Impaired Endogenous Fibrinolysis Status:

A Potential Prognostic Predictor in Ischaemic Stroke

Brief title: Impaired Endogenous Fibrinolysis In Ischaemic Stroke

Yang Chen, MBBS, MMS [a], Ying Gue, MBChB, PhD [a], Garry McDowell, PhD [a b]

Diana A. Gorog, MD, PhD [c d] Gregory Y.H. Lip, MD [a e]

From the [a]Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom; [b]School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool, United Kingdom; [c]School of Life and Medical Sciences, Postgraduate Medical School, University of Hertfordshire, United Kingdom; [d]Faculty of Medicine, National Heart and Lung Institute, Imperial College, London, United Kingdom; [e]Department of Clinical Medicine, Aalborg University, Denmark.

*Corresponding author: Dr Ying Gue, PhD. Liverpool Centre for Cardiovascular Science, William Henry Duncan Building, 6 West Derby St, Liverpool, Merseyside L7 8TX, United Kingdom. Phone/Fax: +44 (0) 1517064070. Email address: Y.Gue@liverpool.ac.uk

Abstract

Stroke confers a severe global healthcare burden, hence exploring risk factors for stroke occurrence and prognosis is important for stroke prevention and post-stroke management strategies. Endogenous fibrinolysis is a spontaneous physiological protective mechanism that dissolves thrombus to maintain vascular patency. Recently, impaired endogenous fibrinolysis has been considered as a potential novel cardiovascular risk factor, but its link with ischaemic stroke in the past has been underappreciated.

In this review, we summarise the latest mechanisms of endogenous fibrinolysis, review the current evidence and data on endogenous fibrinolysis in ischaemic stroke. It includes the structure of thrombus in ischaemic stroke patients, the effect of fibrin structure on the endogenous fibrinolytic efficiency, and the association between intravenous thrombolytic therapy and endogenous fibrinolysis in ischaemic stroke. It also includes the single factors (tissue plasminogen activator, urokinase plasminogen activator, plasminogen activator inhibitor-1, thrombin activatable fibrinolysis inhibitor, complement component 3, complement component 5, alpha-2-antiplasmin, plasmin-alpha-2-antiplasmin complex, and lipoprotein[a]), and the global assessments of endogenous fibrinolysis status (thromboelastography, rotational thromboelastometry, and global thrombosis test), and their potential as predictors to identify occurrence or unfavourable functional outcomes of ischaemic stroke.

All of these assessments present advantages and limitations, and we suggest that the global thrombosis test may be more appropriate for detecting impaired endogenous fibrinolysis status in ischaemic stroke patients.

Key Words Endogenous fibrinolysis; ischaemic stroke; risk factor; global thrombosis test

1. Introduction

Stroke is one of the most common and severe manifestations of cerebrovascular disease. More than 25% of adults over 25 will experience a stroke in their lifetime, and more than 110 million people worldwide have already experienced a stroke, with over 80% occurring in adults over 50 years old. This has been associated with huge mortality and morbidity burden on healthcare. In 2019, there were more than 12.2 million new strokes, 6.5 million stroke deaths, and over 143 million disability-adjusted life years from stroke. [1]

Thrombus formation is a complex multistep process involving platelet activation and aggregation, and procoagulant and fibrinolytic pathways. Impaired endogenous fibrinolysis may contribute to persistent thrombus, and therefore, assessment of endogenous fibrinolysis status might identify those at high-risk of IS or provide prognostic information to post-IS patients. Further evidence to support this is provided by observations of recurrent thrombotic events despite conventional antithrombotic therapy,[2] and a significant proportion of recurrent ischaemic events occurring in post ischaemic stroke (IS) patients despite antiplatelet therapy. [3]

In this review, we aim to review the evidence on impaired endogenous fibrinolysis in IS and its role in prognostication and risk stratification in post IS patients.

2. Mechanisms of Endogenous Fibrinolysis

Endogenous fibrinolysis is a spontaneous protective mechanism that promotes fibrin degradation and regulates thrombosis. Tissue-plasminogen activator (t-PA) or urokinase plasminogen activator (u-PA) first activates plasminogen, which then breaks down fibrin to generate fibrin degradation

products, ultimately clearing the thrombus and restoring blood flow. [4] Abnormal endogenous fibrinolysis implies disrupting the dynamic balance between thrombosis and thrombolytic capacity. If fibrinolysis is hyperactive, it will lead to a bleeding tendency; conversely, if it is impaired, it can promote thrombosis and vascular occlusion.

These are several factors which regulate endogenous fibrinolysis (shown in Figure 1):

(a) Thrombin indirectly inhibits fibrinolysis through activation of thrombin activatable fibrinolysis inhibitor (TAFI) on the one hand, [5] and upregulation of plasminogen activator inhibitor-1 (PAI-1) through protease activated receptors-1/4 (PAR-1/4) on the other. [6]

(b) Factor XIII (FXIII) can regulate fibrin pore size and density. Additionally, it cross-links fibrinolysis inhibitors with fibrin, thereby enhancing fibrinolysis resistance. [7]

(c) In addition to cross-linking with FXIII, alpha-2-antiplasmin (α2AP) as a plasmin inhibitor can enhance fibrinolytic resistance by binding to plasmin to form the plasmin-alpha-2-antiplasmin complex (PAP) and inhibiting plasmin adsorption to fibrin. [8]

(d) Lipoprotein(a) [Lp(a)] reduces fibrin production by increasing the synthesis of PAI-1 and competitively prohibiting the binding of plasminogen to fibrin. [9]

(e) The complement system inhibition of fibrinolysis is mediated by upregulation of PAI-1 expression by complement component 5a (C5a), [10] and binding C3 to β chain of fibrinogen. [11] Additionally, plasmin can cleave C5 to C5a, which in turn inhibits plasmin production. [12]

(f) Apart from the factors mentioned within the previous mechanisms, other inhibitors of fibrinogen conversion to fibrin or fibrin inhibitors are PAI-2, [13] protein C inhibitor, [14] protease nexin-1, [15] α2-macroglobulin, [16] and α1-antitrypsin. [17]

Platelets also play an important dynamic role from the initial thrombus formation. Platelets contain very large amounts of PAI-1 in the alpha granules, which is released upon platelet activation. [18]

