Published manuscript at **https://doi.org/10.1016/j.jbiomech.2021.110693**

In vitro and in silico modeling of endovascular stroke treatments for acute ischemic stroke

Giulia Luraghi[1,2], Rachel M. E. Cahalane[3], Emma van de Ven[1], Serena Overschie[1], Frank J. H. Gijsen[1,3], Ali C. Akyildiz[1,3]

[1] Department of Biomechanical Engineering, Delft University of Technology, Delft, the Netherlands

[2] Department of Chemistry, Materials and Chemical Engineering "Giulio Natta", Politecnico di Milano, Milan, Italy

[3] Department of Biomedical Engineering, Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands

Corresponding author

Giulia Luraghi, PhD

Laboratory of Biological Structure Mechanics (LaBS), Department of Chemistry, Materials and Chemical Engineering "Giulio Natta", Piazza L. da Vinci 32, 20133 Milan, Italy.

giulia.luraghi@polimi.it

Phone: +39 02 2399 3169

Keywords

Thrombectomy, acute ischemic stroke, stent-retriever, aspiration

Abstract

Acute ischemic stroke occurs when a thrombus obstructs a cerebral artery, leading to sub-optimal blood perfusion to brain tissue. A recently developed, preventive treatment is the endovascular stroke treatment (EVT), which is a minimally invasive procedure, involving the use of stent-retrievers and/or aspiration catheters. Despite its increasing use, many critical factors of EVT are not well understood. In this respect, in vitro, and in silico studies have the great potential to help us deepen our understanding of the procedure, perform further device and procedural optimization, and help in clinical training. This review paper provides an overview of the previous in vitro and in silico evaluations of EVT treatments, with a special emphasis on the four main aspects of the adopted experimental and numerical set-ups: vessel, thrombus, device, and procedural settings.

1. Introduction

An acute ischemic stroke (AIS) occurs when a blood clot (thrombus) blocks a cerebral artery and hence, prevents blood perfusion to a region in the brain. A blood clot is a solid mass, mainly consisting of a fibrin network, platelets, red blood cells, and leukocytes in varying amounts (Johnson et al., 2017). AIS induces a rapid reduction in neurological function and it is one of the main causes of both mortality and long-term disability worldwide (World Health Organization, 2019). AIS can affect different cerebral arteries, but it mainly occurs at the level of the internal carotid arteries (ICA), the middle cerebral arteries (MCA, M1, and M2 segments), the anterior cerebral artery (ACA), and the posterior cerebral artery (PCA) (Dutra et al., 2019).

The so-far-established treatment strategies for AIS have aimed at restoring the blood flow as quickly as possible after symptom onset. Until about 15 years ago the only treatment approved by the Food and Drug Administration was thrombolysis with intravenous administration of alteplase. Recently, endovascular stroke treatment (EVT) was introduced in clinical practice, which is a collective term for the minimally invasive interventional procedures that involve the mechanical removal of the blood clot. The current means of EVT are based on either stent-retriever technology or aspiration technique or the combination of these two (Ospel et al., 2019). The effectiveness and safety of EVTs have been demonstrated in the recent MR CLEAN trial (Berkhemer et al., 2015) and subsequent clinical trials (Campbell et al., 2015; Goyal et al., 2016; Jovin et al., 2015; Lapergue et al., 2017; Saver et al., 2015; Turk et al., 2019).

The introduction of EVT revolutionized the AIS treatment but still almost 2 out of 3 patients with an AIS have an unfavorable outcome and become functionally dependent (Fransen et al., 2016; Goyal et al., 2016). This clearly indicates that EVTs may greatly benefit from further improvement, which is to be achieved by deepening our understanding of various aspects of EVT, such as clot-device interaction and the causes of negative outcomes. Even though EVT has been a widespread clinical procedure, different aspects of the treatment require proper analysis and exploration. A systematic in vivo study of EVT with detailed sensitivity analysis of each individual aspect of the procedure is hard, if not impossible, to be performed due to ethical considerations, as well as due to the un-planned, interventionalist-experience-based and patient-specific nature of EVT. In this respect, in vitro and in silico studies have the great potential to help us deepen our understanding of the procedure, perform further optimization and help in clinical training.

In this review, we present a non-exhaustive overview of the literature published within the field of in vitro and in silico evaluation of EVTs. We examined the studies that involved the

mechanical interaction between the clot and the vessel or the clot and the device or both. We outline the existing literature on in vitro and in silico analyses separately in dedicated sections, where each section evaluates the previous research efforts concerning the four main aspects of an EVT analysis: i. vessel model/geometry, ii. clot material, iii. mechanical device, and iv. procedural settings. We furthermore provide a discussion and future perspectives on the in vitro and in silico analyses of EVT.

2. In vitro studies of thrombectomy

In vitro studies have either focused on the performance of the EVT or evaluated a specific aspect/condition of the procedure (e.g., cyclic vs. static suction in aspiration treatment), or investigated the device performance in an experimental setting. The studies involved clot aspiration procedure or removal of a clot with a stent-retriever or combination of the two.

Of the studies with the focus on aspiration-only procedures, the ones performed by (Simon et al., 2014) and (Lally et al., 2016) examined the impact of different suction conditions. (Madjidyar et al., 2020) compared various aspiration procedures and devices in terms of flow characteristics, and the number of aspiration attempts and distal emboli. (Good et al., 2020) made use of an in vitro test model to validate the in silico model that they developed to investigate the effect of cyclic aspiration.

Some of the studies that involved in vitro analyses of stent retrieval thrombectomy compared the performance of different stent-retrievers. (Chueh et al., 2013) tested three different stent-retrievers and identified the effects of clot type and temporary flow arrest with a balloon-guided catheter on the risk of distal emboli and flow restoration. (Machi et al., 2017) performed an extensive comparison of 18 stent-retrievers for their mechanical properties and clot retrieval performance. (Ohshima et al., 2019) tested five stent-retrievers for their clot capturing capability, for which (Van Der Marel et al., 2016) also developed a novel method and tested for one stent-retriever. (Weafer et al., 2019) characterized the embedding of the stent retriever struts into clots using clot analogs. (Wenger et al., 2013) investigated the efficacy of intervention with a by-then newly developed stent-retriever by comparing it to three other standard stent-retrievers. Both (Fennell et al., 2018) and (Girdhar et al., 2020) investigated the performance of several stent-retrievers specifically for the removal of fibrin-rich clots. (Tanyildizi et al., 2020) developed a novel tip shape for distal access catheters and tested its performance with two stent-retrievers. In a recent study, (Giulia Luraghi et al., 2021) performed in vitro tests with three different vessel replica models to validate their in silico stent-retrieval model.

