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Lumen-oriented versus wall-oriented treatment strategies for intracranial aneurysms – A systematic review of suggested therapeutic concepts

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Abstract

The development of new treatment strategies for intracranial aneurysms (IAs) has been and continues to be a major interest in neurovascular research. Initial treatment concepts were mainly based on a physical-mechanistic disease understanding for IA occlusion (lumen-oriented therapies). However, a growing body of literature indicates the important role of aneurysm wall biology (wall-oriented therapies) for complete IA obliteration. This systematic literature review identified studies that explored endovascular treatment strategies for aneurysm treatment in a preclinical setting. Of 5278 publications screened, 641 studies were included, categorized, and screened for eventual translation in a clinical trial. Lumen-oriented strategies included (1) enhanced intraluminal thrombus organization, (2) enhanced intraluminal packing, (3) bridging of the intraluminal space, and (4) other, alternative concepts. Wall-oriented strategies included (1) stimulation of proliferative response, (2) prevention of aneurysm wall cell injury, (3) inhibition of inflammation and oxidative stress, and (4) inhibition of extracellular matrix degradation. Overall, lumen-oriented strategies numerically still dominate over wall-oriented strategies. Among the plethora of suggested preclinical treatment strategies, only a small minority were translated into clinically applicable concepts (36 of 400 lumen-oriented and 6 of 241 wall-oriented). This systematic review provides a comprehensive overview that may provide a starting point for the development of new treatment strategies.

Keywords

Aneurysm, animal model, endovascular treatment, lumen, wall

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Introduction

The development of new strategies for treatment of intracranial aneurysms (IAs) has remained a major interest in neurovascular research for decades. Endovascular treatments (EVT) have become increasingly popular since the introduction of detachable coils (GDCs) by Guido Guglielmi in 1990.[1] Initial concepts were based on a rather physical-mechanistic aneurysm understanding, specifically, focused on occlusion of the intra-aneurysmal blood flow, or so-called lumen-oriented therapies. Better understanding of the pathophysiological processes that trigger aneurysm formation, growth, and eventually rupture would reveal the important role of IA vessel wall biology for

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long-lasting IA obliteration after treatment. Accordingly, therapeutic concepts emerged to investigate the IA wall-mediated healing process after EVT, so called wall-oriented therapies.

This systematic review aims to identify all strategies that have been suggested for treatment of aneurysms in an experimental setting. Furthermore, we identified which of the various preclinical strategies reviewed were then tested in a clinical setting. Studies were categorized as lumen-oriented or wall-oriented concepts and then further grouped into subcategories of similar concepts.

Material and methods

Search strategy

Using the Medline/PubMed database, we conducted our systematic literature search to identify preclinical studies that presented a treatment strategy for IAs. The search, performed on January 1, 2021, was restricted to "animals" and used the keywords "aneurysm" in combination with "mice," "rat," "rabbit," "dog," and "swine" with the Boolean operator [AND]. Two investigators (BG and FvFC) independently screened 5278 titles and abstracts to select studies that met our predefined eligibility criteria. Confirmation of articles for inclusion and resolution of any disagreement about a particular study's eligibility was resolved by the third author (SM). Details of our search algorithm and reasons for exclusion are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[2] (Figure 1).

Eligibility criteria and analyzed features

Included were all studies that used intracranial and extracranial *in-vivo* cerebral aneurysm models conducted in mice, rats, rabbits, dogs, and swine (Supplementary Figures 1 and 2).[3,4] Excluded were studies on abdominal aortic aneurysms (AAA), non-English publications, non-original research (e.g., reviews, letters, editorials), and studies using non-*in-vivo* animal models (i.e., computer models, cell cultures).