The PAI-1 release from activated platelets is an important mediator of the impaired fibrinolysis in the local thrombotic milieu. In addition, platelets contribute an fibrinolysis resistance through clot contraction (thereby making the centre of the thrombus less accessible to fibrinolytic enzymes) and the release of fibrinolysis inhibitors. [19] Whyte *et al.* reported enhanced t-PA or u-PA-mediated fibrinolytic activity and enhanced fibrinogen binding on platelet membranes stimulated with thrombin/convulxin, and the presence of PAI-1 binding sites on the platelet surface was observed. [20]

4. IS Thrombus Composition

Atherosclerotic plaque formation, high-shear blood flow status due to stenosis, plaque rupture and endothelial dysfunction and subsequent thrombosis is the main cause of IS. [21] Due to the widespread use of mechanical vascular thrombectomy, researchers have evaluated thrombus composition in greater detail. Scanning electron microscopy reported that 80% of the thrombus samples from IS patients possessed a specific shell-nucleus structure, a dense shell wrapped around a loose red blood cell (RBC)-rich core with presence of fibrin, von Willebrand factor (VWF), and deoxyribonucleic acid (DNA) in the thrombus shell. [22] IS thrombus was highly heterogeneous compared to common platelet thrombus, with two distinct regions, that were red blood cell-rich/platelet-deficient/fibrin-deficient region and the red blood cell-deficient/platelet-rich/fibrin-rich region, the former consisting of a thin fibrin meshwork surrounded by a dense accumulation of red blood cells and a few uniformly distributed leukocytes, while the latter is more complex, with fibrin, VWF and DNA forming a dense scaffold structure filled with abundant platelets and a few erythrocytes. [23] Histological analysis of thrombus from IS patients demonstrated the presence of neutrophil-rich regions in IS thrombus, where neutrophil extracellular traps (NETs),

act as a scaffold for RBCs, platelets, and coagulation-associated factors, thereby promoting thrombus formation. [24]

Meglio and colleagues reported that the shell of thrombus from IS patients was insensitive to t-PA-induced lysis *in vitro*, [22] and no study has demonstrated the association between the dense external structure of thrombus and hypofibrinolysis in IS patients. In other thrombotic disorders, such as acute limb ischemia of unknown cause and trauma-related venous thromboembolism, impaired fibrinolysis and dense fibrin clots are associated with poorer response to treatment. [25] [26] Thus, it is possible that this particular shell in IS patients might be associated with impaired endogenous fibrinolysis and could further inhibit fibrinolysis, resulting in poorer outcomes. (shown in Central Illustration).

5. Treatment effects on endogenous fibrinolysis

There are various medical treatments for IS, some of which have direct and indirect pleiotropic effects on endogenous fibrinolysis [27] and can affect markers of endogenous fibrinolysis when measured.

Szegedi *et al.* reported a transient decrease in PAI-1 activity in IS patients immediately post intravenous thrombolysis ($P < 0.001$), while after 24 hours, PAI-1 was significantly elevated and higher than on admission ($P < 0.001$). [28] The initial decrease in PAI-1 activity may be due to the direct action of thrombolytics on the thrombus, which transiently reduces PAI-1 activity. However, the subsequent rise in PAI-1 levels may reflect the fact that the body may reduce excessive fibrinolysis activity by increasing PAI-1 activity, preventing bleeding and promoting vascular repair.

Apart from showing the effect of IVT, biomarkers of endogenous fibrinolysis can be used to predict outcomes. Elevated PAI-1 levels were associated with failed thrombolysis,[29] and predicts thrombolytic resistance. [30] Reduced Lp(a) was significantly associated with early recanalization. [30] Low α2AP antigen levels before thrombolysis was associated with the occurrence of higher 3-month mRS scores in acute IS patients. [31] These shows the potential role of fibrinolytic markers in the prediction of outcomes in patients presenting with IS treated with IVT.

Antithrombotics such as aspirin indirectly enhance endogenous fibrinolysis via acetylation of fibrinogen [32] whilst apixaban when used for stroke prevention in patients with atrial fibrillation had a stronger effect on enhancing endogenous fibrinolysis than aspirin, attributable to inhibition of thrombin generation. [33] Statins, which are commonly used to regulate lipid levels also have a potential beneficial impact on endogenous fibrinolysis via inhibiting PAI-1 expression in endothelial cells and increasing tPA expression in endothelial cells. [34]

Some emerging thrombolytic agents for the treatment of IS have recently emerged. For example, staphylokinase is a protein produced by staphylococci, and its greatest advantage over traditional thrombolytic agents is that it forms a complex with fibrinogen in the thrombus, activating the conversion of plasminogen to plasmin only specifically where the thrombus is present, thus effectively reducing the risk of bleeding.[35, 36] However, staphylokinase may cause an immune response in clinical application, and further studies are still needed.

7. Assessment of Endogenous Fibrinolysis in IS

Assessment of endogenous fibrinolysis can largely be divided into two main categories (Figure 2): firstly, measurements of single factors in the coagulation and fibrinolytic pathways and secondly,

assays of global endogenous fibrinolysis status, including viscoelastic tests like thromboelastography (TEG) or rotational thromboelastometry (ROTEM), and the Global Thrombosis Test (GTT).

7.1 Single factorial assessments of impaired Endogenous Fibrinolysis in IS

In this section, we included cross-sectional studies of differences in endogenous fibrinolysis single factors between IS and general controls, and prospective/retrospective studies assessing the relationship between endogenous fibrinolysis single factors and occurrence/prognosis of IS.

7.1.1 T-PA & u-PA

Past studies of t-PA, u-PA, and su-PAR with IS are summarised in Table 1. Given the abundance of studies in Table 1 and the fact that older studies may not reflect current clinical practice, we excluded studies before year 2000. In studies exploring the risk factors for IS, most studies in Table 1 have shown that, compared to healthy controls, IS patients had lower t-PA activity, t-PA antigen (actually detecting the formation of the t-PA/PAI-1 complex by rapid binding of newly released free t-PA to PAI-1), and high su-PAR levels. These show the potential for predicting IS in healthy patients using t-PA and su-PAR, but the relationship between su-PAR and endogenous fibrinolysis is unclear. In post-IS patients, t-PA, u-PA and su-PAR have been related to worse outcomes, which indicates a potential use as a biomaker in post-stroke management.

