1022.
[43] D.A. Manly, J. Boles, N. Mackman, Role of tissue factor in venous thrombosis, Annu. Rev. Physiol. 73 (2011) 515–525.
[44] A.P. Owens 3rd, N. Mackman, Role of tissue factor in atherothrombosis, Curr. Atheroscler. Rep. 14 (5) (2012 Oct) 394–401.
[45] L. Iacoviello, A. Di Castelnuovo, A. de Curtis, C. Agnoli, G. Frasca, A. Mattiello, et al., Circulating tissue factor levels and risk of stroke: findings from the EPICOR study, Stroke 46 (6) (2015 Jun) 1501–1507.
[46] L. Spiezia, V. Rossetto, E. Campello, S. Gavasso, B. Woodhams, D. Tormene, et al., Factor VIIa-antithrombin complexes in patients with arterial and venous thrombosis, Thromb. Haemost. 103 (6) (2010 Jun) 1188–1192.
[47] A. Słomka, M. Świtońska, W. Sinkiewicz, E. Żekanowska, Assessing circulating factor VIIa-antithrombin complexes in acute ischemic stroke: a pilot study, Clin. Appl. Thromb. Hemost. 23 (4) (2017 May) 351–359.
[48] J.C. Welch, K. Erkmen, N. Gentile, Changes in procoagulant blood biomarkers after mechanical thrombectomy, J. Stroke Cerebrovasc. Dis. 30 (6) (2021 Jun) 105772.
[49] S. Lopaciuk, J. Windyga, C.W. Watala, K. Bykowska, T. Pietrucha, H. Kwiecinski, et al., Polymorphisms in the factor VII gene and ischemic stroke in young adults, Blood Coagul. Fibrinolysis 21 (5) (2010 Jul) 442–447.
[50] N.C. Olson, L.M. Raffield, L.A. Lange, E.M. Lange, W.T. Longstreth Jr., G. Chauhan, et al., Associations of activated coagulation factor VII and factor VIIa-antithrombin levels with genome-wide polymorphisms and cardiovascular disease risk, J. Thromb. Haemost. 16 (1) (2018 Jan) 19–30.
[51] T.M. Stanne, E. Hanson, S. Olsson, J. Höglund, K. Jood, C. Blomstrand, et al., Factor VII antigen levels are differentially associated to etiological subtypes of ischaemic stroke, Thromb. Haemost. 110 (6) (2013 Dec) 1305–1306.
[52] S. Massberg, L. Grahl, M.L. von Bruehl, D. Manukyan, S. Pfeiler, C. Goosmann, et al., Reciprocal coupling of coagulation and innate immunity via neutrophil serine proteases, Nat. Med. 16 (8) (2010 Aug) 887–896.
[53] E. Laridan, F. Denorme, L. Desender, O. François, T. Andersson, H. Deckmyn, et al., Neutrophil extracellular traps in ischemic stroke thrombi, Ann. Neurol. 82 (2) (2017 Aug) 223–232.
[54] C. Kleinschnitz, G. Stoll, M. Bendszus, K. Schuh, H.U. Pauer, P. Burfeind, et al., Targeting coagulation factor XII provides protection from pathological thrombosis in cerebral ischemia without interfering with hemostasis, J. Exp. Med. 203 (3) (2006 Mar 20) 513–518.
[55] N.S. Key, Epidemiologic and clinical data linking factors XI and XII to thrombosis, Hematology Am. Soc. Hematol. Educ. Program 2014 (1) (2014 Dec 5) 66–70.
[56] T. Renné, M. Pozgajová, S. Grüner, K. Schuh, H.U. Pauer, P. Burfeind, et al., Defective thrombus formation in mice lacking coagulation factor XII, J. Exp. Med. 202 (2) (2005 Jul 18) 271–281.
[57] M. Pham, C. Kleinschnitz, X. Helluy, A.J. Bartsch, M. Austinat, V.C. Behr, et al., Enhanced cortical reperfusion protects coagulation factor XII-deficient mice from ischemic stroke as revealed by high-field MRI, Neuroimage 49 (4) (2010 Feb 15) 2907–2914.