The 641 studies included were reviewed and categorized as primarily a lumen-oriented or wall-oriented treatment strategy published from 1963 to 2021. Lumen-oriented strategies included (1) enhanced intraluminal thrombus organization, (2) enhanced intraluminal packing, (3) bridging the intraluminal space, and (4) other, alternative concepts. Wall-oriented strategies included (1) stimulation of proliferative response, (2) prevention of aneurysm wall cell injury, (3)

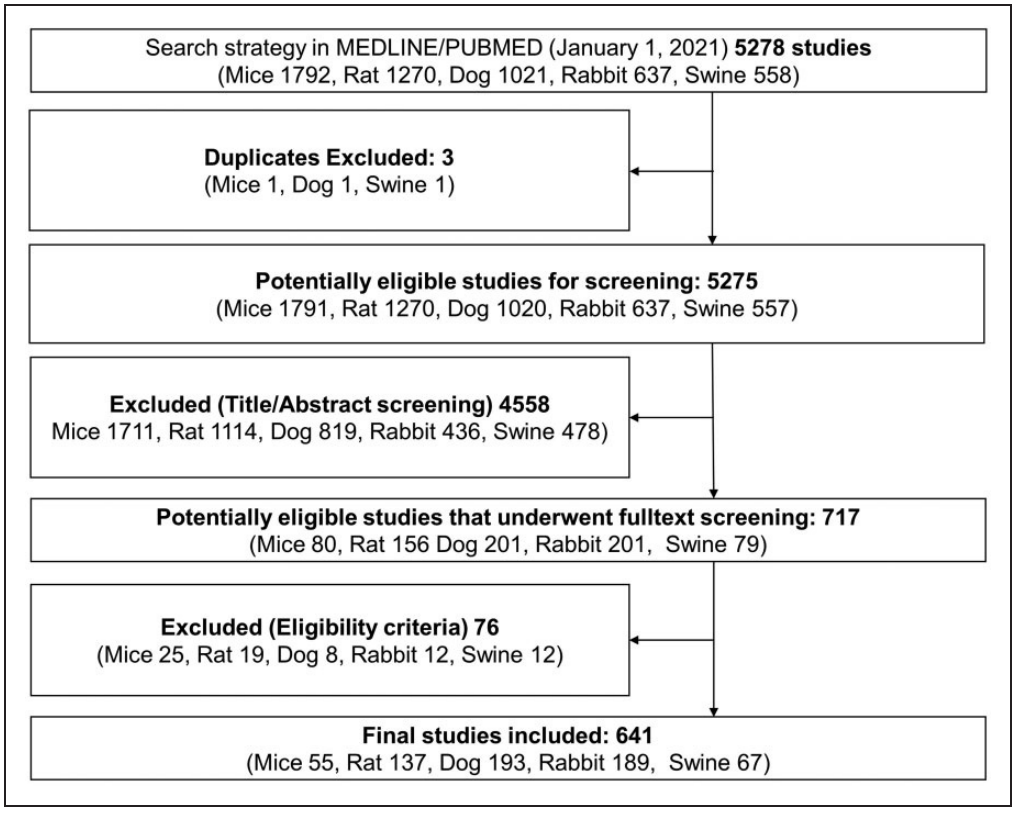

Figure 1. PRISMA Flow chart for study selection and exclusion.

inhibition of inflammation and oxidative stress, and (4) inhibition of extracellular matrix degradation. Overall numbers of publications of lumen-oriented and wall-oriented strategies were counted and listed by year of publication. We also grouped studies by treatment concept, specifically as a novel treatment reported for the first time or a major modification of a previously reported strategy. Uncertainty about the novelty of a particular study was discussed by at least two authors and consensus reached by the above-mentioned criteria. Finally, we performed a specific search on Medline/PubMed and clinicaltrials.gov to identify any possible clinical counterpart using any of the preclinical strategies included in this review.

Results

Of the 5278 studies screened, 641 studies met our inclusion criteria (Figure 1). Although published research on IA treatments was scant until the early 1990s, the number of publications on lumen-oriented therapies drastically increased after the introduction of GDCs in 1991. Wall-oriented strategies, which remained on a low level for another decade, increased steeply after 2005 and eventually outnumbered the studies published on lumen-oriented therapies in recent years (Figure 2).

