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Thrombus composition and efficacy of thrombolysis and thrombectomy in acute ischaemic stroke

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Abstract

Thrombi retrieved from patients with acute ischaemic stroke (AIS) are highly heterogeneous. Recent data suggest that thrombus composition may impact on mechanical thrombectomy, the number of recanalization manoeuvres, resistance to retrieval, and on thrombolytic potential. Our aim was to summarise evidence describing the impact of thrombus composition on efficacy of mechanical thrombectomy and thrombolysis in patients with AIS. The scoping review methodology guided by the Joanna Briggs Institute, an adaption of the Arksey and O'Malley, was followed. Comprehensive searches were conducted in MEDLINE, EMBASE, SCOPUS and Web of Science. Articles were classified into four key themes: (i) composition of stroke thrombi; (ii) thrombus composition and mechanical thrombectomy; (iii) thrombus composition and thrombolytic therapy; (iv) novel imaging and endovascular approaches. Our search identified 698 articles published from 1987 to June 2020. Additional articles were extracted from reference lists of the selected articles. Overall, 95 topic-specific articles identified for inclusion published in 40 different journals were included. Reports showed that thrombus composition in stroke was highly heterogeneous, containing fibrin, platelets, red blood cells (RBC), von Willebrand Factor (vWF), and neutrophil extracellular traps. Thrombi could roughly be divided in fibrin- and RBC-rich clots. Fibrin-rich clots were associated with increased recanalization manoeuvres, longer procedure time and less favourable clinical outcomes compared RBC-rich clots. Advances in detection or treatment of thrombi that take into account clot heterogeneity may be able to improve future endovascular and thrombolytic treatment of stroke.

Non-standard Abbreviations and Acronyms

AIS: acute ischaemic stroke

RBC: red blood cell

tPA: tissue plasminogen activator

vWF: von Willebrand factor

Introduction

Stroke is the second leading cause of mortality and third leading cause of disability worldwide.[1] Acute ischaemic stroke (AIS), one of the two main subtypes of stroke, occurs due to brain ischaemia as a result of thrombosis of a cerebral blood vessel.[2] Even though someone dies of stroke every 4 minutes in the United States, little was previously known about the general composition and structural organization of the occlusive thrombi, due to unavailability of thrombus material.[3] However, in recent years, advancements in retrieval of stroke thrombi using thrombectomy devices such as stent retrievers and aspiration catheters has allowed for detailed analysis of the morphological and histological composition of stroke thrombi.[4]

Prior to the introduction of mechanical thrombectomy devices, thrombolysis using intravenous tissue plasminogen activator (tPA) was the only approved recanalization therapy for AIS; however due to several contraindications including its narrow treatment window, it could only be delivered to a small fraction of AIS patients.[5] Significant advances in endovascular therapy to retrieve clots and achieve recanalization have substantially improved treatment options for a greater number of patients with AIS with a potential for significant improvements in recovery.[6] Although the rates of recanalization have improved significantly, a proportion of AIS patients still do not achieve complete recanalization.[7] It has been suggested that the histopathological composition of thrombi to be retrieved contributes to the difficulty in removing the clot.[8] Studies indicate that fibrin-rich thrombi are associated with an increased number of recanalization manoeuvres during thrombectomy procedure and increased resistance to thrombolysis compared to red blood cell-rich thrombus.[8,9] Growing knowledge

about the properties of stroke thrombi may result in the development of novel approaches to better detect and remove occlusive clots. The purpose of this review is to summarise recent studies on the composition of stroke thrombi and their impact on the efficacy of stroke treatment, with the aim to enhance the knowledge of how thrombus research can help shape future treatment options for AIS.

Methods

A scoping review method was selected to provide an overview of the available research evidence on the impact of thrombus composition on AIS treatment. This is useful for this research area as we were able to map a range of different study designs and methods to report on this particular topic. Our review was developed based on the scoping review framework proposed by Arskey and O'Malley, which was later refined by the Joanna Briggs Institute.[10,11] The PRISMA Extension for Scoping Reviews (PRISMA-ScR) was used to further guide the reporting in this review.[12]

The authors declare that all supporting data are available within the article.

Research question

The research questions underpinning our review were: (i) what are the histopathological characteristics of AIS thrombi? (ii) how does the composition of AIS thrombus affect the efficacy of mechanical thrombectomy and thrombolysis? (iii) what are the potential approaches to identify and improve treatment outcomes in patients with AIS?

Eligibility criteria

Articles were limited to peer-reviewed journal and review articles to ensure quality was maintained throughout. There was no limit set on language, if only it can be translated to English. Studies deemed eligible for inclusion met the following criteria: types of publication - journal articles, time frame - published prior to June 2020, study population - patients with AIS, types of intervention - interventions targeted at understanding, identifying and/or removing AIS thrombus.

Information sources

The most recent search was carried out on June 5, 2020 on four electronic databases. Searches were carried out in MEDLINE (biomedical sciences, 1946-present), EMBASE (biomedical sciences, 1947-present), Scopus (multidisciplinary, 2004-present) and Web of Science (multidisciplinary, 1997-present). In addition to the literature search, the reference list of each relevant articles was inspected thoroughly to obtain additional publications that were not identified in the literature search.