Various other in vitro studies compared the efficacy of stent-retrieval procedures and direct aspiration (Chueh et al., 2012; Tennuci et al., 2011). (Madjidyar et al., 2015) examined the influence of additional aspiration in stent-retrieval procedure with four different stent-retrievals. Similar work was performed by (Maxim Mokin et al., 2015), but only for one stent-retriever. The same group also evaluated the recanalization success of four different thrombectomy procedures: stent-retrieval only, stent-retrieval combined with a balloon-guided catheter, stent-retrieval combined with aspiration, and aspiration only (M. Mokin et al., 2015). (Chueh et al., 2020b) evaluated the performance of a new thrombectomy device that combines stent-retrieval and aspiration. (Johnson et al., 2020b, 2020a) compared the recanalization rates of stent-retriever-only and aspiration-only procedures specifically for calcified clots and platelet-contracted clots. (Sanchez et al., 2020) tested a new thrombectomy device against the procedures with stent-retrieval combined with distal access catheter and stent-retrieval combined with a balloon-guided catheter. A summary of all in vitro studies is presented in Table 1.

[table 1 goes here]

2.1 Vascular models

The purpose of a vascular model is to replicate the cerebrovasculature relevant in the setting of acute ischemic stroke. Vascular models can be simplified to a straight model to represent an arterial segment (Lally et al., 2016; Tennuci et al., 2011) or an enlarged cerebral artery (Good et al., 2020). Two articles describe vascular reconstructions of the carotid and middle cerebral artery segments (Chueh et al., 2012; Machi et al., 2017). Other articles extend the models to include the A1 segment (Wenger et al., 2013), M1 and M2 divisions (Sanchez et al., 2020), M1-4 segments, anterior and posterior communicating arteries (Fennell et al., 2018), and the ophthalmic arteries (Girdhar et al., 2020). Others describe full Circle of Willis models (Chueh et al., 2020b; Maxim Mokin et al., 2015; Van Der Marel et al., 2016) or use a commercial model of the cerebrovasculature (Johnson et al., 2020a, 2020b; Madjidyar et al., 2020, 2015; Tennuci et al., 2011). The majority of vascular models are tubular in design, apart from two studies where a hollowed-chamber was utilized (Good et al., 2020; Machi et al., 2017).

The middle cerebral artery (MCA) is the target vessel described in all articles, apart from where the M1 segment is specified (Fennell et al., 2018; Johnson et al., 2020a, 2020b; Madjidyar et al., 2020; Sanchez et al., 2020), or there is no target vessel identified (Giulia Luraghi et al., 2021; Machi et al., 2017; Ohshima et al., 2019; Simon et al., 2014; Weafer et al., 2019; Wenger et al., 2013). Overall, the range of geometries of the vascular models includes straight tubes (Fig. 1a) (Lally et al., 2016; Ohshima et al., 2019; Simon et al., 2014; Tanyildizi et al., 2020;

Tennuci et al., 2011; Weafer et al., 2019) or straight chambers (Good et al., 2020), sharp bends (Fig. 1b) (Wenger et al., 2013), U-bends (Fig. 1c) (Giulia Luraghi et al., 2021), funnel-shaped vessels (Fig. 1d) (Giulia Luraghi et al., 2021), 3-dimensional models in one plane (Fig. 1e) (Machi et al., 2017) or in multiple planes (Fig. 1f) (Maxim Mokin et al., 2015). The majority of the articles incorporated the most realistic 3-dimensional models in multiple planes.

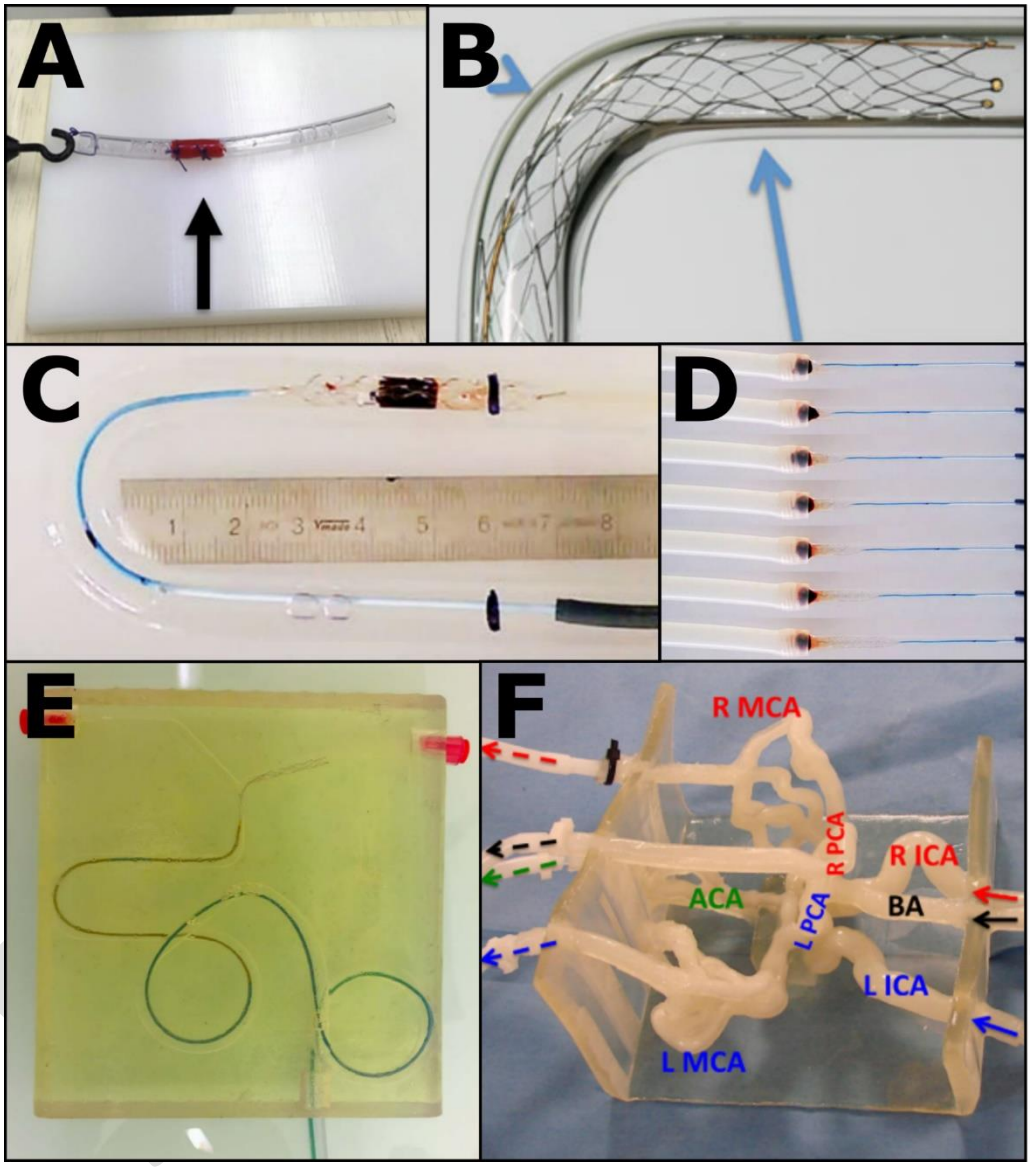

Figure 1: The in vitro cerebrovascular model geometry configurations. **(A)** Straight (Ohshima et al., 2019). **(B)** 90 degree bend (Wenger et al., 2013). **(C)** U-bend (Luraghi et al., 2021). **(D)** Funnel-shaped vessel (Luraghi et al., 2021). **(E)** 3D (one plane, hollow chamber) (Machi et al., 2017). **(F)** 3D (multiple planes) (Maxim Mokin et al., 2015).