Overall, most of the available EVT modalities and large research efforts were directed toward treatment of the visible IA lumen. We found that most approaches fell into one of three groups of strategies (Figure 3) as follows: first, methods to enhance intraluminal healing by means of increased thrombosis and fibrosis after EVT; second, methods to increase intraluminal packing volume and maximize packing of the aneurysm lumen; and third, methods to exclude intraluminal space from the circulation system by bridging the aneurysm neck. In addition to these three categories, few alternative treatment concepts have been investigated. Of 400 lumen-oriented preclinical concepts, 36 studies were translated into clinical trials (see summary in Supplementary Table 1).

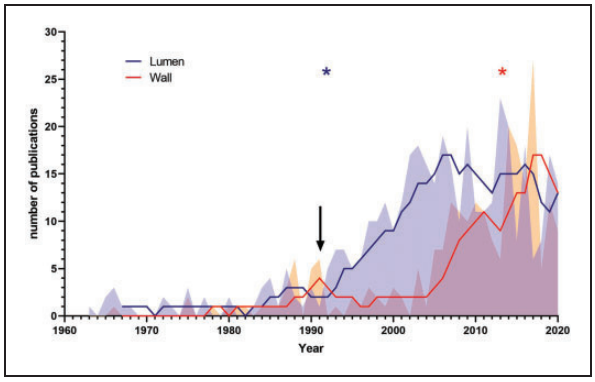

Figure 2. Comparison of lumen-oriented and wall-oriented therapies per year. Line shows the five-year average for lumen-oriented (blue) and wall-oriented (red) therapies, and the corresponding shadow shows the number of publications for each strategy per year. For most years, publications of lumen-oriented strategies outnumber wall-oriented strategies. In recent years, wall-oriented strategies became more popular, which is shown by the light-red peaks (i.e., in 2018) and the consistent rise of the red line. Introduction of Guglielmi detachable coils (black arrow) and the first publications (*) for a new treatment concept in a clinical setting, in 1992 (lumen) and in 2013 (wall), respectively.

Wall-oriented therapies were organized into four categories (Figure 4): first, stimulation of smooth muscle cells (SMC) to undergo proliferation and reinforce the aneurysm wall; second, protection or enhancement of endothelial cell (EC) and SMC cell function; third, reduction or inhibition of inflammation and oxidative stress; and fourth, inhibition of extra cellular matrix (ECM) degradation. Of 241 lumen-oriented preclinical concepts, 6 were translated into clinical trials and among these, 1 trial was withdrawn. A summary of the lumen-oriented treatment approaches and strategies tested in clinical trials appear in Supplementary Table 2. In Supplementary Table 3, species and models used, and conclusions of all preclinical studies are given.

Discussion

This systematic review analyzed the findings from 641 studies during a 57-year period that included a plethora of *in vivo* cerebral aneurysm models using select animals, of which a minority (n = 42) were translated into clinically applicable concepts. Overall numbers of lumen-oriented strategies exceeded wall-oriented strategies. By comparing these strategies, we identified key trends that can further advance our understanding of the mechanisms leading to IA recurrence. Human histological studies suggesting that the intraluminal thrombus remains unorganized after GDC treatment, and that the intracranial aneurysm does not heal by means of intraluminal scar formation led to the innovation of lumen-oriented treatments aimed to increase thrombogenicity and hasten healing. This review provides an effective starting point for the development of new treatment strategies.

Enhanced intraluminal thrombus organization

These strategies aim to enhance the aneurysm healing process with lumen-derived factors that will stimulate thrombus organization, neointima formation, and fibrosis of the former aneurysm lumen. With GDCs long recognized as biologically inert, other strategies emerged to increase the biological activity that initially included silk,[5] dacron,[6] and nylon[7] fibers. Platinum coils coated