Search terms

A full electronic search was conducted on MEDLINE, EMBASE, Scopus and Web of Science using MESH terms. The terms included were "embolectomy" or "thrombectomy" or "thrombolytic therapy" or "mechanical thrombolysis", AND a combination of "acute ischaemic stroke" or "brain ischaemia" AND a combination of "fibrin" or "fibrin-rich thrombus".

Selection of sources of evidence

Title and abstract screening were guided by the PRISMA flow diagram.[12] Application of inclusion criteria ensured that the content of the studies was relevant to the research question.

The identified articles were transferred to a reference management software, Endnote XP software, where all duplicates were removed. Primary (PJ) and secondary author (RA) used the inclusion criteria to determine the relevance of selected articles. A full-text screening of all eligible articles was conducted by PJ. Reasons for exclusion of articles were only recorded at the full-text stage.

Data charting process

Extraction of data included relevant information that informed the review objectives and questions. For articles eligible for inclusion, a data extraction tool developed in previous scoping review protocols was utilised for our data charting process[13-15]. The following terms were used: (1) title, year; (2) journal; (3) study location; (4) objective(s) of the study; (5) relevant findings; (6) limitations.

Collating, summarising and reporting results

For the qualitative analysis, PJ conducted the initial categorisation of the key components independently using Microsoft Excel 2020 and the results were discussed with the secondary author, RA. The studies were categorised into one of the four key themes: (i) composition of stroke thrombi; (ii) thrombus composition and mechanical thrombectomy; (iii) thrombus composition and thrombolytic therapy; (iv) novel imaging and endovascular approaches.

Results

Selection and characterisation of sources of evidence

The searches from the four electronic databases retrieved 698 peer-reviewed journal articles (MEDLINE: 35; EMBASE: 157; Scopus: 320; Web of Science: 186). After vigorously inspecting the reference list of the selected articles, a further 82 articles were included. 539

articles and duplicates were excluded after abstract and title screening. 164 articles were eligible for a full-text article screening. Of these, 55 articles from the literature search were not included in the final review. A total of 109 topic-specific articles from both searches were included in the final review (*Fig.1*), in addition to 6 references for the scoping review methodology. Research on the impact of thrombus composition on the efficacy of AIS treatment is fairly recent and has increased considerably in the last few years (*Table.1*). Among the included studies, approximately 82% were published in the last decade (2011-2020). The 109 articles eligible for inclusion were published in 47 different journals.

Composition of stroke thrombi

An increasing number of studies have focussed on investigating the composition of thrombi in patients with AIS. Hematoxylin and eosin (H&E) staining and Martius Scarlet Blue (MSB) staining have been extensively used alongside immunohistochemistry to identify the composition of thrombus retrieved from patients with AIS after their thrombectomy procedure. The components of a typical thrombus consist of a variable proportion of fibrin, platelets, red blood cells (RBCs), white blood cells, von Willebrand factor (vWF) and extracellular DNA.[16-19] Analysis of retrieved stroke clot carried out in a recent study showed two main types of thrombus areas, with distinct composition: areas that are (i) RBC-rich and fibrin-poor; or (ii) platelet-rich and fibrin-rich (*Fig.2*).[18] The relationship between fibrin and the other two components suggests that fibrin interacts differently with both RBCs and platelets. Staining showed the presence of dense fibrin throughout the platelet-rich thrombus, which is in stark contrast to the thin fibrin network that surrounded RBC-packed areas (*Fig.2*).[18] Another study of the structure of stroke thrombi revealed a common structural feature, an inner core of RBC-rich material surrounded by an outer shell made up of densely packed thrombus components including fibrin shell and aggregated platelets.[16] It is important to note that retrieved thrombi

are highly heterogeneous and vary in composition and organization; consequently, the common components identified in their composition may affect their response to AIS treatment.

To begin to understand the implications of the histological composition of thrombi retrieved from patients with AIS on disease severity, outcome or treatment, an understanding of the formation of the thrombi is essential. Thrombus evolution has been relatively better studied in cardiovascular conditions such as venous thromboembolism and pulmonary embolism, showing that as time elapses, the biochemical composition of the thrombus changes.[20] During the initial phases of thrombus formation, blood platelets are rapidly activated and aggregate to the site of thrombosis, immediately followed by the conversion of fibrinogen to fibrin by thrombin to create a fibrin mesh that consolidates the clot *(Fig.3)*.[21] Initially, lower thrombin levels may form a fresh thrombus with a porous fibrin scaffold. The clot can be easily dissolved by tissue plasminogen activator (tPA) at this stage, particularly because crosslinking of fibrin and fibrinolysis inhibitors into fibrin by activated factor XIII has not yet taken place.[22,23] In the initial phases the clot is mainly composed of activated platelets, fibrin and RBCs. As fibrin deposition increases, the thrombus become more compact with smaller pores, which results in lower infiltration of tPA into the thrombus.[22,24,25] Platelet contraction of cross-linked clots results in retraction and stabilisation of the thrombus, and to the compression of discoid RBCs into polyhedrocytes which further increases thrombus density and increases resistance to thrombolysis *(Fig.3)*.[26] In addition, clot formation subsequently triggers inflammatory responses resulting in a cascade of cytokines which further perpetuates coagulation.[27] Activated platelets help promote infiltration of leukocytes such as neutrophils, monocytes and macrophages *(Fig.3)*.[28] As leukocytes invade and become activated, the thrombus further becomes resistant to thrombolysis.[29] Infiltrated neutrophils release pro-inflammatory mediators to form neutrophil extracellular traps (NETs) which act as a scaffold for RBCs, platelets and