7.1.2 PAI-1

PAI-1 is a glycoprotein that primarily inhibits the functional activity of t-PA and u-PA, thereby inhibiting plasminogen activation and fibrinolysis. Besides inhibiting fibrinolysis, PAI-1 promotes

vascular remodelling, proliferation, migration and apoptosis of vascular smooth muscle cells, thus participating in the atherogenesis, which contributes to the development and progression of IS. [37] Despite PAI-1's multiple molecular conformations and the poor stability of prior assays for PAI-1 antigen or activity, most studies report a significant upregulation of PAI-1 expression in the IS population (also in the post-IVT IS patients) compared to healthy controls (Table 1), which supports the concept of impaired endogenous fibrinolysis in IS patients. Also, previous studies have shown that high PAI-1 levels are associated with IS occurrence and unfavourable prognosis post- IS.

Table 1. Studies (since 2000) to Assess the t-PA, u-PA, su-PAR and PAI-1 in IS.

First Author (Ref. #; year)	Population	Biomarker	Results
Incidence of IS			
Hoekstra *et al*. [38] (2003)	Subjects with unknown history of disease (n = 637)	PAI-1	Follow up was 7.8 years. PAI-1 activity was associated with incident stroke (lowest tertile as reference group; second tertile, RR: 4.9, 95% CI: 2.1-11.8; highest tertile, RR: 6.1, 95% CI: 2.5-14.6; P_{trend} = 0.001; adjusted for cardiovascular risk factors and other confounders).
Haapaniemi *et al.* [39] (2004)	IS patients (n = 55) vs. subjects without vascularand hematological disease (n = 55)	t-PA, PAI-1	t-PA antigen: IS at acute phase (11.2 ± 4.9 ng/ml) vs. controls (7.3 ± 2.9 ng/ml) , $P < 0.01$; No significant difference between the two groups at 1 week/1 month/ 3 months. PAI-1 activity: IS at acute phase (17.2 ± 7.8 AU/ml) vs. controls (11.8 ± 9.5 AU/ml), $P < 0.01$; IS at 3 months (15.8 ± 8.4 AU/ml) vs. controls (11.8 ± 9.5 AU/ml), $P < 0.005$; No significant difference between the two groups at 1 week/1 month.
Jian *et al.* [40] (2005)	IS patients (n = 60) vs. healthy subjects (n = 60)	t-PA, PAI-1	t-PA antigen: IS (12.4 ± 3.3 μg/l) vs. controls (6.6 ± 2.1 μg/l), $P < 0.0001$. t-PA activity: IS (1.1 ± 0.4 × 10^3 AU/l) vs. controls (2.0 ± 0.5 × 10^3 AU/l), $P < 0.0001$. PAI-1 activity: IS (22.7 ± 5.9 × 10^3 AU/l) vs. controls (12.7 ± 3.5 × 10^3 AU/l), $P < 0.0001$.
van Goor *et al.* [41] (2005)	IS patients (n = 124) vs. healthy subjects without a history of stroke (n = 125)	PAI-1	PAI-1 antigen was not a strong risk factor for ischemic stroke.
Smith *et al.* [42] (2005)	2208 subjects without a history of IS and cardiovascular disease	t-PA, PAI-1	Median of follow-up was 13.4 years. After adjustment for cardiovascular risk factors and other confounders, t-PA antigen and PAI-1 activity were not risk factors for IS.
Tuttolomondo *et al.* [43] (2009)	IS patients (n = 107) vs. subjects without IS (n = 102)	t-PA, PAI-1	t-PA antigen: IS [21 (10.55, 39) pg/ml] vs. controls [55 (29, 88) pg/ml], $P < 0.001$. PAI-1 antigen: IS [137 (99.5, 155) ng/ml] vs. controls [23 (11, 24) ng/ml], $P < 0.001$.
Biljana *et al.* [44] (2010)	IS patients (n = 60) vs. healthy subjects (n =	t-PA, PAI-1	t-PA antigen: IS (11.1 ± 7.1 ng/ml) vs. controls (6.2 ± 3.7 ng/ml), $P = 5.2\times10^{-5}$.

	30)		PAI-1 antigen: IS (48.5 ± 17.1 ng/ml) vs. controls (27.1 ± 10.1 ng/ml), $P = 6.2\times10^{-11}$.
Kario *et al*. [45] (2011)	Subjects (clinic blood pressure ≥ 140/90 mmHg) without a history of stroke	PAI-1	Mean of follow-up was 41 months. Highset quartiles of PAI-1 antigen was significantly associated with stroke (including ischaemic, haemorrhagic, and undefined storke) compared to the lower quartiles of PAI-1 (OR: 2.5, 95% CI: 1.3-4.6, $P < 0.01$, adjusted for cardiovascular risk factors and other confounders).
Pikula *et al.* [46] (2012)	Subjects without stroke (n = 3127)	PAI-1	Median of follow-up was 9.2 years. PAI-1 antigen was not associated with stroke.
An *et al.* [47] (2013)	Stroke patients (n = 188, including 175 acute IS patients) vs. stroke-mimic subjects (n = 90)	PAI-1	PAI-1 antigen was significantly associated with the risk of stroke (OR: 1.41, 95% CI: 1.08-1.85, $P = 0.012$, adjusted for cardiovascular risk factors and other confounders).
Persson *et al.* [48] (2014)	Healthy subjects without MI or stroke	su-PAR	Mean of follow-up was 14.9 years. The risk of IS was higher in the highest tertile of su-PAR compared to the lowest tertile of su-PAR (HR: 1.50, 95% CI: 1.06-2.11, $P < 0.05$, adjusted for cardiovascular risk factors and other confounders).
Akhter *et al.* [49] (2017)	IS patients (n = 100) vs. healthy subjects (n = 100)	PAI-1	PAI-1 antigen: IS (6.08 ± 3.78 ng/ml) vs. controls (4.92 ± 2.82 ng/ml), $P = 0.03$.
Prognosis of IS			
Haapaniemi *et al*. [50] (2000)	IS patients (n = 55)	PAI-1	Follow up was 3 months. PAI-1 (unknown type) was not a predictor for recurrent thrombosis post-IS.
Woodward *et al.* [51] (2005)	Patients with a history of stroke or TIA (n = 6105)	t-PA	Mean of follow-up was 3.9 years. t-PA (unknown type) was not associated with the risk of recurrent stroke.
Pedersen *et al.* [52] (2016)	IS patients (n = 548)	t-PA	Median of follow-up was 101 days. t-PA was an independent risk predictor for vascular death post-IS (HR: 1.27, 95 % CI: 1.00-1.61, $P = 0.047$, adjusted for cardiovascular risk factors and other confounders), but not associated with stroke recurrence and coronary events post-stroke.
Onatsu *et al.* [53] (2017)	IS patients with suspected	su-PAR	Follow-up was 5 years. suPAR was associated with 5-year mortality post-IS (HR: 1.60, 95% CI: 1.10-