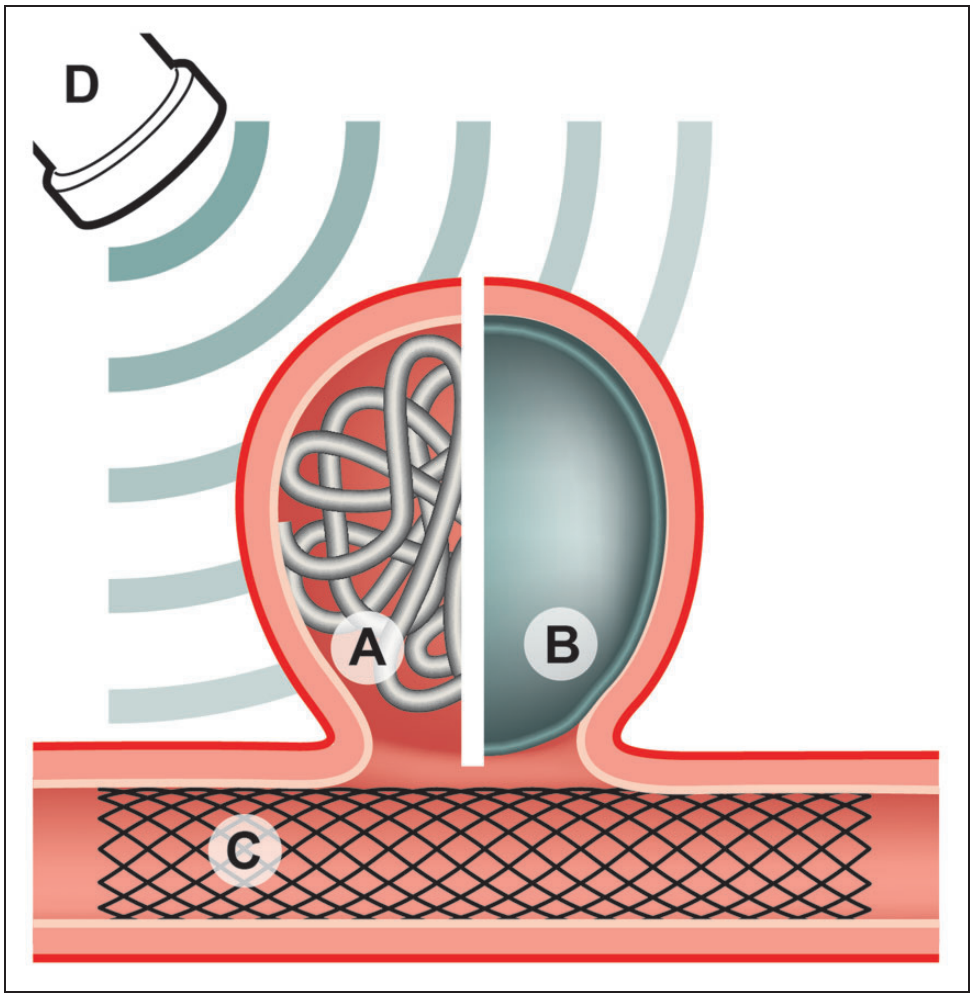

Figure 3. Lumen-oriented treatment strategies are grouped into four types with the following aims: (a) enhance intraluminal thrombus organization; (b) enhance intraluminal packing; (c) bridge the intraluminal space; and (d) alternative concepts (i.e., other strategies for endothelial denudation, navigation of microparticles inside the aneurysm lumen, application of focused ultrasound, and application of γ-knife irradiation).

with three different polyurethanes demonstrated improved thrombogenicity.[8] Based on the combined characteristics of potent thrombogenic agents and promotion of chemotaxis and cell adhesion, collagen and other extracellular matrix proteins represented ideal coating materials to enhance intraluminal thrombus organization.[9,10] Type I collagen proved superior to type IV collagen in terms of *in-vitro* cellular proliferation. Ion implantation in combination with a protein coating improved the strength of cell adhesion when exposed to flow shear stress.[11,12] Later developments included the incorporation of biodegradable polymeric materials (polyglycolic/poly-L-lactic acid copolymers) into the coil core platinum frame and polyglycolic acid into the lumen of the primary platinum wind of the coil.[13–15]