prothrombotic molecules, hence contributing to thrombus stability and remodelling.[30-32] During the thrombus remodelling stage, RBC breakdown occurs as the process of thrombus organisation continues.[33] However, it is important to note that even though cardiovascular thromboembolic conditions follow this pattern, this mechanism is not specific to stroke. Therefore, further research into the specific evolution of stroke thrombi compositions will need to be carried out. Clots obtained from patients undergoing mechanical thrombectomy also contain a variable amount of vWF, a plasma glycoprotein responsible for organising the clot by linking platelets with collagen and fibrin.[34] Unsurprisingly, an investigation has shown a high level of plasma vWF to be a strong predictor of ischaemic stroke.[35] All these components contribute to the highly variable composition of occlusive thrombi.

Several studies have sought to explore possible relationships between the primary site of thrombus formation and clot composition. Thrombi retrieved from patients with AIS may be from a cardioembolic origin, large artery atherosclerotic origin, small-vessel occlusion, stroke of other determined aetiology, or stroke of undetermined aetiology.[30] The distinction between stroke subtypes may be determined based on the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification. For a probable diagnosis of cardioembolic stroke, clinical and imaging findings must identify the presence of at least one cardiac source of embolus. For the purpose of this review, all other stroke subtypes other than cardioembolic causes will be referred to as non-cardioembolic. Therefore, a non-cardioembolic thrombus will refer to any occlusive clot without any potential cardiac source of embolus. Published histopathologic studies indicate that cardioembolic thrombi have a higher percentage of fibrin-platelet conglomerates compared to non-cardioembolic thrombi.[17,19,37,38] Cardioembolic thrombi are composed of platelets clustered within fibrin-rich areas; this is in contrast with non-cardioembolic thrombi which showed RBC masses as its most abundant and dominant cell

type. Therefore, RBC-rich thrombi were significantly associated with non-cardioembolic stroke, whereas fibrin-rich thrombi significantly correlated with cardioembolic stroke. Comparing these two histopathological characteristics using clinical parameters showed significant differences in modified Rankin Scale (mRS), NIH Stroke Scale (NIHSS), number of retractions manoeuvres and recanalization time using thrombectomy devices, with cardioembolic thrombi resulting in the worse outcome.[38] The different interventional and outcome characteristics could be in line with the highly organised nature of the fibrin-rich cardioembolic thrombi being more resistant to retrieval compared to RBC-rich thrombi. However, caution should be taken when interpreting these data as findings have often been controversial. Some investigations reported no significant association between cardioembolic stroke and fibrin-rich thrombi, or even a relationship between cardioembolic stroke and RBC-rich thrombi.[39-44] These contradictory findings on the composition of cardioembolic thrombi could result from differences in study populations or staining methods. Furthermore, and to our knowledge, the mechanism(s) that would lead to cardioembolic thrombi being fibrin- and platelet-rich, and non-cardioembolic thrombi RBC-rich, remain(s) largely unknown.

Thrombus composition and mechanical thrombectomy

Large randomized trials have demonstrated the effectiveness of using thrombectomy devices in addition to thrombolytic therapy, compared to using medical treatment alone.[45-49] Mechanical thrombectomy has proven to be a revolutionary endovascular tool used to retrieve occlusive clot from a cerebral vessel. However, despite the overwhelming difference made using thrombectomy devices, recanalization remains difficult in certain patients. Consequently, several studies that evaluated clinical and interventional outcomes have demonstrated that the mechanical property and composition of the thrombus could have a significant impact on the efficacy and risk of the intervention. These studies have provided a valuable means for gaining

a deeper insight into preclinical testing of thrombectomy devices by assessing their ability to catch and extract the occlusive thrombus, the number of attempts needed and the risk of perioperative embolism.[50]