	cardioembolic stroke (n = 117)		2.30, $P = 0.012$, adjusted for cardiovascular risk factors and other confounders).
Pedersen *et al.* [54] (2018)	IS patients (n = 268)	t-PA	Follow-up was 7 years. t-PA was not associated with long-term cognitive outcome (Barrow Neurological Institute Screen for Higher Cerebral Functions) post-IS.
Lasek-Bal *et al.* [55] (2019)	IS patients (n = 138)	u-PA	Plasma u-PA levels was significantly associated with mRS on the 30th days post-IS (OR = 0.102, 95% CI: 0.008-0.694, $P = 0.031$, adjusted for cardiovascular risk factors and other confounders).
Szegedi *et al.* [28] (2019)	IS patients receiving thrombolysis (n = 131)	PAI-1	PAI-1 activity on admission: ASPECTS (0-7) 24h after thrombolysis [3.43 (1.79-6.76) U/ml] vs. ASPECTS (8-10) 24h after thrombolysis [1.91 (1.38-3.79) U/ml], $P = 0.038$. PAI-1 antigen on admission: ASPECTS (0-7) 24h after thrombolysis [14.08 (7.61-26.31) ng/ml] vs. ASPECTS (8-10) 24h after thrombolysis [7.33 (3.99-20.24) ng/ml], $P = 0.041$. PAI-1 antigen 1h after thrombolysis: ASPECTS (0-7) 24h after thrombolysis [19.23 (6.15-43.63) ng/ml] vs. ASPECTS (8-10) 24h after thrombolysis [9.53 (3.99-18.91) ng/ml], P = 0.023. PAI-1 levels had no influence on long-term outcomes (sICH and mRS) post-IS.
Różański *et al.* [56] (2021)	IS patients (n = 51)	su-PAR	Follow-up points were 2-year and 3-year. suPAR on day 3 was associated with the mRS 2 years post-IS (r = 0.29, $P = 0.04$, unadjusted for cardiovascular risk factors). suPAR was not associated with 2-year mortality post-IS.
Śmiłowska *et al.* [57] (2022)	IS patients (n = 80)	su-PAR	suPAR on day 1 was associated with the NIHSS on day 1, 3, 7 (r = 0.48, 0.47, 0.41, respectively, all $P < 0.05$, unadjusted for cardiovascular risk factors); suPAR on day 3 was associated with the NIHSS on day 3 (r = 0.28, $P < 0.05$, unadjusted for cardiovascular risk factors); suPAR on day 1 was associated with the NIHSS on day 1 (r = 0.27, $P < 0.05$, unadjusted for cardiovascular risk factors). suPAR on day 1 and the suPAR on the day 3 were effective in predicting post-stroke in-hospital mortality (AUC: 0.80 and 0.89, respectively).

ASPECTS = alberta stroke programme early computed tomography score; CI = confidence interval; HR = hazard ratio; IS = ischaemic stroke; mRS = modified rankin scale; OR = odds ratio; PAI-1 = plasminogen activator inhibitor-1; sICH = symptomatic intracerebral hemorrhage; su-PAR = soluble urokinase plasminogen activator receptor; TIA = transient ischaemic attack; t-PA = tissue plasminogen activator; u-PA = urokinase plasminogen activator.

7.1.3 TAFI

TAFI is a glycoprotein that inhibits fibrinolysis by inhibiting t-PA-mediated plasminogen activation and down-regulating plasmin production in the fibrinolytic system in its active form, TAFIa. Most previous studies in Table 2 showed significantly higher TAFI expression in IS patients than in general controls. However, there were other studies with contradictory results, which may be due to the inconsistent TAFI measurements, for example, TAFI antigen is converted to TAFIa in the acute phase and thus will be lower in IS than in healthy controls. Current evidence suggests that higher TAFI is significantly associated with the occurrence of IS, higher mRS score and death 3-month post-IS.

Table 2. Studies to Assess the TAFI in IS.

First Author (Ref. #; year)	Population	Results
Incidence of IS		
Montaner *et al.* [58] (2003)	IS patients (n = 30) vs. healthy subjects (n = 30)	TAFI antigen: IS (158.4 ± 53.2%) vs. controls (105.6 ± 30.2%), $P < 0.001$. No relationship between TAFI antigen and worsened IS.
Santamaría *et al.* [59] (2003)	IS patients (n = 114) vs. subjects without a history of arterial disease (n = 150)	TAFIa: IS (113.7 ± 25.0%) vs. controls (102.6 ± 19.0%), $P < 0.05$. TAFIa > 120% was significantly associated with the risk of IS compared to TAFIa < 120%. (OR: 5.7, 95%CI: 2.3-14.1, $P < 0.05$, adjusted for cardiovascular risk factors and other confounders).
Leebeek *et al.* [60] (2005)	IS patients (n = 124) vs. subjects without stroke (n = 125)	Functional TAFI: IS (19.5 ± 4.2min) vs. controls (17.7 ± 3.7min), P = 0.0012. Functional TAFI levels were not significantly different between the acute (22.25 ± 4.0min) and convalescence phase (22.33 ± 3.9min). The clot lysis time in the presence of potato carboxypeptidase inhibitor was still increased after 3 months in IS patients (31.4 ± 0.3min) than controls (26.4 ± 0.24min), $P < 0.0001$. The highest quartile functional TAFI was significantly associated with the risk of IS compared to the lowest quartile (OR: 4.0, 95%CI: 1.6-9.8, P not given, adjusted for cardiovascular risk factors and other confounders).
Ladenvall *et al.* [61] (2007)	IS patients (n = 600) vs. healthy subjects (n = 600)	Intact TAFI and TAFI AP were significantly higher in IS patients than in control subjects during the acute phase and at 3 months of follow-up ($P < 0.001$), data not given. AP (OR: 2.22, 95% CI: 1.89-2.61, $P < 0.001$, adjusted for cardiovascular risk factors and other confounders) and intact TAFI (OR: 1.21, 95% CI: 1.06-1.38, $P < 0.01$, adjusted for cardiovascular risk factors and other confounders) were significantly associated with risk of IS at 3 months follow-up.
de Bruijne et al. [62] (2009)	Patients with IS or TIA (n = 109) vs. subjects without a history of arterial thrombosis (n = 332)	TAFIa: IS patients (145.8 ± 34.8%) vs. controls (137.5 ± 31.3%), P = 0.04; but TAFI-AP and intact TAFI were no difference between IS patients and controls.
Brouns *et al.* [63] (2010)	IS patients (n = 136)	Plasma TAFI levels from admission to 72 hours in patients with mRS score ≥ 3 compared with those with moderate prognoses (ΔTAFI 72h: 147 ± 168 vs. 127 ± 107 U/l, P < 0.001) and a positive correlation between mRS at 3 months and ΔTAFI 72h ($\rho = 0.30$, $P = 0.001$). ΔTAFI 72h was positively correlated with NIHSS score at admission and IS progression. ($r = 0.23$, $P = 0.010$; $\rho = 0.21$, $P = 0.021$).
Alessl *et al.* [64] (2016)	IS patients with non-thrombolysis (n = 68) vs. IS patients post-	TAFIa/ai at admission: non-thrombolysis IS [34.1 (2.6) ng/ml] vs. thrombolysis IS [30.3 (2.6) ng/ml] vs. controls [22.6 (1.58) ng/ml], P not given.