Around half of the studies used idealized model geometries, some citing patient vessel dimensions from literature (Girdhar et al., 2020; Lally et al., 2016; Giulia Luraghi et al., 2021;

Machi et al., 2017; Ohshima et al., 2019; Sanchez et al., 2020; Simon et al., 2014; Tanyildizi et al., 2020; Tennuci et al., 2011; Wenger et al., 2013). The others used vascular models reconstructed from imaging data, where some utilized a commercial model developed from patient imaging data (Johnson et al., 2020a, 2020b; Madjidyar et al., 2020, 2015; Tennuci et al., 2011), or designed their own model from brain Magnetic Resonance Angiography scans (Chueh et al., 2020b, 2012; Van Der Marel et al., 2016), Computed Tomography Angiography scans (Maxim Mokin et al., 2015) or both Digital Subtraction Angiography and Computed Tomography Angiography scans (Fennell et al., 2018). One study used a chamber that represented an enlarged (5-times) cerebral artery (Good et al., 2020).

The majority of studies used models made of silicone, while three used glass (Lally et al., 2016; Giulia Luraghi et al., 2021; Wenger et al., 2013), three used rigid plastic (Machi et al., 2017; Ohshima et al., 2019; Simon et al., 2014), two used a 3D print material (TangoPlus (Maxim Mokin et al., 2015) or unspecified (Good et al., 2020)) and one used IV line material (Tanyildizi et al., 2020). (Chueh et al., 2009) previously described the mechanical properties of silicone strips used in vascular models and concluded that the stress-strain tensile behavior of silicone is similar to human MCA tissue. (M. Mokin et al., 2015; Maxim Mokin et al., 2015) determined the tensile strength of 3D print material TangoPlus to be 0.8–1.5 MPa and within the range of the human arterial wall. The compliance and appropriateness of the IV line material were not evaluated. Rigid plastic and glass were assumed to be completely rigid.

2.2 Clots

Blood clots are composed of highly variable amounts of fibrin, red blood cells (RBCs), platelets and white blood cells (WBCs) (Staessens and De Meyer, 2020). Literature indicates that fibrin-rich clots may be more difficult to retrieve (Yuki et al., 2012), while RBC-rich clots may be more susceptible to fragmentation (Fereidoonnezhad et al., 2020). The fragmentation of clots creates distal emboli and negatively affects the clinical outcome of patients (Kaesmacher et al., 2017).

The clot analogs used in the considered works were modeled to represent those from atherosclerotic plaques (Chueh et al., 2012), elastic clots (Madjidyar et al., 2015), rigid clots (Wenger et al., 2013), and fibrin-rich clots (Fennell et al., 2018; Girdhar et al., 2020). (Giulia Luraghi et al., 2021) used a clot model which was intermediate between a white and red clot. Six studies used two different thrombi to represent the extremes of hard and soft (Chueh et al., 2013, 2020b; Van Der Marel et al., 2016), red and white (Machi et al., 2017) or fibrin-rich and RBC-rich clots (Madjidyar et al., 2020; Sanchez et al., 2020). (Weafer et al., 2019) used five

different thrombus analogs with varying hematocrits. (Johnson et al., 2020b) also modeled five different hematocrits of platelet-contracted clots and three different hematocrits of non-contracted clots. Recently, a model for calcified cerebral emboli clots was also described.

Five studies used ovine blood to create clot analogs (Fennell et al., 2018; Johnson et al., 2020a, 2020b; Lally et al., 2016; Weafer et al., 2019), five used human (Chueh et al., 2013; Machi et al., 2017; Madjidyar et al., 2020, 2015; Van Der Marel et al., 2016), four used bovine (Chueh et al., 2013, 2020b, 2012; Van Der Marel et al., 2016), two used porcine (Girdhar et al., 2020; Tanyildizi et al., 2020) and one used lamb (Tennuci et al., 2011). In another study, it is unclear whether porcine or bovine blood was used (Wenger et al., 2013). While the majority of studies utilized blood from various species to model thrombus, two studies used polyurethane (Simon et al., 2014) or urethane foam (Ohshima et al., 2019) while another used neoprene rubber (Good et al., 2020).

Static or dynamic conditions can be employed to developed clot models. Six studies used static conditions to form blood clots (Chueh et al., 2012; Johnson et al., 2020a, 2020b; Madjidyar et al., 2020; Tennuci et al., 2011; Weafer et al., 2019). Clotting agents are required to promote rapid coagulation in static environments. Calcium chloride (Fennell et al., 2018; Girdhar et al., 2020; Johnson et al., 2020a, 2020b; Machi et al., 2017; Madjidyar et al., 2020; Weafer et al., 2019; Wenger et al., 2013), thrombin (Chueh et al., 2013, 2020b, 2012; Girdhar et al., 2020; Van Der Marel et al., 2016), fibrinogen (Chueh et al., 2020b; Girdhar et al., 2020) and calcium phosphate apatite (in the case of stiff clots) (Chueh et al., 2020b) were used as clotting agents. Four studies used the Chandler Loop system to form clots in a dynamic environment (Madjidyar et al., 2020, 2015; Tanyildizi et al., 2020; Wenger et al., 2013). In three studies the blood was allowed to clot naturally (Lally et al., 2016; Tanyildizi et al., 2020; Tennuci et al., 2011). The temperature at which the blood was allowed to coagulate included 37°C, 38.5°C, or room temperature. The thrombus analog recipes of (Chueh et al., 2011) and (Duffy et al., 2017) were utilized in four and five other articles, respectively.

The size of the clots inserted into the in vitro models was largely based on the dimensions of the target vessel. The majority of studies dissected clots into a cylindrical shape with diameters ranging from 2 to 5mm (Machi et al., 2017; Sanchez et al., 2020; Tennuci et al., 2011; Weafer et al., 2019) and lengths ranging from 3 to 30mm (Simon et al., 2014) (Tennuci et al., 2011). Otherwise, rectangular dimensions were defined (Chueh et al., 2020b; Fennell et al., 2018; Johnson et al., 2020a, 2020b; Madjidyar et al., 2020). (Lally et al., 2016) defined a thrombus weight instead (12-14g). Another study used an enlarged model of the cerebral artery and an enlarged synthetic clot (5-times) (Good et al., 2020).

(Simon et al., 2014) used qualitative evaluation and clinical experience to conclude that the bulk properties of polyurethane are similar to that of human clots. Neoprene rubber was selected because of its viscoelastic behavior to develop and validate a viscoelastic computational framework (Good et al., 2020). The soft clot models utilized by (Van Der Marel et al., 2016) and (Chueh et al., 2020b) were previously characterized by (Chueh et al., 2011) and determined to be similar to clinical specimens retrieved from stroke patients. (Machi et al., 2017) used flat plate compression tests to compare the mechanics of their white and red clot analogs. Two studies used Dynamic Mechanical Analysis to investigate the compressive behavior of the clot analogs (Girdhar et al., 2020; Johnson et al., 2020a). The modulus of fibrin-rich clots was found to be 0.138 ± 0.08 MPa (Girdhar et al., 2020). Platelet-contracted clots examined using unconfined compression were all stiffer than non-contracted clots with the same RBC content, indicating that the degree of clot contraction can have a significant effect on the clot properties. However, the authors concluded that all clot analogs had comparable stiffness to clots retrieved AIS procedures but only at large strains (Johnson et al., 2020a). The calcified cerebral emboli model was also characterized utilizing unconfined compression testing and was deemed to successfully replicate the properties of calcified tissue from cardiac valves and carotid atherosclerotic plaques (Johnson et al., 2020b). (Giulia Luraghi et al., 2021) also characterized the clot samples to produce material models for use in an in silico analysis.