In patients with AIS, two angiographically similar occluded vessels may react differently to mechanical thrombectomy for causes that are not angiographically apparent.[8] Studies have suggested that vessels occluded with fibrin-rich thrombi require more passes with the thrombectomy device to achieve recanalization compared to a vessel occluded with RBC-rich thrombi.[8,50-55] In addition to this, a study by Bourcier et al, 2019 demonstrated that the rate of successful reperfusion decreased as time elapsed after arrival at the stroke endovascular centre.[56] Data from a meta-analysis have identified a significant correlation between clinical outcome and the arrival to recanalization time interval.[57] Even though the therapeutic window for thrombectomy (>6 hours) is larger compared to thrombolysis (>4.5 hours), it is crucial to start preparing eligible patients for thrombectomy intervention soon after stroke onset as favourable outcome rapidly diminishes as time progresses.[58,59] The enhanced efficacy of recanalizing RBC-rich thrombi may be attributed to its physical characteristics, which exhibit decreased stiffness and increased deformability compared to other fibrin-rich clots (*Fig.3*).[50] On the other hand, the increasing presence of fibrin within the thrombus makes the clot stiffer and more elastic, thus reducing the likelihood of successful engagement and interaction with the mechanical thrombectomy device.[8,60-62] Moreover, Gunning et al. showed that fibrin-rich thrombus analogues have a higher friction coefficient than RBC-rich thrombus, which contributes to the increased difficulty in extracting the clot.[7] During the thrombectomy procedure, the dislodged fibrin-rich thrombus exhibits an increased sliding resistance along the inside of the vessel and/or catheter when it is retrieved, which was suggested to be a result of its reduced ability to retain moisture and its increased susceptibility to compression during each

thrombectomy attempt.[7,63] Therefore, development of newer stent retrievers equipped to capture rather than penetrate the thrombus may perform better. This could be achieved by using an intermediate catheter to pin the thrombus against the stent retriever.[63] Alternatively, larger bore aspiration catheters designed to envelop the entire clot can also be utilised.[63]

The mechanical stability of a thrombus, i.e. its toughness, elasticity and stiffness, is largely determined by fibrin.[64] Interestingly, the stiff and frictional nature of fibrin-rich thrombus makes the clot less likely to fragment when compared to RBC-rich thrombi (*Fig.4*).[54] It is important to note that all mechanical thrombectomy methods are accompanied by the risk of peri-interventional thrombus fragmentation and subsequent downstream embolism which prevents complete recanalization and reduces neurological improvement rates.[54,65,66] Consequently, understanding the variables contributing to fragmentation may be beneficial in maximising therapeutic benefit. Previous studies have established that clots that can be easily retrieved are more vulnerable to peri-interventional thrombus fragmentation; these clots tend to have a higher level of RBC and a lower amount of fibrin (*Fig.4*).[54,62,67] This is in agreement with a study by Maegerlein et al showing RBC-rich clots are prone to migration as a result of its increased fragility and lower coefficient of friction.[66] Therefore, the question arises whether technical or procedural measures should be taken into account when planning and performing mechanical thrombectomy in patients with suspected RBC-rich thrombi. The use of proximal balloon catheters to minimize antegrade blood flow may be one potential approach to reduce the possibility of clot migration.[68,69] A study by Nguyen et al showed improved recanalization rates, shorter procedure and better clinical outcome among patients treated with the adjunctive use of a balloon guide catheter with a stent retriever during mechanical thrombectomy.[70] This is supported by a similar study by Zaidat et al which found that balloon guide catheter significantly improved rates of functional independence and early revascularization.[71] Another

promising approach may be to use stent retriever assisted vacuum-locked extraction (SAVE) technique to capture the thrombus as a whole by partially retrieving the stent retriever into the aspiration catheter during thrombectomy procedure.[69,72,73] Signs of clot migration and thrombus fragmentation are detected less when the SAVE technique is used. However, a significant limitation of the studies is the reported lack of improvements in clinical outcome after 90 days; [72,73] therefore, data should be interpreted with caution.

Thrombus composition and thrombolytic therapy

Recent guidelines indicate that intravenous tissue plasminogen activator (tPA) should be considered for eligible patients with AIS even if mechanical thrombectomy is used.[74] Thrombolysis with tPA is a well-established treatment option for AIS if given within 4.5 hours of symptom onset.[59,75] Successful treatment of AIS with tPA is particularly time-dependent with efficacy quickly declining with time.[76] Patients with large thrombus burden and stroke due to occlusion to the proximal anterior circulation respond poorly to tPA alone.[77,78] As a consequence, contra-indications such as large vessel occlusion (LVO) and borderline coagulation status which increases the risk of intracranial haemorrhage (ICH) often results in patients undergoing direct mechanical thrombectomy alone.[79,80] Previous studies comparing direct mechanical thrombectomy with tPA bridging therapy indicated that tPA might prove beneficial to the thrombectomy procedure by increasing the rate of successful recanalization.[79,81-83] Although alteplase is currently the only FDA-approved tPA medication for AIS, its administration increases the patient's risk of intracranial haemorrhage.[84] Although not FDA-approved for acute stroke, studies have shown that tenecteplase has both a greater fibrin specificity and longer half-life compared to alteplase, resulting in greater reperfusion on imaging studies and superior clinical neurological outcomes at 24 hours.[85,86] However, the benefits of bridging therapy with intravenous thrombolysis remain unclear according to the

SKIP studies; this meta-analysis questions the additional benefits of the use of thrombolysis before thrombectomy.[87]