	thrombolysis vs. subjects without stroke (n was unknown)	TAFI antigen at admission: non-thrombolysis IS [10.15 (0.24) μg/ml] vs. thrombolysis IS [10.92 (0.55) μg/ml] vs. controls [13.05 (0.56) μg/ml], *P* not given. Total TAFI zymogen at admission: non-thrombolysis IS [100.5 (2.30) %] vs. thrombolysis IS [100.6 (3.93) %] vs. controls [106.6 (3.51) %], *P* not given. TAFIa/ai was higher in higher severity patients (NIHSS > 7 or mRS >= 2) than in lower severity patients on admission or within 90 days of admission in either non-thrombolysis IS or thrombolysis IS (all P < 0.05).
Dai et al. [65] (2017)	IS patients (n = 180) and healthy subjects (n = 128)	TAFI was higher in IS patients than in controls (*P* = 0.036). Only the third quartile of TAFI was associated with the risk of IS (OR: 2.34, 95% CI: 1.16-4.74, *P* = 0.018) compared to the first quartile of TAFI. With the increase of TAFI, the risk of IS first increased and then decreased.
Mertens *et al.* [66] (2018)	Patients with IS or TIA (n = 72) vs. subjects without stroke, an intact BBB and no apparent abnormalities in biochemical and microbiological tests (n = 32)	TAFI levels in the CSF: IS/TIA patients [4.36 (0.23) U/l] vs. controls [3.50 (0.23) U/l], *P* < 0.05.
Prognosis of IS		
Pedersen et al. [52] (2016)	IS patients (n = 548)	Median of follow-up was 101 days. TAFI AP was not associated with stroke recurrence, vascular death and coronary events post-IS.
Mertens *et al.* [66] (2018)	Patients with IS or TIA (n = 72)	CSF/plasma TAFI ratio was significantly associated with stroke progression (ρ = 0.30, *P* < 0.01, unadjusted for cardiovascular risk factors), mRS at 3 months post-IS (ρ = 0.30, *P* < 0.05, unadjusted for cardiovascular risk factors), and 3-month mortality (ρ = 0.31, *P* < 0.01, unadjusted for cardiovascular risk factors), but not with stroke severity or recurrence.

AP = activation peptide; CI = confidence interval; CSF = cerebrospinal fluid; IS = ischaemic stroke; mRS = modified rankin scale; NIHSS = National Institutes of Health Stroke Scale; OR = odds ratio; TAFI = thrombin activatable fibrinolysis inhibitor; TIA = transient ischaemic attack.

7.1.4 Complement C3 & C5

The complement system plays an essential role in the body, including humoral immunity, cell lysis, cleavage of immune complexes and inhibition of fibrinolysis. The involvement of the complement system in the development and progression of IS is probably due to its role in promoting endothelial cell activation, stimulating the release of cytokines from smooth muscle cells, promoting plaque rupture and inhibiting macrophage apoptosis. [67] Most studies in Table 3 show that C3/C3a and C5/C5a are significantly higher in IS patients than in healthy controls, and C3 is a potential predictor of death or major disability post-IS.

7.1.5 α2AP & PAP

α2AP is a glycoprotein that is the most potent plasma protein inhibitor, accounting for approximately 90% of plasma protein inhibition. It binds to plasmin to produce PAP and inhibits chymotrypsin at adjacent overlapping sites. The limited studies in Table 3 revealed that despite variations in PAP expression in IS patients of different etiologies, PAP is significantly increased in IS patients compared to general controls, which supports that plasmin is being generated and subsequently inhibited by α2AP. However, α2AP activity was not significantly different between IS and controls before or after thrombolysis. One of these studies reported low levels of α2AP antigen before thrombolysis was the predictor of 3-month unfavourable prognosis (mRS score ≥ 3) in IS.

Table 3. Studies to Assess the Complement C3, Complement C5, α2AP and PAP in IS.