Growth factors have been studied intensively for their role in enhancing intraluminal IA scar formation. Basic fibroblast growth factor (bFGF) has been applied to coils in various techniques. Coils have been coated with genetically modified bFGF-secreting fibroblasts,[11] gauze-wrapped gelatin hydrogel-incorporated bFGF,[16] coated with hydrogel-releasing bFGF,[17] hydrogel incorporated in hollow fibers of polyethylene releasing bFGF,[18] or a polyvinyl alcohol core delivering bFGF.[19,20] Comparison of type I collagen coated GDC with and without additional vascular endothelial growth factor (VEGF) suggested that VEGF may be beneficial in promoting endothelialization, clot organization, and tissue integration of the coil.[21] Transforming growth factor-β (TGF-β) delivered with alginate did not show added benefits when compared with alginate gelatin sponges alone.[22] Testing of autologous mesenchymal stem cell, endothelial progenitor cell, and most often fibroblast cell endografts augment intraluminal scar formation and hasten endothelialization.[11,23–25]

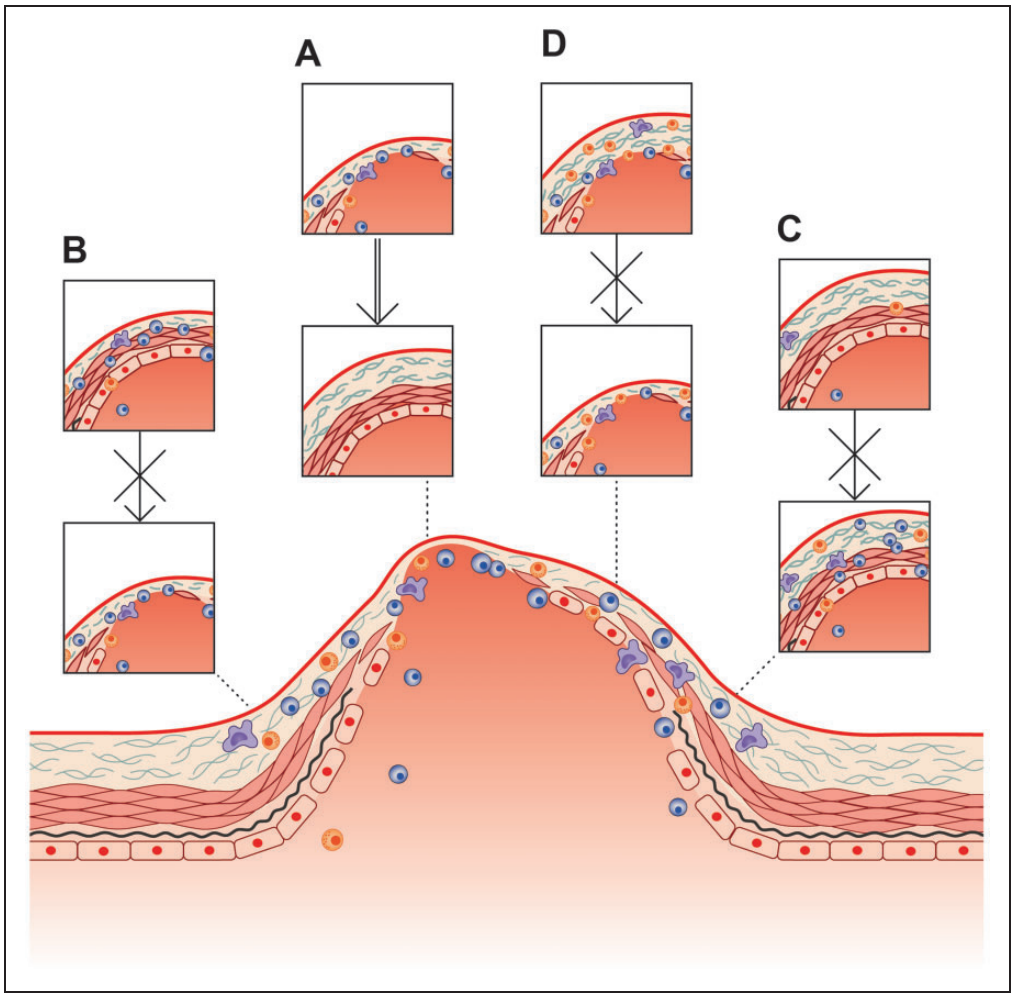

Figure 4. Wall-oriented treatment strategies. Strategies were categorized with to aim to stimulate the proliferative response (a), prevent aneurysm wall cell injury (b), inhibit the inflammation and oxidative stress (c), and inhibit the extracellular matrix degradation (d).

Increased intraluminal packing

Initial complete IA occlusion and high intraluminal packing density were recognized as important factors in reducing recurrence. Rather than accelerating thrombus organization, devices were developed to minimize thrombus formation by packing the IA lumen as completely as possible. Platinum coils used as carriers for expandable hydrogel materials produced a ninefold increase in volume when placed into a physiological environment.[26] Packing volume can be increased by complex-shaped coils that seek out the true aneurysm periphery[27] and by liquid embolic agents engineered for the same purpose. However, the high risk of migration of liquid embolic agents necessitated protection of the neck by neck-bridging and embolic-containing devices.[28,29]

Bridging the intraluminal space