Owing to their complex interaction, tPA sensitivity is associated with fibrin clot architecture in the thrombus. Fibrinolysis involves dissolving the fibrin meshwork in a thrombus through activation of plasminogen by tPA to plasmin.[88] Plasmin subsequently hydrolyses fibrinogen and fibrin into degradation products, resulting in clot lysis. Studies on the effect of thrombolysis on clot properties revealed dissociation of fibrin fibres, which Krajickova et al termed as "thinning".[81] Thinning refers to changes in the superficial layers of the fibrin, which was remarkedly notable after treatment with tPA. This finding is in line with other research showing that the mean fibre width of the thrombus increases after thrombolysis, with the clot being more porous with more branching points.[89] Both studies suggest that thrombolytic therapy is associated with significant changes in the structural composition of the thrombus, particularly with regards to the fibrin network architecture.

Unsurprisingly, RBC-rich thrombi demonstrate increased sensitivity to tPA compared to fibrin-rich thrombi (*Fig.4*).[90,91] The concentration of RBCs in the thrombus has been indicated to influence the structure of fibrin and contribute to looser clot architecture.[92] This is in agreement with another study showing that a rise in RBC fraction leads to enlargement of the architectural pore within the fibrin networks, allowing for an increased penetration of thrombolytic agents into the thrombi.[93] As a consequence, faster rates of fibrinolysis of loosely packed RBC-dominant thrombi has been reported, which is related to improved clinical outcome after 24 hours.[9]

Recent reports suggest that the outer shell of retrieved AIS thrombi is composed of fibrin, RBC, vWF, leukocytes and nucleated cells which act as a protective barrier against thrombolysis.[16] However, there is an increase in the rate of thrombolysis if the external shell is compromised. Therefore, targeting other components other than fibrin can introduce breaches to the shell, which in turn can enhance the efficacy of thrombolytic treatments.[16] DNAse 1 has been shown to target NETs and extracellular DNA in thrombi retrieved from patients with AIS.[30,94] Additionally, preclinical studies indicate that administration of recombinant ADAMTS13 targeting vWF dissolved an occlusive thrombus rich in vWF, which in turn may enhance recanalization rates.[95-98] These potential novel treatment options require further study and may be considered in addition to fibrinolytics to increase thrombolytic potency in future new treatment regimes.

Novel imaging and endovascular approaches

Advances in thrombus research has contributed to development of novel devices and strategies to identify and retrieve the thrombus, with the aim to increase the efficacy of AIS treatment. According to the NICE guidelines, brain imaging with non-enhanced computed tomography (CT) should be performed immediately on patients with suspected stroke, with computed tomography angiography (CTA) following CT if thrombectomy is indicated.[99] However, choice of imaging tests used prior to initiation of thrombolysis can vary across different practices and countries.[100] Studies indicate that MRI and CTA may be able to reveal features associated with the composition of the occlusive clot. Several studies have shown the presence of early vessel signs on CT and MRI, including the hyperdense middle cerebral artery sign (HMCAS) seen on CT and blooming artefact (BA) seen on susceptibility-weighted imaging.[9,101-106] In every case where either HMCAS or BA were identified, the thrombi has been classified as being RBC-rich. Unsurprisingly, the presence of these early vessel signs has

been associated with increased rate of successful recanalization, indicative of RBC-rich thrombus.[104] Inversely, the absence of HMCAS or BA has been associated with fibrin-rich thrombi. These findings can be explained by the CT density in unenhanced scans proportionally increasing with the haematocrit levels within the clot.[60,101,107-111] Interestingly, a study by Mahmoud et al seeking to assess whether HMCAS could serve as an imaging biomarker for guiding first-line device selection in mechanical thrombectomy demonstrated that patients with HMCAS may have a better response to stent retrievers compared to contact aspiration for first pass effect.[112] However, even though the association between clot density and clot composition is specific, the highly heterogenous nature of AIS clot limits the sensitivity of this technique.[104] Despite the relationship between HMCAS and BA with RBC-rich thrombi, emphasis should not be placed heavily on using these signs to predict successful clot retrieval as many other factors may influence recanalization. Nonetheless, this investigative tool has the potential to assist clinicians in determining which therapeutic approach is more suitable for individual patients, until better imaging modalities that are able to characterise clot composition in more detail become available in the future.