First Author (Ref. #; year)	Population	Biomarker	Results
Incidence of IS			
Ono *et al.* [68] (1991)	IS patients (n = 98) vs. healthy subjects (n = 50)	PAP	PAP: IS (1.00 ± 0.05 μg/ml) vs. controls (0.63 ± 0.05 μg/ml), $P < 0.01$.
Uchiyama *et al.* [69] (1997)	Patients with CEI (n = 23) vs. patients ATI (n = 10) vs. patients LI (n = 12) vs. control subjects (details unknown, n = 27)	PAP	PAP: CEI (2.2 ± 3.5 μg/ml) vs. controls (0.8 ± 0.4 μg/ml, $P < 0.05$). No significant difference between ATI or LI and controls.
Kataoka *et al.* [70] (2000)	Patients with CEI (n = 38) vs. patients with ATI (n = 41) vs. patients with LI (n = 58) vs. subjects without cerebrovasular disease (n = 32)	PAP	At <48 hours, 1 week and 3 weeks, changes in PAP was significantly higher in ATI and CEI groups than in control subjects (ATI vs. controls: $P < 0.05$ for < 48h, $P < 0.001$ for 1 week, $P < 0.001$ for 3 weeks; CEI vs. controls: $P < 0.0001$ for <48h, $P < 0.0001$ for 1 week, $P < 0.001$ for 3 weeks). LI group might have a higher PAP than controls at < 48 hours, 1 week and 3 weeks, but P was not given.
Mocco *et al.* [71] (2006)	IS patients (n = 16) vs. subjects without stroke (n = 16)	C3, C5	C3a was higher in IS patients than in controls on post-IS day 1, 3, 7, 28 (day 1: 1609 ± 422 ng/ml, $P = 0.0008$; day 3: 1520 ± 317 ng/ml, $P = 0.0005$; day 7: 1526 ± 386 ng/ml, $P = 0.001$; day 28: 1448 ± 386 ng/ml, $P = 0.004$; controls: 1080 ± 189 ng/ml); but not on post-IS day 2, 14, 21. C5a was significantly higher in IS patients than in controls on post-IS day 7, 14 (day 7: 6.86 ± 3.5 ng/ml, $P = 0.005$; day 14: 7.65 ± 4.6 ng/ml, $P = 0.004$; controls: 3.33 ± 2.1 ng/ml), but not on post-IS days 1, 2, 3, 21, 28.
Engström *et al*. [72] (2007)	Healthy men at baseline (n = 5850)	C3	Mean of follow up was 18.2 years. After adjustments for cardiovascular risk factors and other confounders, C3 was not associated with IS.
Cojocaru *et al.* [73] (2008)	IS patients (n = 179) vs. healthy subjects (n = 156)	C3	C3 was significantly higher in IS patients than in controls at <24 hours, 48-72 hours and at discharge [<24 h: 1.49 ± 0.24 ($P < 0.05$), 48-72h: 1.58 ± 0.27 ($P < 0.01$), at hospital discharge: 1.66 ± 0.28 ($P < 0.001$), controls: 1.42 ± 0.38].

Skalny *et al.* [74] (2017)	IS patients (n = 30) vs. healthy subjects (n = 30)	C3a	C3a: IS [5.68 (2.12, 11.39) g/l] vs. controls [1.3 (1.15, 1.56) g/l], $P < 0.001$.
Prognosis of IS			
Yang *et al.* [75] (2021)	IS patients (n = 3405)	C3	The highest tertile C3 was significantly associated with an increased risk of 3 months death or major disability post-IS compared to the lowest tertile (OR: 1.30, 95% CI: 1.02-1.65; *P*-trend = 0.038, adjusted for cardiovascular risk factors and other confounders); Log-transformed C3 was associated with risk of death or major disability post-IS (HR: 1.13, 95% CI: 1.02-1.25, *P* not given, adjusted for cardiovascular risk factors and other confounders).
Székely *et al.* [31] (2022)	IS patients undergoing thrombolysis (n = 421)	α2AP	α2AP antigen was significantly associated with unfavorable outcome 90-day post-IS (mRS score: 3-6; hightest quartile as reference group; lowest quartile, OR: 2.10, 95% CI: 1.21-3.66, $P = 0.008$; adjusted by hyperlipidemia, BMI, diabetes mellitus, sex, and CRP) and mortality 3-month post-IS (mRS score: 6; hightest quartile as reference group; lowest quartile, OR: 2.22, 95% CI: 1.15-4.31, $P = 0.018$; adjusted by hyperlipidemia, BMI, diabetes mellitus, sex, and CRP). But further adjustments for age and NIHSS, the effects of α2AP were not significant.

α2AP = α2-Antiplasmin; ATI = atherothrombotic infarcts; BMI = body mass index; C3/5 = complement component 3/5; CI = confidence interval; CEI = cardioembolic infarcts; CRP = C-creative protein; HR = hazard ratio; IS = ischaemic stroke; LI = lacunar infarcts; mRS = modified rankin scale; NIHSS = National Institutes of Health Stroke Scale; OR = odds ratio; PAP = plasmin-alpha-2-antiplasmin; TIA = transient ischaemic attack.

7.1.6 Lp (a)

Lp(a) is a macromolecular complex with a partial structure similar to plasminogen that competitively inhibits plasminogen activation, reduces plasmin production and ultimately inhibits the endogenous fibrinolysis. As there are abundant studies on Lp(a) and IS in the past, we only included studies with a larger sample size of over 1000. As seen in Table 4, Lp(a) has the potential as a prognostic biomarker for IS, as most previous studies have shown that Lp(a) is highly expressed in IS patients compared to general controls and higher Lp(a) is significantly associated with stroke recurrence, unfavourable functional outcome post-IS.

Table 4. Studies (over 1000 samples) to Assess the Lp(a) in IS.