[58] I. Hagedorn, S. Schmidbauer, I. Pleines, C. Kleinschnitz, U. Kronthaler, G. Stoll, et al., Factor XIIa inhibitor recombinant human albumin Infestin-4 abolishes occlusive arterial thrombus formation without affecting bleeding, Circulation 121 (13) (2010 Apr 6) 1510–1517.
[59] J. Krupka, F. May, T. Weimer, I. Pragst, C. Kleinschnitz, G. Stoll, et al., The coagulation factor XIIa inhibitor rHA-infestin-4 improves outcome after cerebral ischemia/reperfusion injury in rats, PloS One 11 (1) (2016 Jan 27) e0146783.
[60] P. Kraft, T. Schwarz, L. Pochet, G. Stoll, C. Kleinschnitz, COU254, a specific 3-carboxamide-coumarin inhibitor of coagulation factor XII, does not protect mice from acute ischemic stroke, Exp Transl Stroke Med. 2 (1) (2010 Feb 15) 5.
[61] P.Y. Leung, S. Hurst, M.A. Berny-Lang, N.G. Verbout, D. Gailani, E.I. Tucker, et al., Inhibition of factor XII-mediated activation of factor XI provides protection against experimental acute ischemic stroke in mice, Transl. Stroke Res. 3 (3) (2012 Sep) 381–389.
[62] B. Siegerink, F.R. Rosendaal, A. Algra, Antigen levels of coagulation factor XII, coagulation factor XI and prekallikrein, and the risk of myocardial infarction and ischemic stroke in young women, J. Thromb. Haemost. 12 (5) (2014 May) 606–613.
[63] J.L. Rohmann, S. Huo, P.S. Sperber, S.K. Piper, F.R. Rosendaal, P.U. Heuschmann, et al., Coagu- lation factor XII, XI, and VIII activity levels and secondary events after first ischemic stroke, J. Thromb. Haemost. 18 (12) (2020 Dec) 3316–3324.
[64] P. Kraft, C. Drechsler, I. Gunreben, P.U. Heuschmann, C. Kleinschnitz, Regulation of blood coagulation factors XI and XII in patients with acute and chronic

cerebrovascular disease: a case-control study, Cerebrovasc. Dis. 38 (5) (2014 Nov 21) 337–343.
[65] B. Siegerink, J.W.P. Govers-Riemslag, F.R. Rosendaal, H. Ten Cate, A. Algra, Intrinsic coagulation activation and the risk of arterial thrombosis in young women: results from the risk of arterial thrombosis in relation to Oral contraceptives (RATIO) case-control study, Circulation 122 (18) (2010 Nov 2) 1854–1861.
[66] M. Visser, S. Heitmeier, H. Ten Cate, H.M.H. Spronk, Role of factor XIa and plasma kallikrein in arterial and venous thrombosis, Thromb. Haemost. 120 (6) (2020 Jun) 883–993.
[67] E. Göb, S. Reymann, F. Langhauser, M.K. Schuhmann, P. Kraft, I. Thielmann, et al., Blocking of plasma kallikrein ameliorates stroke by reducing thromboinflammation, Ann. Neurol. 77 (5) (2015 May) 784–803.
[68] C. Storini, L. Bergamaschini, R. Gesuete, E. Rossi, D. Maiocchi, M.G. De Simoni, Selective inhibition of plasma kallikrein protects brain from reperfusion injury, J. Pharmacol. Exp. Ther. 318 (2) (2006 Aug) 849–854.
[69] Z. Zhang, C. Shen, M. Fang, Y. Han, C. Long, W. Liu, et al., Novel contact-kinin inhibitor sylvestin targets thromboinflammation and ameliorates ischemic stroke, Cell. Mol. Life Sci. 79 (5) (2022 Apr 13) 240.
[70] X. Wang, S. Kurowski, W. Wu, G.A. Castriota, X. Zhou, L. Chu, et al., Inhibition of factor XIa reduces the frequency of cerebral microembolic signals derived from carotid arterial thrombosis in rabbits, J. Pharmacol. Exp. Ther. 360 (3) (2017 Mar) 476–483.