The most effective way to completely exclude the IA lumen from the blood circulation system is likely achieved by bridging the intraluminal space with a stent or stent-like device that redirects the blood away from the lumen. Experimental work demonstrated that pore density of these devices may be the critical factor in treatment success.[30] Compared with standard stents, asymmetrical vascular stents containing areas with a near solid or very low-porosity patch to close the aneurysm orifice demonstrated superior results in advanced thrombus organization.[31,32] Despite excellent occlusion rates, clinical utility of devices spanning the aneurysm neck is limited by a number of potential complications and restricted by the possibility to treat ruptured aneurysm. Flow diverters require dual

antiplatelet therapy; immediate aneurysm occlusion is not guaranteed. Intraluminal flow diverters have therefore been proposed as a stand-alone therapy.[33,34] Nevertheless, many new devices in the marked are being tested in clinical trials.

Alternative concepts

Various alternative concepts emerged to achieve aneurysm thrombosis through a transcranial energy application. For instance, strategies included gamma knife,[35] focused ultrasound,[36] and navigation of intra-arterially applied magnetic microparticles by an external magnetic field.[37] Lastly, some have suggested that aneurysm recurrence after EVT occurs because of the persistence of endothelialized clefts that promote blood flow inside the former aneurysm dome and in the thrombus. Consequently, denudation of this endothelium seemed to be a promising strategy. Therefore, mechanical and radiofrequency endothelial ablation were suggested to prevent recanalization after endovascular coil occlusion.[38,39]

Wall-oriented therapies

Over recent years, the importance of IA wall pathobiology in aneurysm healing after EVT has becoming increasingly recognized. Therefore, novel EVT interventions not only target the visible lumen but also the molecular pathways relevant in aneurysm wall (patho-) biology. Better insights into the complex relationship of blood flow, intraluminal thrombosis, and aneurysm wall remodeling allowed for development of new therapeutic approaches with the aim to eventually enable a clinical curative IA treatment. Initial wall-oriented therapies were preliminarily based on systemic medications. However, more elaborate techniques that targeted local drug release subsequently led to a continuous merging of lumen-oriented and wall-oriented strategies, such as covering coils and stents with a drug-releasing surface. For many of the newly emergent treatments, dichotomization between lumen and wall orientation is not always clear but may represent a merging of both.