First Author (Ref. #; year)	Population	Results
Incidence of IS		
Ohira *et al*. [76] (2006)	Subjects without clinical cardiovascular disease (n = 14221)	Mean of follow up was 13.5 years. Lp(a) ≥ 300 ug/ml had higher risk of IS compared to Lp(a) < 100 ug/ml in black women (RR:1.84, 95% CI: 1.05-3.20, $P < 0.05$, adjusted for cardiovascular risk factors and other confounders) and in white women (RR:2.42, 95% CI: 1.30-4.53, $P < 0.05$, adjusted for cardiovascular risk factors and other confounders).
Wiberg *et al*. [77] (2006)	Healthy male subjects (n = 2313)	Median of follow up was 29.3 years. Lp(a) was significantly associated with IS (HR: 1.12, 95% CI: 1.01-1.26, $P < 0.05$, adjusted for cardiovascular risk factors and other confounders).
Virani *et al*. [78] (2012)	Subjects without clinical cardiovascular disease (n = 15792)	Follow up was 20 years. Lp(a) > 24mg/dl had higher risk of IS compared to Lp(a) ≤ 6.1 mg/dl in African Americans (HR: 1.60, 95% CI: 1.10-2.34, $P = 0.0004$, adjusted for cardiovascular risk factors and other confounders), but not in Caucasians. Log-transformed Lp(a) was significantly associated with IS in African Americans (HR: 1.21, 95% CI: 1.06-1.39, $P < 0.05$, adjusted for cardiovascular risk factors and other confounders).
Aronis *et al*. [79] (2017)	Subjects without stroke (n = 10127)	Median of follow up was 15.8 years. In subjects without AF, Lp(a) > 50 mg/dl had higher risk of IS compared to Lp(a) ≤ 10 mg/dl (HR: 1.42, 95% CI: 1.07-1.90, $P < 0.05$, adjusted for cardiovascular risk factors and other confounders), but Lp(a) was not associated with IS in subjects with AF.
Langsted *et al*. [80] (2019)	Subjects without IS (n = 48022)	Follow up was unclear. Lp(a) > 93 mg/dl had higher risk of IS compared to Lp(a) < 10mg/dl (HR: 1.60, 95% CI: 1.24-2.05, $P < 0.05$, adjusted for cardiovascular risk factors and other confounders). The risk of IS was significantly higher for every 50mg/dl Lp (a) level (OR: 1.20, 95% CI: 1.13-1.28, $P < 0.05$, adjusted for cardiovascular risk factors and other confounders).
Fu *et al*. [81] (2020)	IS patients (n= 1953) vs. healthy subjects (n = 1953)	Log-transformed Lp(a) was significantly associated with IS (lowest quartile as reference group; second quartile, HR: 1.74, 95% CI: 1.30-2.33; third quartile, HR: 1.98, 95% CI: 1.47-2.68; fourth quartile, HR: 1.88, 95% CI: 1.40-2.53; all $P < 0.001$, adjusted for cardiovascular risk factors and other confounders).
Patel *et al*. [82] (2021)	Healthy subjects without atherosclerotic coronary artery disease (n =	Median of follow up was 11.2 years. Lp(a) ≥ 70mg/dl was significantly associated with IS (OR: 1.16, 95% CI: 1.07-1.25, $P < 0.0001$, adjusted for cardiovascular risk factors and other confounders).

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Simony *et al*. [83] (2022)	General population (n = 70042)	Follow up was unclear. No significant difference in the risk of IS with Lp(a) > 40 mg/dl compared to Lp(a) < 10 mg/dl.
Littmann *et al*. [84] (2022)	Healthy subjects (n = 23398)	Follow up was 14 years. No significant association between Lp(a) and IS.
Prognosis of IS		
Jiang *et al*. [85] (2021)	IS patients (n = 9709)	For 3 months post-IS, the third and fourth quartile of Lp(a) were significantly associated with an increased risk of patients with mRS score ≥ 3 (lowest quartile as reference group; third quartile, OR: 1.24, 95% CI: 1.03-1.50; fourth quartile, OR: 1.33, 95% CI: 1.11-1.61; both $P < 0.05$, adjusted for cardiovascular risk factors and other confounders). For 1 year post-IS, only the fourth quartile of Lp(a) was significantly associated with an increased risk of patients with mRS score ≥ 3 (lowest quartile as reference group; fourth quartile, OR: 1.25, 95% CI: 1.04-1.51, $P < 0.05$, adjusted for cardiovascular risk factors and other confounders).
Arnold *et al*. [86] (2021)	IS patients (n=1732)	Lp(a) ≥ 100 nmol/L was not associated with 1-year recurrent stroke post-IS, but it was predictive of 1-year recurrent stroke in the large-artery atherosclerosis IS (HR: 2.18, 95% CI: 1.08-4.40, $P = 0.03$, adjusted for cardiovascular risk factors and other confounders) and in the IS aged <60 (HR: 2.40, 95% CI: 1.05-5.47, $P = 0.04$, adjusted for cardiovascular risk factors and other confounders).
Xu *et al*. [87] (2022)	Patients with IS or TIA (n = 9899)	Lp(a) ≥ 50 mg/dL had higher risk of 1-year stroke recurrence compared to Lp(a) < 50 mg/dL (HR:1.20, 95% CI: 1.02-1.42, $P < 0.05$, adjusted for cardiovascular risk factors and other confounders).

CI = confidence interval; HR = hazard ratio; IS = ischaemic stroke; Lp(a) = lipoprotein(a); mRS = modified rankin scale; OR = odds ratio; RR = relative risk;

TIA = transient ischaemic attack.

7.1.7 Other Potential Biomarkers

Endothelial glycocalyx (eGC) is proteoglycan complexes covering the surface of endothelial cells, and increased evidence suggests that eGC is associated with cardiovascular diseases. Syndecan-1 belongs to the eGC biomarkers, and elevated syndecan-1 indicates endothelial injury, which may relate to thrombosis and endogenous fibrinolysis. Ostrowski et al. showed that elevated syndecan-1 was independently associated with hypocoagulable status as assessed by TEG in a severe sepsis cohort ($\beta = 0.64$, $P = 0.013$, adjusted for confounders). [88] Zhao et al. reported that syndecan-1 was independently associated with poor prognosis (mRS:3-6) after 3 months in IS patients with thrombolysis (OR: 1.024, 95% CI: 1.010-1.038, $P < 0.05$, adjusted for cardiovascular risk factors and other confounders). [89] However, other eGC biomarkers such as syndecan-4 has been shown to associate with annexin A2, which connects to t-PA and thus affects the endogenous fibrinolysis, [90] but no relevant clinical study. Although eGC biomarkers may be associated with thrombosis and endogenous fibrinolysis, their role in ischaemic stroke requires further observation.

7.2 Global assessments of impaired endogenous fibrinolysis in IS

Single factors are measured directly to evaluate their contribution to the fibrinolytic system, but they are interrelated, hence comprehensive assessments for global endogenous fibrinolysis status are required. In this section, we discuss studies on the differences in metrics of endogenous fibrinolysis global assessments between IS and general controls, and its role in prognosis in patients post IS.

7.2.1 Thromboelastography & Rotational thromboelastometry

TEG is a point-of-care viscoelastic method that assesses clot formation and endogenous fibrinolysis by simulating the coagulation process of blood in vivo under static coagulation conditions, whilst ROTEM is considered a modern modification of the TEG technique, with the main difference being that the needle, rather than the cup, is subjected to a constant rotational force. [91] The Lysis 30 (LY30) indicate the percentage reduction in clot stability 30 minutes from the start of the maximal amplitude of the TEG graph, which is commonly used for assessing endogenous fibrinolysis status. Table 5 shows that the available publications suggest that LY30 is affected by thrombolysis, but there is no significant relationship between LY30 and the incidence and prognosis of IS, either in non-thrombolysis or thrombolysis IS patients. There was only one study where ROTEM was applied in IS cohort, and no significant association was found between and the incidence/prognosis of IS.