[71] D. Gill, M.K. Georgakis, M. Laffan, M. Sabater-Lleal, R. Malik, I. Tzoulaki, et al., Genetically determined FXI (factor XI) levels and risk of stroke, Stroke 49 (11) (2018 Nov) 2761–2763.
[72] D. Appiah, O.E. Fashanu, S.R. Heckbert, M. Cushman, B.M. Psaty, A.R. Folsom, Relation of coagulation factor XI with incident coronary heart disease and stroke: the Cardiovascular Health Study, Blood Coagul. Fibrinolysis 28 (5) (2017 Jul) 389–392.
[73] H. Essa, A.M. Hill, G.Y.H. Lip, Atrial fibrillation and stroke, Card Electrophysiol Clin. 13 (1) (2021 Mar) 243–255.
[74] G. Maura, C. Billionnet, J. Coste, A. Weill, A. Neumann, A. Pariente, Non-bleeding adverse events with the use of direct oral anticoagulants: a sequence symmetry analysis, Drug Saf. 41 (9) (2018 Sep) 881–897.
[75] C. Martinez, C. Wallenhorst, S. Rietbrock, B. Freedman, Ischemic stroke and transient ischemic attack risk following vitamin K antagonist cessation in newly diagnosed atrial fibrillation: a cohort study, J. Am. Heart Assoc. 9 (2) (2020 Jan 21) e014376.
[76] R.G. Hart, L.A. Pearce, M.I. Aguilar, Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation, Ann. Intern. Med. 146 (12) (2007 Jun 19) 857–867.
[77] N.N. Hariharan, K. Patel, O. Sikder, K.S. Perera, H.C. Diener, R.G. Hart, et al., Oral anticoagu- lation versus antiplatelet therapy for secondary stroke prevention in patients with embolic stroke of undetermined source: a systematic review and meta-analysis, Eur. Stroke J. 7 (2) (2022 Jun) 92–98.
[78] T. Geisler, T. Keller, P. Martus, K. Poli, A. Kraft, F. Hoffmann, et al., Apixaban for TreatmenT of embolIC stroke of undetermined source - ATTICUS randomized trial - explorative analysis of AF burden in the ATTICUS cohort, Eur. Heart J. 9;44 (Supplement_2) (2023 Nov) ehad655.426.
[79] J. Zhang, X. Wang, X. Liu, T.B. Larsen, D.M. Witt, Z. Ye, et al., Comparative effectiveness and safety of direct acting oral anticoagulants in nonvalvular atrial fibrillation for stroke prevention: a systematic review and meta-analysis, Eur. J. Epidemiol. 36 (8) (2021 Aug) 793–812.
[80] D.O. Kleindorfer, A. Towfighi, S. Chaturvedi, K.M. Cockroft, J. Gutierrez, D. Lombardi-Hill, et al., 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association, Stroke 52 (7) (2021 Jul) e364–e467.
[81] K.R. McQuaid, L. Laine, Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials, Am. J. Med. 119 (8) (2006 Aug) 624–638.
[82] X. Liu, S. Guo, Z. Xu, Meta-analysis of oral anticoagulants and adverse outcomes in atrial fibrillation patients after intracranial hemorrhage, Front Cardiovasc Med. 15 (9) (2022 Jul) 961000.
[83] J. Bouget, F. Balusson, D. Viglino, P.M. Roy, K. Lacut, L. Pavageau, et al., Major bleeding risk and mortality associated with antiplatelet drugs in real-world clinical practice. A prospective cohort study, PLoS One 15 (8) (2020 Aug 7) e0237022.
[84] M. Sun, W. Cui, L. Li, Comparison of clinical outcomes between ticagrelor and clopidogrel in acute coronary syndrome: a comprehensive meta-analysis, Front Cardiovasc Med. 8 (2021) 818215.
[85] N.F. Chi, C.P. Wen, C.H. Liu, J.Y. Li, J.S. Jeng, C.H. Chen, et al., Comparison between aspirin and clopidogrel in secondary stroke prevention based on real-world data, J. Am. Heart Assoc. 7 (19) (2018 Oct 2) e009856.