2.3 Devices

The most commonly used aspiration systems in the in-vitro studies were Penumbra systems and manual aspiration with a 20 ml or 60 ml syringe. Some other devices and pumps were used as well, including a vacuum pump of Welch Vacuum Technology, the ASPIRE device (Control Medical Technology, LLC), Dominant Flex suction pump (Medela, Baar, Switzerland), Hersill V7 Plus AC aspiration pump (Hersill Medical Devices, Madrid, Spain), and Gwen Pearce thrombus aspiration device. The accompanying aspiration catheters included Penumbra 041, 054, 4MAX, 5MAX, and 5MAX ACE; Navien 058; Sofia 5F and 6F; Kimal 4 Fr. Many SRs were utilized in the in-vitro studies, including Merci V-series, X-series, L-series; Aperio (Acandis, Germany); Trevo Provue (Stryker, Kalamazoo, Michigan, USA); Solitaire (Medtronic, Irvine, California, USA); Catch (Balt, Montmorency, France); Eric (Microvention, Aliso Viejo, California, USA); Embotrap (Cerenovus, Galway, Ireland); Separator 3D (Penumbra Inc, Alameda, California, USA); Revive (Codman, Raynham, Massachusetts, USA); Mindframe (Medtronic, Irvine, California, USA); ThrombX Retriever (TXR; ThrombX Medical Inc., Santa Clara, CA). Various types and sizes of distal access catheters, intermediate

catheters, microcatheters, and balloon guide catheters were used. Table 1 provides the complete list of analyzed devices in each study.

2.4 Procedural settings

The fluid used in the models included saline, a 60%/40% solution of water/glycerin, and water. (Tennuci et al., 2011) used Hartmann's fluid. (Girdhar et al., 2020) used a 0.2%v/v soap and water solution. (Ohshima et al., 2019) used no fluid. The majority of articles used a physiologically realistic flow waveform to simulate cardiac output. Otherwise, the vascular models were simply submerged in a fluid (Simon et al., 2014; Tanyildizi et al., 2020; Weafer et al., 2019) or subjected to a static flow (Giulia Luraghi et al., 2021; Machi et al., 2017; Sanchez et al., 2020) with a physiologically relevant mean pressure (Lally et al., 2016; Sanchez et al., 2020). The temperature of the in vitro tests was conducted at either room temperature or 37°C. To decrease the friction in the silicone models, three articles described the use of a lubricant (Chueh et al., 2012; Madjidyar et al., 2020, 2015). (Girdhar et al., 2020) also employed a 0.2%v/v soap and water mixture which the authors state mimics the friction between the stent and the vessel wall.

2.5 Main findings

Cyclic aspiration was shown to outperform static aspiration with respect to both the time taken to clear the clot and the degree of clot removability (Simon et al., 2014). It was demonstrated that aspiration can be combined with a balloon-guided catheter (Madjidyar et al., 2020). Additionally, better recanalization rates were suggested for funnel-shaped catheter tips compared to cylindrical-shaped tips (Tanyildizi et al., 2020). In the in vitro analysis of stent retrievers, the devices were typically deployed using the device operator guidelines (Tennuci et al., 2011). Placing a stent retriever 1 cm distal to the thrombus was shown to increase the chance of engaging the entire clot (Wenger et al., 2013). Additionally, larger (Machi et al., 2017) and longer (Girdhar et al., 2020) devices increased the probability of retrieving the thrombus. Stent retrievers were also tested in combination with aspiration (Chueh et al., 2013, 2020b), which was shown to have an improved efficacy of the EVTs (Machi et al., 2017; Madjidyar et al., 2015; M. Mokin et al., 2015; Maxim Mokin et al., 2015). Also, a balloon-guided catheter can be used to control the proximal flow (Chueh et al., 2013, 2012; M. Mokin et al., 2015). (Sanchez et al., 2020) suggested the use of a stent retriever together with the Advanced Thrombectomy System for better procedural outcomes. Currently, there are three main stent deployment techniques: standard (unsheathing), push-and-fluff, and wire-push.

(Ohshima et al., 2019) found that the wire push technique worked best for Solitaire devices whereas the push-and-fluff technique proved to be most effective for Trevo and Revive devices. Various integration time windows were used for stent retrievers, to embed with the thrombus (30-60 s (Fennell et al., 2018), 3 min (Chueh et al., 2020b), and 5 min (Van Der Marel et al., 2016; Weafer et al., 2019)). The embedding time was shown to be more important for fibrin-rich clots (Weafer et al., 2019). (Van Der Marel et al., 2016) demonstrated maximized integration of Trevo stent-retriever with fibrin-rich clots when the push-and-fluff technique was combined with 5 min embedding time.

3. In silico studies of thrombectomy

In silico studies involving mechanical thrombectomies or a mechanical evaluation of only one analyzed component (i.e., vessel, clot, device) are studied and categorized in this section. Focusing on the clot, a combined in vitro-in silico approach was used by (Tutwiler et al., 2020) to understand the relationship between fibrin toughness (ability to deform and absorb energy without fracture) and embolization; (Mukherjee and Shadden, 2018) studied the flow around and within the realistic clot, which was modeled with hybrid particle–continuum fluid-structure interaction (FSI) approach. Even though the literature is full of numerical evaluation of stents, especially with the finite element analysis (FEA), the same does not apply to stent-retrievers. Only two studies proposed by (Gu et al., 2018, 2017) focus on stent-retriever performance with FEA. The former investigated the stent-retriever performance under in vivo loading conditions by including idealized deformable clot and vessel; the other evaluated the ability of the device to remain in close contact with curved vessel walls during the migration. (Giulia Luraghi et al., 2021) developed and validated a numerical framework with FEA to model all the thrombectomy with stent-retriever steps, stent crimping, catheter, and sent tracking, deployment, and retrieval. The same authors virtually performed the first patient-specific thrombectomy (Giulia; Luraghi et al., 2021). Focusing on aspiration thrombectomy, different numerical methods have been proposed to analyze the performance of aspiration catheters in idealized/simplified geometry. (Shi et al., 2017) evaluated the suction force vs. the distance between clot and catheter using a computation fluid-dynamic (CFD) analysis. (Pennati et al., 2010) implemented a two-phase flow in CFD analysis to investigate the factors affecting the thrombus suction by changing the catheter design. The evaluation of two aspiration catheters performance was also modeled by (Chitsaz et al., 2018) with an FSI method combining FEA with a Runge-Kutta method for the clot. (Good et al., 2020) developed a numerical framework to study the clot-vessel interaction during cyclic aspiration by combining a viscoelastic

thrombus model with a cohesive zone (CZ) model. Different studies have been proposed by Romero and Talayero group, where a bound-graph-based lumped parameter model (LPM) was developed to analyze the clot and the adhesion force during the aspiration thrombectomy (Romero et al., 2013, 2012; Talayero et al., 2019). These authors later used this method to calibrate a coupled FEA-CFD approach (Romero et al., 2020; Talayero et al., 2020). (Neidlin et al., 2016) proposed a coupled 1D-3D with a Volume of Fluid (VOF) technique to study the blood flow in the circle of Willis during aspiration. A summary of all in vitro studies is presented in Table 2.