To overcome the difficulty in recanalization presented by organized fibrin-rich thrombi, a novel thrombectomy device was specifically aimed at retrieving resistant fibrin-rich clots.[113] The geometric clot extractor (GCE) was compared with the commonly used Solitaire stent retriever to achieve successful recanalization. The GCE obtained a higher rate of successful recanalization compared to the stent retriever due to its unique geometry which facilitates microcatheter assisted grip retrieval of the clot without the assistance of adjunctive aspiration, making the device effective at extracting fibrin-rich thrombus. While it might not always be evident at the outset that an occlusion will be difficult to extract, various indicators such as the patient's medical history and imaging may help distinguish such cases. Although the GCE is

promising, it is important to note that the study was carried out *in-vitro* with a single fibrin clot analogue. Another study investigating whether the speed of retrieval influences the efficacy in removing clots found that fast retrieval provided a stronger advantage to fibrin-rich clots.[114] The general approach of extracting by stent retriever is to slowly and gradually pull back the retriever to protect the vessel from possible perforator injury, especially to the distal arteries that are less robust and more loosely connected to the parenchyma.[37] However, Soize et al found an improvement in recanalization rates using fast compared to slow retrieval.[115] Fast retrieval quickly mobilized the clot which allowed for a higher pulling force. While fast retrieval seems promising in terms of recanalization, perforating arteries cannot be modelled accurately, and the likelihood of damage remains unclear. Finally, the study by Girdhar et al demonstrated that the use of the newer-generation stent retriever which are longer and/or larger in diameter improved first pass success of fibrin-clot retrieval without increasing the risk of vessel damage.[114] However, several assumptions were made in this study, such as the shape of the clot and the viscosity of fluid used. Overall, further investigations including *in-vitro* and *in-vivo* studies with representations in different anatomical models and a range of clot analogues should be carried out for each of these devices.

Concluding remarks

In recent years, research characterising thrombi in AIS has shown that the histological, biochemical and structural composition of the clot has a significant impact on treatment success rates. RBC-rich thrombi are typically associated with favourable outcomes such as higher recanalization success, shorter intervention time and increased tPA sensitivity. Fibrin-rich thrombi on the other hand have a less favourable outcome, mostly due to their increased stiffness and resistance to both mechanical thrombectomy and thrombolysis. Future developments to better identify and remove occlusive thrombi through early vessel signs,

innovative imaging and diagnostic methods to determine clot composition, and adjuvant treatments are likely to be key for future improvements in AIS treatment, care and outcomes.

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Disclosures

None.

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Table.1. Percentage of included articles by decade (1981-2020)