[86] CAPRIE Steering Committee, A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee, Lancet 348 (9038) (1996 Nov 16) 1329–1339.
[87] M. Paciaroni, B. Ince, B. Hu, J.S. Jeng, K. Kutluk, L. Liu, et al., Benefits and risks of clopidogrel vs. aspirin monotherapy after recent ischemic stroke: a systematic review and meta-analysis, Cardiovasc. Ther. 1 (2019) (2019 Dec) 1607181.
[88] K. Bhatia, V. Jain, D. Aggarwal, M. Vaduganathan, S. Arora, Z. Hussain, et al., Dual antiplatelet therapy versus aspirin in patients with stroke or transient ischemic attack: meta-analysis of randomized controlled trials, Stroke 52 (6) (2021 Jun) e217–e223.
[89] Y. Wang, W. Chen, Y. Lin, X. Meng, G. Chen, Z. Wang, et al., Ticagrelor plus aspirin versus clopidogrel plus aspirin for platelet reactivity in patients with minor stroke or transient ischaemic attack: open label, blinded endpoint, randomised controlled phase II trial, BMJ 6 (365) (2019 Jun) l2211.
[90] J.S. Balami, P.M. White, P.J. McMeekin, G.A. Ford, A.M. Buchan, Complications of endo- vascular treatment for acute ischemic stroke: prevention and management, Int. J. Stroke 13 (4) (2018 Jun) 348–361.
[91] N. Matei, J. Camara, J.H. Zhang, The next step in the treatment of stroke, Front. Neurol. 11 (2020) 582605.
[92] M.A.H. Sonneveld, M.P.M. de Maat, M.L.P. Portegies, M. Kavousi, A. Hofman, P. L. Turecek, et al., Low ADAMTS13 activity is associated with an increased risk of ischemic stroke, Blood 126 (25) (2015 Dec 17) 2739–2746.
[93] A.S. Putzer, H. Worthmann, G.M. Grosse, F. Goetz, J. Martens-Lobenhoffer, M. Dirks, et al., ADAMTS13 activity is associated with early neurological improvement in acute ischemic stroke patients treated with intravenous thrombolysis, J. Thromb. Thrombolysis 49 (1) (2020 Jan) 67–74.
[94] F. Denorme, F. Langhauser, L. Desender, A. Vandenbulcke, H. Rottensteiner, B. Plaimauer, et al., ADAMTS13-mediated thrombolysis of t-PA-resistant occlusions in ischemic stroke in mice, Blood 127 (19) (2016 May 12) 2337–2345.
[95] K. South, O. Saleh, E. Lemarchand, G. Coutts, C.J. Smith, I. Schiessl, et al., Robust thrombolytic and anti-inflammatory action of a constitutively active ADAMTS13 variant in murine stroke models, Blood 139 (10) (2022 Mar 10) 1575–1587.
[96] M. Scully, P. Knöbl, K. Kentouche, L. Rice, J. Windyga, R. Schneppenheim, et al., Recombinant ADAMTS-13: first-in-human pharmacokinetics and safety in congenital thrombotic thrombocytopenic purpura, Blood 130 (19) (2017 Nov 9) 2055–2063.
[97] L.M. Asmis, A. Serra, A. Krafft, A. Licht, E. Leisinger, J. Henschkowski-Serra, et al., Recombinant ADAMTS13 for hereditary thrombotic thrombocytopenic purpura, N. Engl. J. Med. 387 (25) (2022 Dec 22) 2356–2361.
[98] J. Wilbs, X.D. Kong, S.J. Middendorp, R. Prince, A. Cooke, C.T. Demarest, et al., Cyclic peptide FXII inhibitor provides safe anticoagulation in a thrombosis model and in artificial lungs, Nat. Commun. 11 (1) (2020 Aug 4) 3890.
[99] D. Pawaskar, X. Chen, F. Glassman, F. May, A. Roberts, M. Biondo, et al., Pharmacokinetic/ pharmacodynamic modeling for dose selection for the first-in-human trial of the activated Factor XII inhibitor garadacimab (CSL312), Clin. Transl. Sci. 15 (3) (2022 Mar) 709–720.