[table 2 goes here]

3.1 Vascular models

In the in silico models of EVT, either with stent-retrievers or with aspiration catheters, the inclusion of the vessel model is mandatory. The majority of the analyzed in silico studies evaluating the aspiration treatment simplified the cerebral vessels geometry with an idealized cylindrical domain (Fig. 2A&B), by neglecting the tortuosity and curvature of the physiological segments (Chitsaz et al., 2018; Good et al., 2020; Gu et al., 2017; Mukherjee and Shadden, 2018; Pennati et al., 2010; Romero et al., 2020, 2013, 2012; Shi et al., 2017; Talayero et al., 2019, 2020). The diameter of the straight idealized vessels varied from 6 mm representing the larger ICA segment to 1 mm representing the smaller segment of the MCA. A "C-shaped" idealized geometry was considered by (Gu et al., 2018) evaluating the wall apposition performance of a stent-retriever. (Giulia Luraghi et al., 2021) virtually reproduced in vitro bench-top tests in different vessel geometries, a "U-bent" vessel, a funnel-shaped vessel, and a patient-like 3D vascular branch (Fig. 2C). The segmentation process from real patient CTA scan to obtain patient-specific geometries (Fig. 2D) was proposed in a coupled 1D-3D CFD analysis, that analyzed the blood flow of the cerebral branch during the aspiration treatment (Neidlin et al., 2016) and in a patient-specific thrombectomy modeling (Giulia; Luraghi et al., 2021).

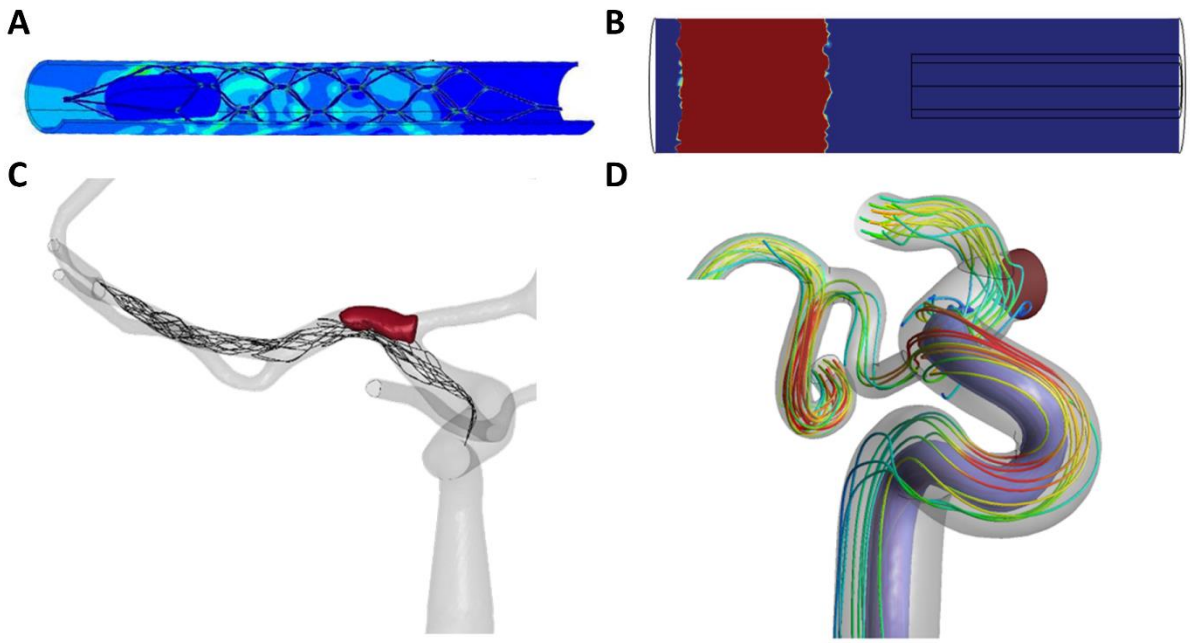

Figure 2: In silico thrombectomy models in different vessel geometry complexity. **(A)** Thrombectomy in straight vessels with stent-retriever (Gu et al. 2017) and **(B)** with aspiration (Chitsaz et al. 2018). **(C)** Thrombectomy in 3D patient-like vessels with stent-retriever (Luraghi et al. 2021) and **(D)** with aspiration (Neidlin al. 2016).

Regarding the mechanical behavior of the vessel walls, a typical nonlinear anisotropic law could be adopted, as well the presence of different layers should be introduced (Holzapfel et al., 2004). From a numerical point of view, this complexity of modeling could not be necessary to the virtual thrombectomy investigation. Added to the well-known complexity of modeling "soft tissue", there is a lack of a pragmatic mechanical catheterization of cerebral arteries particularly in the state-of-the-art. These are the main justifications for considering the vessels as rigid walls (Chitsaz et al., 2018; Good et al., 2020; Gu et al., 2018; Giulia Luraghi et al., 2021; Giulia; Luraghi et al., 2021; Mukherjee and Shadden, 2018; Neidlin et al., 2016; Pennati et al., 2010; Shi et al., 2017). On the contrary, Romero and Talayero group assumed a linear elastic behavior for the vessel (Romero et al., 2020, 2013, 2012; Talayero et al., 2020, 2019) while (Gu et al., 2017), who aimed at evaluating artery wall injury or rupture, employed a hyperelastic material.

3.2 Clot models

Different models have been reported in the literature, employing both solid and fluid approaches, to efficaciously capture blood clots' viscoelastic, compressible behavior. A Bond-

graph technique is used by the Talayero and Romero group in various thrombectomy studies (Romero et al., 2020, 2013, 2012; Talayero et al., 2020, 2019). Talayero et al. (2019) applied a 3D multi-body geometrical model for the thrombus, based on a 2D Bond Graph model. Talayero et al. (2020) and Romero et al. (2020) both used a Bond Graph technique, in one case to compare it to FEA and CFD analyses, in which the thrombus was modeled using a hyperelastic Mooney-Rivlin material model. In the other case, the Bond-Graph technique was applied to define the thrombus properties for a computational model as an isotropic, nonlinear, incompressible, elastic material (Talayero et al., 2020).