Year	Percentage (%)
1981-1990	0.9
1991-2000	1.8
2001-2010	15.6
2011-2020	81.7

Figures

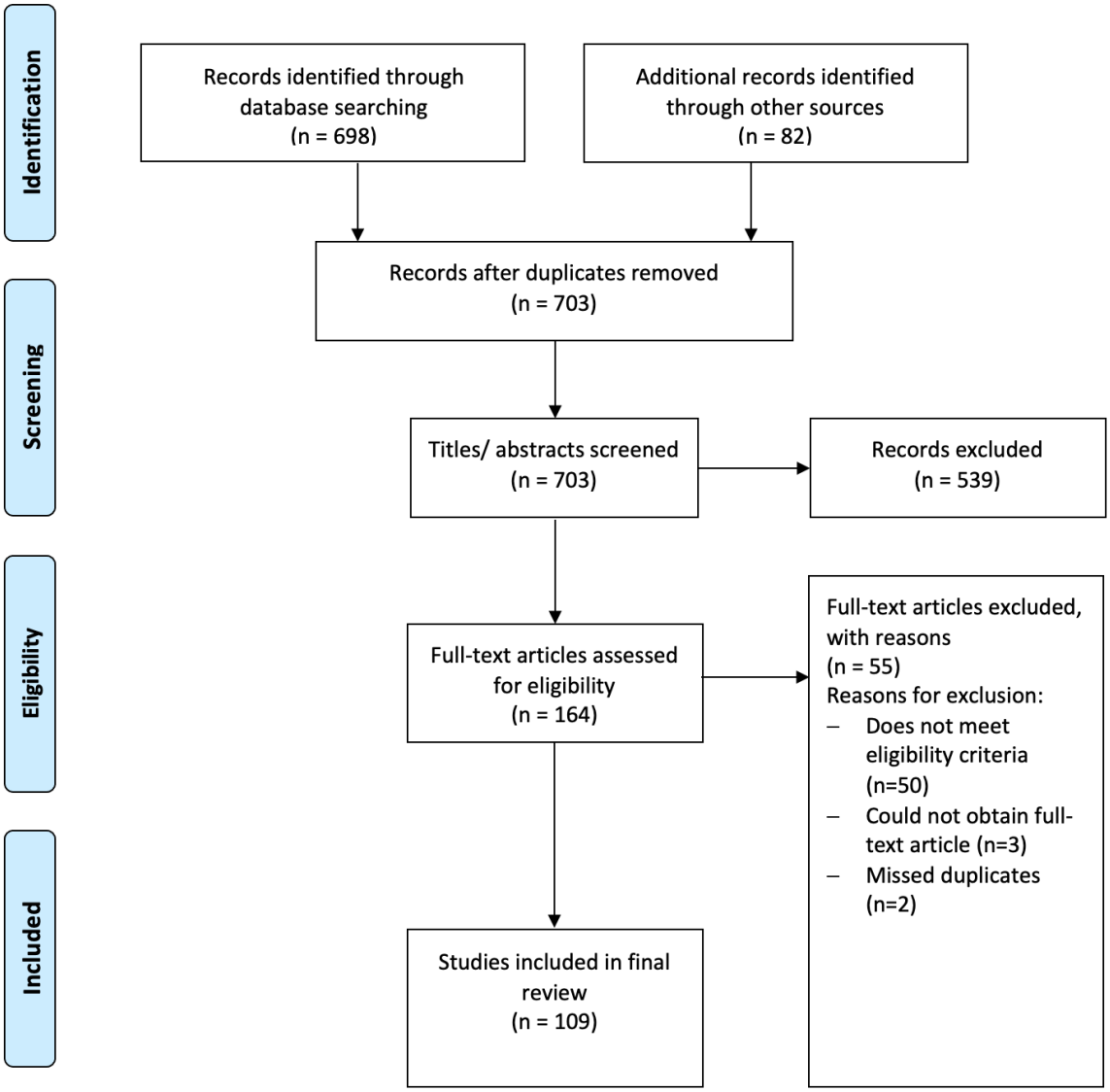

Fig.1: PRISMA flow diagram. Flowchart of the results of the literature search and selection of articles at each stage.

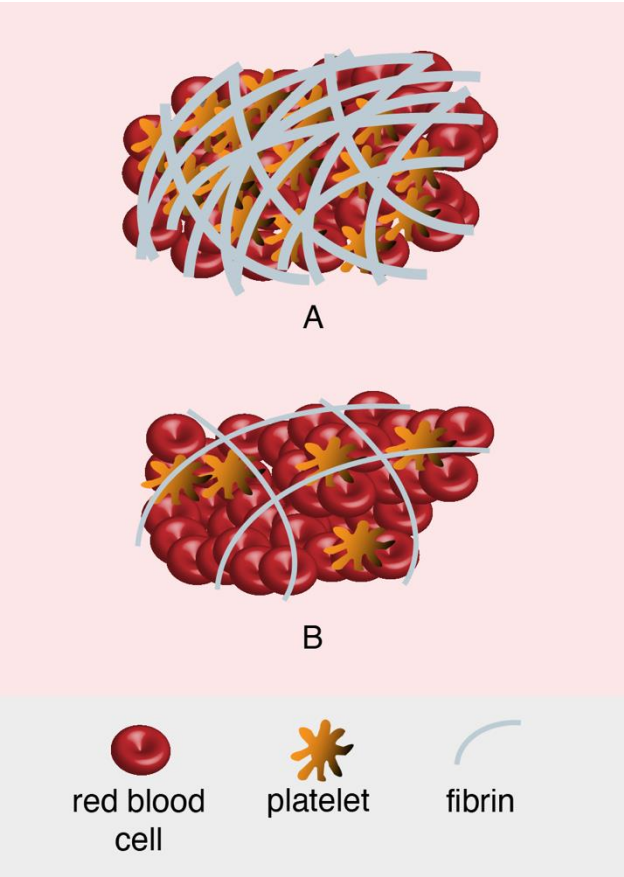

Fig.2. Components of stroke thrombi. Diagram showing (A) fibrin-rich thrombus and (B) red blood cell-rich thrombus. (A) Fibrin-rich thrombi are composed of platelets-rich zones interspersed in dense fibrin fibres. (B) Red blood cell-rich thrombi are mainly composed of red blood cells with thin fibrin fibres. Clot components are not drawn to scale.