Table 5. Studies using TEG and ROTEM to assess endogenous fibrinolysis status in IS.

First Author (Ref. #; year)	Population	Measurement tools	Results
Incidence of IS			
Elliott *et al.* [92] (2015)	Pre-thrombolysis IS patients (n = 49) vs. post-thrombolysis IS patients (n = 30) vs. healthy subjects (n = 49)	TEG	LY30 was undetectable in controls. LY30: pre-thrombolysis IS [0 (0-0.4)%] vs. post-thrombolysis IS [94.4 (15.2-95.3)%], $P < 0.0001$.
Stanford et al. [93] (2015)	IS patients without thrombplysis at baseline (n = 72) vs. healthy subjects (n = 71)	ROTEM	ML was not significantly different between IS patients and controls.
Bliden *et al.* [94] (2019)	IS patients without thrombolysis (n = 30) vs. stroke mimic (n = 31)	TEG	LY30 was not significantly different in the IS patients and stroke mimic.
Prognosis of IS			
Stanford et al. [93] (2015)	IS patients with thrombolysis (n = 22)	ROTEM	ML is not associated with the difference in 24-hour NIHSS scores in IS patients post-thrombolysis.
McDonald *et al*. [95] (2016)	IS patients with thrombolysis (n = 141)	TEG	LY30 was not significantly different in the presence/absence of rapid clinical improvement (an eight point decrease on NIHSS or total NIHSS of 0, 1 at 36 h), presence/absence of hemorrhagic transformation, and presence/absence of hyperdense middle cerebral artery sign on imaging, respectively.
Shi *et al.* [96] (2018)	IS patients without thrombolysis (n = 246)	TEG	There was no significant difference in LY30 between IS patients with or without early neurological deterioration (an increase in the NIHSS compared with the baseline NIHSS) within 3 days after admission.
Wiśniewski *et al.* [97] (2021)	IS patients without thrombolysis (n = 40)	TEG	LY30 was not significantly different between large (>2cm^3) and small (<2cm^3) infarcts post-IS.

IS = ischaemic stroke; LY30 = lysis 30; NIHSS = National Institutes of Health Stroke Scale; ROTEM = rotational thromboelastometry; TEG = thromboelastography.

7.2.3 Global thrombosis test (GTT)

Although TEG and ROTEM have overcome the shortcomings of single factorial assessments, but they focus primarily on the coagulation function of the blood (such as thrombosis and coagulation strength) and simulate low-shear conditions in which fibrinolysis is relatively limited, hence their sensitivity to fibrinolytic capacity is low. [98] The GTT which utilises the principles of high shear to assess thrombotic potential and endogenous fibrinolysis (Figure 3) is likely more applicable in evaluating endogenous fibrinolysis status, particularly within the arterial system. In short, blood passes through narrow gaps between ceramic balls generating high shear rate resulting in platelet activation and subsequent thrombus formation, indicated by occlusion time (OT). Following endogenous fibrinolytic activity, rebleeding through the thrombus occurs which is detected by a photosensor to indicate lysis time (LT).

There are limited studies of GTT in IS. Taomoto *et al.* using GTT to assess the thrombotic status of stroke patients (including haemorrhagic stroke patients) showed that longer LT ($P < 0.0001$) and shorter OT ($P < 0.0001$) in stroke patients compared to normal controls and LT in lacunar infarction or atherosclerotic infarction patients were higher than that in overall stroke patients. [99] However in patients with acute coronary syndrome (ACS), endogenous fibrinolysis has shown promise in being an independent risk predictor of future adverse events. [100] Given the similarities between the pathophysiology of IS and ACS, there may be potential for endogenous fibrinolysis assessed via GTT to provide prognostic information in patients with ischemic stroke.

8. Endogenous fibrinolysis and AF

One of the main causes of stroke is AF and being able to identify AF early prevents stroke. This is even more important in patients post- IS as identification of AF would allow initiation of treatment to prevent future stroke from AF. The assessment of endogenous fibrinolysis in patients with AF whilst not discussed in this review is an important aspect in stroke prevention and needs to be considered as well in future studies.

9. Conclusions and perspectives

Based on the recent exploration of the microstructure of thrombus and substantial clinical studies in IS patients, impaired endogenous fibrinolysis is likely prevalent among IS patients and may have a role in prognostication. Due to the inherent limitations of single factorial assessment in complex, dynamic fibrinolytic process, assessment of the endogenous fibrinolysis in patients with IS with global assays may be beneficial in terms of identifying high risk patients which may translate to improvement in initial treatment, follow up and subsequent management of these patients.

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Figure 1. IS Thrombus Structure and Mechanisms of Endogenous Fibrinolytic System. α2AP, alpha-2-antiplasmin; C5, complement component 5; DNA, deoxyribonucleic acid; EC, endothelial cell; FXIII, Factor XIII; Lp(a), lipoprotein(a); PAI-1/2, plasminogen activator inhibitor-1/2; PAP, plasmin-alpha-2-antiplasmin complex; PAR-1/4, protease activated receptors-1/4; PCI, protein C inhibitor; PN-1, protease nexin-1; RBC, red blood cell; TAFI, thrombin activatable fibrinolysis inhibitor; t-PA, tissue plasminogen activator; u-PA, urokinase plasminogen activator; VWF, von Willebrand factor; WBC, white blood cell.

Figure 2. Simplified assessment flowchart for endogenous thrombolytic activity.
α2AP, alpha-2-antiplasmin; C3, complement component 3; C5, complement component 5; EPL, estimated percentage of lysis; GTT, global thrombosis test; LI60, lysis index at 60 minutes; Lp(a), lipoprotein(a); LT, lysis time; LY30, lysis at 30 minutes; ML, maximum lysis; mRS, modified rankin scale; PAI-1, plasminogen activator inhibitor-1; PAP, plasmin-alpha-2-antiplasmin complex; ROTEM, thromboelastometry; su-PAR, soluble urokinase plasminogen activator receptor; TAFI, thrombin activatable fibrinolysis inhibitor; TEG, thromboelastogram; t-PA, tissue plasminogen activator; u-PA, urokinase plasminogen activator.

Figure 3. The structure, principle and operation of the GTT-2. ADP, adenosine diphosphate; EF, endogenous fibrinolysis; GTT, global thrombosis test; LT, lysis time; OT, occlusion time; TXA2, thromboxane A2.