(Tutwiler et al., 2020) developed a FEM for thrombus fragmentation using a fibrin hydrogel. The fibrin hydrogel was modeled as a biphasic material with the fibrous network as a solid mass filled with a liquid. (Gu et al., 2017) modeled the clot with a bullet shape and used the Mooney-Rivlin model to describe the hyperelastic material behavior. An FEA Lagrangian approach was selected by (Good et al., 2020) to model the clot with incompressible viscoelastic behavior; both Kelvin–Voigt and Oldroyd-B cases were used by setting the material parameters from experiments. The hybrid particle–continuum approach proposed by (Mukherjee and Shadden, 2018) to model two different clot geometries is part of the non-boundary-fitted FSI family. The so-called Fictitious domain method entails an FEA modeling for the fluid and a collection of mesh-free, off-lattice, discrete elements for the clot. (Chitsaz et al., 2018) modeled the clot as a 3D fibrin network of randomly distributed branch points that are interconnected by fibrins. The clot deformation was simulated by tracking the position of branch points, while the clot dissolution considering the fibrin bonds decay. In two CFD analyses (Neidlin et al., 2016; Pennati et al., 2010), the clot was modeled with an Eulerian-Eulerian two-phase approach in which the higher viscosity material of the clot was tracking with a Volume of Fluid approach. The FEA model of the clot proposed by (Giulia Luraghi et al., 2021) involved a simplified compressible quasi-hyperelastic foam model defined by fitting a single uniaxial load curve from unconfined compression tests based on (Fereidoonnezhad et al., 2021b). In (Giulia; Luraghi et al., 2021), the risk of clot fragmentation during the stent-retriever thrombectomy procedure was considered using the Extended Finite Element Method (Fereidoonnezhad et al., 2021a).

3.3 Devices

Ten of the analyzed papers focused on aspiration thrombectomy, while only three papers on stent-retrieveral thrombectomy. (Gu et al., 2018, 2017) designed a non-commercial Nitinol stent-retriever using a 3D FEM in Abaqus. An axisymmetric model was built to reduce

computational costs. The stent-retriever was modeled as a homogeneous isotropic incompressible deformable body. To describe the behavior of the stent-retriever, the shape-setting cylinder and expanding cylinder were modeled as a semirigid movable cylinder shell. A user subroutine was used to model the NiTi material. In (Giulia Luraghi et al., 2021; Giulia; Luraghi et al., 2021), the EmboTrap II (CERENOVUS, Galway, Ireland) and TREVO ProVue stent (Stryker, US) were modeled with beam finite elements. The NiTi material parameters were calibrated through a coupled in vitro/in silico analysis. Crimping simulations of the device in a microcatheter with an inner diameter of 0.5 mm followed by unconstrained release were used to validate the stent-retriever kinematics.

The clinically used modeled aspiration catheters were Penumbra 5MAX and 4MAX (Penumbra Inc., Alameda, CA, USA), two configurations of the Driver CE catheter (Invatec, Roncadelle, Italy), and the GPTAD (Pearce et al., 2007).

3.4 Procedural settings

Regarding the aspiration thrombectomy evaluation, the range of applied suction pressures varied from 10 kPa to 100 kPa. In the study of (Neidlin et al., 2016), an outflow rate of 100 ml/min was applied. The modeled distance between the catheter tip and the proximal side of the thrombus ranged between 0.0 mm and 5.0 mm. Wall apposition, clot-device interaction, and clot integration play key-roles in the EVT. They are still not well understood and investigated. Different innovative thrombectomy techniques declare to improve these aspects with improved outcomes (Chueh et al., 2020a; Lin et al., 2019; Ospel et al., 2019). From a numerical point of view, there is an important lack of studies on both clot-device and clot-vessel interactions investigation. In four analyzed FEA studies (Gu et al., 2018; Giulia Luraghi et al., 2021; Giulia; Luraghi et al., 2021; Romero et al., 2020), rough contact between the clot and the vessel wall was defined with a friction coefficient varying from 0.1 to 0.4. In the studies with the implemented bound-graph model (Romero et al., 2012; Talayero et al., 2019), a progressive detachment from the vessel wall was modeled by including in the model a force of friction calculated by the platelet adhesion force. In the FEA study proposed by (Good et al., 2020) a viscoelastic CZ model for the thrombus–artery interface has been proposed, whose kinematics consists of the CZ opening displacement and opening displacement rate.

3.5 Main findings

The in silico studies mainly focused on the development of the computational methodologies and appropriate models, as well as the validation of these models. (Romero et al., 2020, 2013;

Talayero et al., 2020, 2019) generated in silico models to estimate the maximum allowed suction force without any clot damage and the force required to extract the clot from the artery. In the case of an aspiration catheter far from the clot, the suction generated a vessel narrowing and consequent potential damage. The aspiration ratio of the clot, aspiration time, amount of free fragments, wall shear stress, and extracted volume of the blood were analyzed to compare 4MAX and 5MAX Penumbra aspiration catheters (Chitsaz et al., 2018). 4MAX catheter was shown to result in greater distal embolization, while 5MAX catheter was demonstrated to increase the risk of vessel wall damage. The peak velocity and the suction force-distance relation were analyzed to optimize (Shi et al., 2017) and compare device geometries (Pennati et al., 2010). A catheter with central and side holes had worse performance than the single central lumen catheter. An in-house designed stent performance was investigated by evaluating the risk of vessel damage (Gu et al., 2018, 2017). The modeling results indicated a possible collapse of the middle segment of the modeled stent inside a curved vessel. An important step for in silico studies is the validation of the numerical models, which of paramount importance for the translation of the modeling findings to the clinical practice with high confidence. Despite the great importance of validation of in silico models, only two papers provided a validation analysis. Both studies used a coupled in vitro - in silico approach for this, one for clot aspiration (Good et al., 2020) and the other one for thrombectomy procedure with stent retrievers (Giulia Luraghi et al., 2021). Only one paper numerically reproduces a complete patient-specific scenario of the EVT (Giulia; Luraghi et al., 2021).

4. Concluding remarks

This review provided an overview of the current state-of-the-art of in vitro and in silico evaluation of EVTs. To this end, we have identified a total of 39 papers, of which 23 performed an in vitro analysis, 16 an in silico analysis, and 2 a combination of both. Considering the multitude of the mechanical aspects of EVT, the variety of the devices and techniques, and the fact that it has been more than 10 years since the introduction of EVT to the clinic, this limited number of papers demonstrates that EVT is still an understudied treatment from an engineering point of view, especially from in silico perspective.

In this review, four main aspects of the in vitro and in silico analyses of EVT were outlined separately in detail: vessel model/geometry, clot material, mechanical devices, and procedural settings. Regarding the vascular model, it was observed that the physical models in in vitro studies and the virtual vessels in in silico studies lacked some essential characteristics of the real vasculature. The importance of having realistic 3D vessel morphologies, especially for

siphon tortuosity in ICA, was highlighted in various papers (Chueh et al., 2012; Good et al., 2020; Gu et al., 2017; Waqas et al., 2020). Yet, many in vitro studies used simplistic geometric models. The choice of the vessel material in in vitro studies is also important. Unfortunately, the commonly used materials (i.e., glass and silicone) do not only lead to inaccurate vessel stiffness in the model but also unrealistic friction behavior and interaction with the clot (Johnson et al., 2020b; Wenger et al., 2013). The majority of the in silico studies entail straight or idealized geometry, and rigid or linear elastic material model for the vasculature. These simplifications are likely to affect the interaction between the stent-retrievers and the vessel walls (Giulia Luraghi et al., 2021), as well as prevent the investigation of possible vessel collapse during the aspiration procedure (Neidlin et al., 2016).