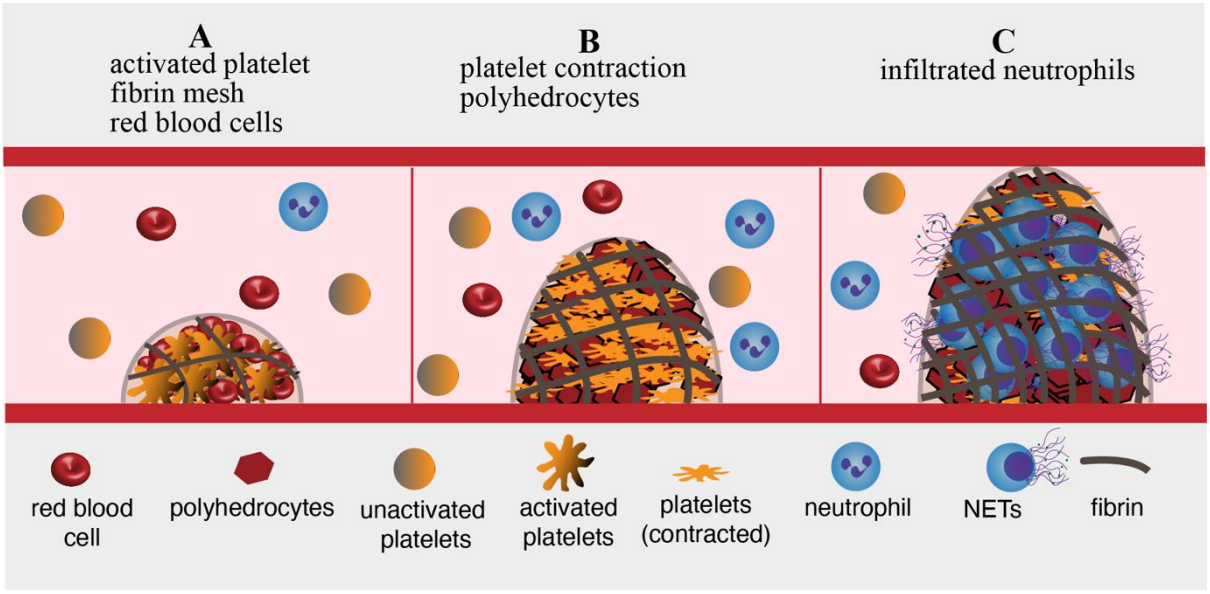

Fig.3: Thrombus evolution with time. (A) During the initial phases, the thrombus is composed of activated platelets, red blood cells and a porous fibrin mesh. (B) As time progress, platelets contract and red blood cells compress into polyhedrocytes. (C) Activated platelets promotes infiltration of leukocytes including neutrophils into the thrombus forming NETs and stabilising the thrombus with much smaller pores. Clot components are not drawn to scale.

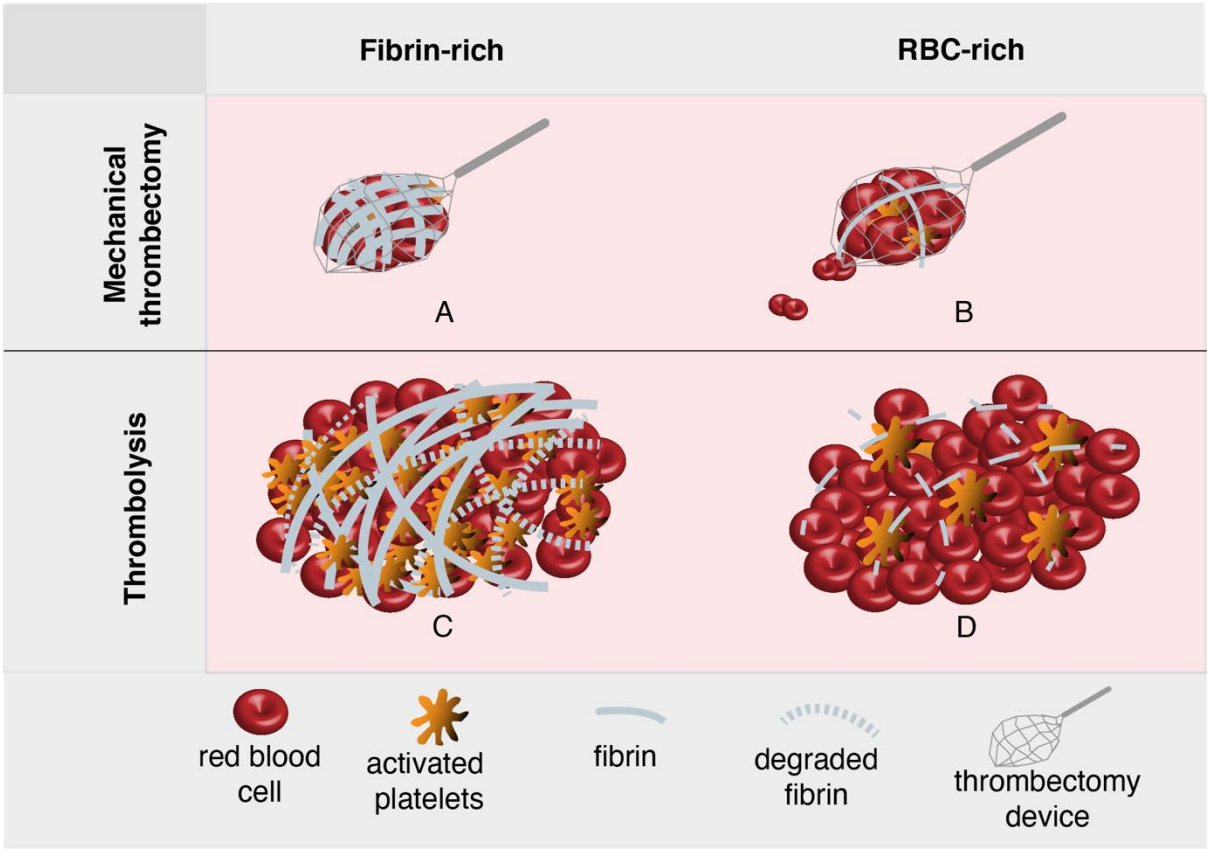

Fig.4. Comparing difference in acute ischaemic stroke treatment between fibrin-rich and red blood cell-rich thrombus. (A) Fibrin-rich thrombi are more difficult to retrieve using mechanical thrombectomy due to their dense and compact structure. (B) RBC-rich thrombi are easier to retrieve, but more vulnerable to fragmentation. (C) Fibrin-rich thrombi have a poorer infiltration of tPA due to their pores being smaller and more compact. (D) RBC-rich thrombi have an increased sensitivity to tPA due to their looser clot architecture. Clot components are not drawn to scale.