[100] T. Craig, M. Magerl, D.S. Levy, A. Reshef, W.R. Lumry, I. Martinez-Saguer, et al., Prophylactic use of an anti-activated factor XII monoclonal antibody, garadacimab, for patients with C1-esterase inhibitor-deficient hereditary angioedema: a randomised, double-blind, placebo-controlled, phase 2 trial, Lancet 399 (10328) (2022 Mar 5) 945–955.
[101] M. Nagy, H. Ten Cate, What to expect from drug targeting factor XI? Cardiovasc. Res. 118 (10) (2022 Jul 27) e72–e74.
[102] P. Verhamme, B.A. Yi, A. Segers, J. Salter, D. Bloomfield, H.R. Büller, et al., Abelacimab for prevention of venous thromboembolism, N. Engl. J. Med. 385 (7) (2021 Aug 12) 609–617.
[103] J.P. Piccini, V. Caso, S.J. Connolly, K.A.A. Fox, J. Oldgren, W.S. Jones, et al., Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study, Lancet 399 (10333) (2022 Apr 9) 1383–1390.
[104] A. Shoamanesh, H. Mundl, E.E. Smith, J. Masjuan, I. Milanov, T. Hirano, et al., Factor XIa inhibition with asundexian after acute non-cardioembolic ischaemic stroke (PACIFIC-stroke): an international, randomised, double-blind, placebo-controlled, phase 2b trial, Lancet 400 (10357) (2022 Sep 24) 997–1007.
[105] A.G. Bayer, https://pharma.bayer.com, [cited 2024 Jan 10]. OCEANIC-AF Study Stopped Early Due to Lack of Efficacy, Available from: https://www.bayer.com/media/en-us/oceanic-af-study-stopped-early-due-to-lack-of-efficacy/, 2023.
[106] J.I. Weitz, J. Strony, W. Ageno, D. Gailani, E.M. Hylek, M.R. Lassen, et al., Milvexian for the prevention of venous thromboembolism, N. Engl. J. Med. 385 (23) (2021 Dec 2) 2161–2172.
[107] B. Gigante, H. Ten Cate, Factor XI inhibitors in patients with cardiovascular disease and a high risk of bleeding: a cautionary tale, Nat Rev Cardiol [Internet] (2023 Apr 5), https://doi.org/10.1038/s41569-023-00872-4. Available from.
[108] M. Bieber, M.K. Schuhmann, A.M. Kollikowski, D. Stegner, B. Nieswandt, M. Pham, et al., Targeting platelet glycoprotein VI attenuates progressive ischemic brain damage before recanalization during middle cerebral artery occlusion in mice, Exp. Neurol. 344 (2021 Oct) 113804.
[109] L. Renaud, K. Lebozec, C. Voors-Pette, P. Dogterom, P. Billiald, M. Jandrot Perrus, et al., Population pharmacokinetic/pharmacodynamic modeling of glenzocimab (ACT017) a glycoprotein VI inhibitor of collagen-induced platelet aggregation, J. Clin. Pharmacol. 60 (9) (2020 Sep) 1198–1208.
[110] C. Voors-Pette, K. Lebozec, P. Dogterom, L. Jullien, P. Billiald, P. Ferlan, et al., Safety and tolerability, pharmacokinetics, and pharmacodynamics of ACT017, an antiplatelet GPVI (glycoprotein VI) fab, Arterioscler. Thromb. Vasc. Biol. 39 (5) (2019 May) 956–964.
[111] M. Mazighi, A. Peeters, S. Richard, C. Molina, R. Lemmens, D. Toni, Y. Plétan, M. Jandrot-Perrus, A. Comenducci, G. Avenard, P. Lyrer, M. Kohrmann, ACTIMIS Study Group, ACTIMIS Trial: safety interim analysis data of glenzocimab, a novel antiplatelet agent on top of acute ischemic stroke standard of care, Res Pract Thromb Haemost. 5 (Suppl. 2) (2021).