Regarding the clot models, in vitro studies used clot analogs and the in silico models mainly used properties extracted from clot analogs, which cannot capture the entire diversity of human clot nature (Simon et al., 2014). The assumption of standardized and/or idealized clots must be taken into account especially because real clots present a variable fragmentation behavior (Tennuci et al., 2011), size and texture (Machi et al., 2017), and irregular distribution of components (Johnson et al., 2020a). The clot material homogeneity assumption, widely employed in in silico models and in creating clot analogs, is also unrealistic (Good et al., 2020; Johnson et al., 2020b). The difficulty in designing appropriate experimental tests for characterizing the clot material properties (Johnson et al., 2017) is also highlighted in some studies (Johnson et al., 2020a; Giulia Luraghi et al., 2021). Yet, ad-hoc experimental characterization tests are of paramount importance for accurate clot behavior implementation in in silico models.

As regards to devices, the most clinically used aspiration catheters and stent retrievers were utilized in in vitro and modeled in silico studies. In in vitro studies, the actual devices can be used and their performance evaluated with direct measurements. For the in silico analyses, the accurate implementation of the treatment device poses a particular challenge, especially for stent retrievers as they entail discretization choice and material model to replicate the original shape memory alloy material of the device. Aspiration catheters have been always modeled rigid, mimicking the real material accurately, while stent-retrievers were discretized with finite elements and non-linear material models (Gu et al., 2018, 2017; Giulia Luraghi et al., 2021; Giulia; Luraghi et al., 2021).

In vitro models aimed at mimicking the in vivo procedural environment during the EVT as close as possible, by implementing physiologically realistic fluid and flow characteristics, pressures, and temperature. In the experimental EVT replica, the operator performance may be

critical when testing treatment efficacy as it could affect the in vitro results. In in silico analyses, the EVT outcomes are not operator-dependent but are affected by the choice of the applied numerical algorithm and boundary conditions. In the in silico analyses, the complexity of implementing the procedure numerically does not allow to model the whole procedural environment, and enforces various simplifications and/or assumptions in the models, such as neglecting the blood flow or assuming rigid material behavior of micro-catheters.

It is clear from the clinical studies that the EVT can still greatly benefit from further procedural improvement and device optimization. In vitro and in silico analyses provide a great platform to advance towards this goal and have been already used to explore, study and investigate different aspects of the EVT and devices. It is extremely important to mimic the procedure and the in vivo environment as realistically as possible in these models. Both in vitro and in silico approaches have certain advantages over the other approach. For instance, in vitro EVT tests are easier to set up as the in silico models require special expertise in numerical modeling of the various aspects of the complex multi-physical problem at hand. Yet, once generated, in silico models enable testing various scenarios more easily via parametric and sensitivity analyses. Hence, both in vitro and in silico tests are of great value and should be considered complementary. For instance, validation analysis is indeed crucial to achieve high fidelity in silico models, before one can make use of their great potential for analyzing practical aspects of EVT and improving the clinical treatment procedures and devices. In vitro models provide a great platform for this crucial validation step of the in silico models. Moreover, in silico models can help in designing experimental set-up while in vitro models are required to define numerical parameters in the in silico models. In conclusion, both in vitro and in silico EVT analyses are essential tools not only for the assessment of the existing devices and/or procedures but also for designing new devices and optimization of treatment.

Conflict of interest: GL has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 777072.

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Table 1: Summary of the in vitro analyzed studies.

Paper	**Focus**	**Procedure**	**Vessel (geometry, material)**	**Clot (type, material)**	**Settings**
Chueh et al. 2012	Characterizing flow restoration and distal emboli	Stent retriever/Aspiration	ICA/MCA, silicone	Unspecified, bovine blood clot analog	60%/40% solution of water/glycerin, use of a lubricant, physiologically realistic flow waveform
Chueh et al. 2013	Evaluating proximal flow control	Stent retriever	ICA/MCA, silicone	1) Hard inelastic clot, bovine blood clot analog and 2) soft elastic clot, human blood clot analog	Saline, peristaltic roller pump
Chueh et al. 2020b	Characterizing recanalization and distal Emboli with a ThrombX retriever	Stent retriever/Aspiration	Circle of Willis, silicone	Bovine clot blood analogs. 1) A stiff elastic clot (calcium phosphate apatite), and 2) a soft friable clot (barium sulfate)	Saline, peristaltic roller pump
Fennell et al. 2018	Evaluating geometric clot extractor	Stent retriever	Near complete circle of Willis, 3D print material (unspecified)	1% RBCs, ovine blood clot analog	Water, 37ºC, continuous flow pump
Girdhar et al. 2020	Stent retriever length effect for fibrin-rich clots	Stent retriever	ICA-M2 segment of the MCA, silicone	Fibrin-rich, porcine blood clot analog	0.2%v/v soap and water solution, 37ºC, pulsatile pump
Good et al. 2020	Developing an in silico model of aspiration (In vitro model used for validation)	Aspiration	Chamber to mimic a 5x enlarged cerebral artery (straight), 3D-print material (unspecified)	Viscoelastic, neoprene rubber	cyclic aspiration pressure waveforms
Johnson et al. 2020a	Effects of platelet-driven contraction on blood clot microstructure and mechanical behavior	Stent retriever/Aspiration	Commercial model (Elastrat Sàrl, Geneva, Switzerland), unspecified	8 different analogs either PCC or NCC with varying hematocrits, ovine blood clot analogs	Saline, 37ºC

Johnson et al. 2020b	Development of an in vitro model of calcified cerebral emboli	Stent retriever/Aspiration	Commercial model (Elastrat Sàrl, Geneva, Switzerland), silicone	Calcified clot analogs, ovine trabecular bone 1) with or 2) without surrounding thrombus matrix	Saline, 37ºC, continuous flow pump
Lally et al. 2016	Effect of suction conditions on perfusate flow during aspiration	Aspiration	Straight, glass	Unspecified, ovine blood clot analog	Perfusate with hematoxylin particles, physiological mean pressure, flow rates= 5 to 40 kPa and 2, 5, and 8 mL/min
Luraghi et al. 2021	Developing an in silico model of thrombectomy (In vitro model used validation)	Stent retriever	1) U-bend, glass, 2) funnel-shape, silicone and 3) vascular branch, silicone	Unspecified, ovine blood clot analog	Saline, static flow, 37ºC
Machi et al. 2017	Interaction between various stent retrievers and thrombi	Stent retriever	Carotid – MCA Chamber, 3D-print material (unspecified, rigid)	Human blood clot analogs: 1) Red thrombi, whole blood and 2) white thrombi, plasma	Saline, static flow, 37ºC
Madjidyar et al. 2015	Stent-thrombus interaction and the influence of additional aspiration	Stent retriever/Aspiration	Custom-made commercial model (Elastrat Sàrl, Geneva, Switzerland), silicone	Elastic and stable, human blood clot analogs	60%/40% solution of water/glycerin, use of a lubricant, 37ºC, pulsatile flow
Madjidyar et al. 2020	Testing efficacy of 6F ADAPT alone and 5F ADAPT combined with 8F balloon guide catheter	Aspiration	Commercial model (Elastrat Sàrl, Geneva, Switzerland), silicone	Human blood clot analogs: 1) red clot, whole blood and 2) white clot, plasma, buffy coat and some RBCs	60%/40% solution of saline/glycerin, use of a lubricant, 37ºC, pulsatile flow
Mokin et al. 2015 JNIS	Comparison of combined stent retriever–aspiration stent and retriever-alone approach	Stent retriever/Aspiration	Intracranial circulation, 3D print material (TangoPlus)	Unspecified, porcine blood clot analogs	60%/40% solution of water/glycerin, Pulsatile pump, 37ºC

Mokin et al. 2015 AJNR	Comparison of recanalization success of four thrombectomy approaches	Stent retriever/Aspiration	Intracranial circulation, 3D print material (*TangoPlus)	Unspecified, porcine blood clot analogs	60%/40% solution of water/glycerin, Pulsatile pump, 37ºC
Ohshima et al. 2019	Measurement of clot-capturing ability of stent retrievers	Stent retriever	Straight, polyvinyl chloride	Unspecified, urethane foam	37ºC
Sanchez et al. 2020	Assessment of efficacy of the Advanced Thrombectomy System	Stent retriever/Aspiration	Carotid arteries and posterior circulation with 1) moderate tortuosity and 2) severe tortuosity, 3D print material (unspecified)	Porcine blood clot analogs 1) fibrin-rich/resistant, and 2) RBC- rich/ fragile, referenced Chueh et al. (2011) and Duffy et al. (2017) methods	Saline, peristaltic pump, 37ºC
Simon et al. 2014	Efficacy of cyclic and static aspiration	Aspiration	Straight, rigid plastic	Unspecified, polyurethane	Aspiration medium is water
Tanyildizi et al. 2020	Evaluation of a new funnel-shaped distal access catheter tip	Stent retriever	Straight, IV line	Unspecified, porcine blood clot analogs	60%/40% solution of water/glycerin, room temperature
Tennuci et al. 2011	Comparison of three recanalization approaches	Stent retriever/Aspiration	Commercial model (Elastrat Sàrl, Geneva, Switzerland), silicone	Unspecified, lamb blood clot analogs	Hartmann's fluid, peristaltic pump, 37ºC
van der Marel et al. 2016	Evaluation of device–clot interaction	Stent retriever	Circle of Willis, silicone	1) Hard inelastic clot, bovine blood clot analog and 2) soft clot, human blood clot analog	Saline, 37ºC
Weafer et al. 2019	Characterization of strut indentation of stent retriever	Stent retriever	Straight, silicone	0% high density, 0% low density, 5%, 40% and 80% RBC, ovine blood clot analogs	Constant pressure of 90 mmHg
Wenger et al. 2013	Efficacy testing of Aperio stent retriever	Stent retriever	Intracranial carotid bifurcation with the M1 and A1 segment, glass	Unspecified, porcine blood clot analogs	Pulsatile blood pump, water, 37ºC

ICA, internal carotid artery; MCA, middle cerebral artery; NCC, non-contracted clot; PCC, platelet-contracted clot; RBCs, red blood cells

* Described previously – assumed to be TangoPlus 3D print material.

Table 2: Summary of the in silico analyzed studies.

Paper	**Focus**	**Numerical model ***	**Vessel (geometry, material)**	**Clot (model, material)**	**Device**	**Thrombectomy settings**
Chitsaz et al. 2018	Aspiration catheter performance	FSI	Straight, rigid	Fibrin network of branch points interconnected by fibrins	Penumbra 4MAX, 5MAX	3 static aspiration pressures (10, -30, -50 kPa)
Good et al. 2020	Clot-vessel interaction during aspiration	FEA (with CZ)	Straight, rigid	Finite-element, incompressible viscoelastic	Penumbra 5MAX	cyclic aspiration pressure (between 0 and -40 mmHg) with two frequencies (0.5 and 1 Hz)
Gu et al. 2017	Stent retrievers performance	FEA	Straight, hyperelastic	Finite-element. incompressible hyperelastic	Non-commercial stent-retirever	Stent crimping, deployment and retrieval
Gu et al. 2018	Stent retrievers radial force	FEA	C-shaped, rigid	-	Non-commercial stent-retirever	-
Luraghi et al. 2021 *Focus*	Thrombectomy with stent retrievers	FEA	U-bent and funnel and patient-like, rigid	Finite element, compressible hyperelastic	EmboTrap II	Stent crimping, deployment and retrieval in different vessels
Luraghi et al. 2021 *JBiomech*	Patient-specific thrombectomy with stent retrievers	FEA	patient-like rigid	Finite element, compressible hyperelastic + fragmentation	TREVO ProVue	Stent crimping, deployment and retrieval in a patient-specific scenario. Clot fragmentation evaluation.
Mukherjee and Shadden 2018	Flow around/within the clot	FSI	Straight, rigid	Blood fluid and fibrin particles	-	-
Neidlin et al. 2016	The circle of Willis flow during aspiration	CFD (coupled 1D-3D)	patient-like rigid	High viscosity blood	Undefined aspiration cathter	Aspiration flow rate (100 ml/min)
Pennati et al. 2010	Impact of aspiration catheter geometries on suction force	CFD	Straight, rigid	High viscosity blood	Driver CE catheter	Static aspiration pressure (-100 mm Hg)

Romero et al. 2012	Aspiration modeling	LPM	Straight, linear elastic	2D Bond Graph, elastoplastic	GPTAD	Static aspiration pressure (from 0 to -100 kPa)
Romero et al. 2013	Comparison of aspiration thrombectomy and stent retriever	LPM	Straight, linear elastic	2D Bond Graph. elastoplastic	GPTAD, Solitaire	Static aspiration pressure (from 0 to -100 kPa)
Romero et al. 2020	Aspiration modeling	LPM, FEA, CFD	Straight, linear elastic	Finite-element, incompressible hyperelastic	GPTAD	Combined axial and torsional load
Shi et al. 2017	Aspiration suction force	CFD	Straight , rigid	-	Penumbra 4MAX	Static aspiration pressure of -30 kPa
Talayero et al. 2019	Aspiration catheter geometries on suction force	LPM	Straight, linear elastic	2D Bond Graph elastoplastic	GPTAD	3 different aspiration pressures (-50, -80 and -100 kPa), progressive detachment of the thrombus from the vessel wall
Talayero et al. 2020	Aspiration catheter geometries on suction force	LPM, FEA, CFD	Straight, linear elastic	Finite-element, incompressible hyperelastic	GPTAD	9 Different catheter tips, 3 different static aspiration pressures (-20, -30 and -40 kPa)
Tutwiler et al. 2020	Clot toughness	FEA	-	Finite-element, fibrin hydrogel	-	-

*FSI: fluid-structure interaction, FEA: finite element analysis, CZ: cohesive zone, CFD: computation fluid-dynamic, LPM: lumped parameter model