Stimulation of proliferative response

Blood coagulation factor XIII or fibrin-stabilizing factor are enzymes (transglutaminase) of the blood coagulation system that crosslink fibrin. Factor XIII is important not only in hemostasis but in wound healing through modulation of adhesion, migration, and proliferation of fibroblasts. In a rat aneurysm model, exogenous administration of factor XIII caused intimal proliferation at sites where aneurysms were expected to develop; therefore, it was proposed as a positive modifier of proliferative response at aneurysm development sites.[40] High-dose bFGF injected intravenously three months after IA induction in rats resulted in various degrees of intimal thickening in aneurysm walls. Immunohistochemistry demonstrated that this effect was mediated by proliferated SMCs.[41]

The protection of endothelial cells (ECs) and SMCs has been another promising therapeutic approach to reduce aneurysm formation and growth. Inducible NO synthase (iNOS), which appears to be involved in EC and SMC injury, was found to be unregulated in early aneurysmal changes. Inhibition of iNOS attenuated aneurysm changes and reduced the incidence of aneurysm formation.[42] Further studies demonstrated that genetic ablation of iNOS (iNOS–/– mice) did not reduce the incidence of induced aneurysms, but significantly reduced the size of aneurysms and the number of apoptotic SMC compared with iNOS+/+ mice.[43] Aligned with the detrimental effect of iNOS is the finding that defective IL-1β (a potent iNOS activator) signaling protects SMC from inflammation associated cell death.[44] These data suggest that regulation of iNOS and NO-induced SMC apoptosis could be a therapeutic target.

Prevention of aneurysm wall cell injury

Estrogen receptors are expressed on EC and SMC, and estrogen is thought to have beneficial effects on EC function and growth. Estrogen prevented induction and progression of experimental aneurysms[45] while estrogen deficiency resulted in endothelial dysfunction and reactive oxygen species (ROS) generation, triggering EC damage that leads to aneurysm formation.[46]

Another approach to protect EC and SMC is decreasing shear wall stress. In a rat aneurysm model, batroxobin (defibrinogenic agent) diminished fibrinogen concentration, lowered blood viscosity, and therefore lowered wall shear stress to reduce EC and SMC damage.[42] Mechanical stress can induce SMC apoptosis via endothelin B receptors (ETBR). Blockage of ETBR reduced SMC apoptosis and prevented formation of advanced IA[47] Erythropoietin treatment is known to increase endothelial progenitor cells (EPC), which are capable of replacing injured endothelial cells and improving endothelial function. Administration of erythropoietin in rats significantly suppressed the formation and progress of aneurysms.[48] Statins exert pleiotropic, cholesterol level independent vascular protective effects. In addition to improvements in endothelial and SMC function (inhibition of IL-1β and iNOS-induced apoptosis in SMC), statins reduce free radical formation and attenuate endothelial inflammatory reactions through inhibition of macrophage recruitment and adhesion. The role of statins in the

treatment and prevention of aneurysms has not yet been assessed; both experimental[49–51] and clinical[52,53] research has produced contradictory data.

Inhibition of inflammation and oxidative stress

A growing body of evidence implicates chronic inflammation as an important contributor to IA pathogenesis. The transcription factor nuclear factor-kappa beta (NF-κβ) has been identified as a major inflammatory mediator involved in IA formation.[54,55] NF-κβ transactivates genes related to endothelial dysfunction. This includes vascular cell adhesion molecule-1 (VCAM-1) and monocyte chemo-attracting protein-1 (MCP-1); both are involved in macrophage recruitment in the IA wall. NF-κβ also regulates the transcription of iNOS (mediates SMC cell death), IL-1β (activates iNOS and inhibits ECM biosynthesis), and MMPs (further increase ECM degradation in addition to the MMP-2 and MMP-9 secretion by macrophages).

Inhibition of DNA binding of NF-κβ by decoy oligodeoxynucleotides prevents IA formation by suppression of proinflammatory genes.[56,57] Nifedipine inhibits NF-κβ transcription activity, reduces IA wall MCP-1 expression, lowers macrophage infiltration, and decreases expression and activity of MMP-2.[58] Inhibition of the transcription factor Ets-1 suppressed MCP-1 expression and macrophage accumulation in IA walls.[59] Anti-MCP-1 gene therapy resulted in inhibition of IA progression in rats.[60] Ibudilast, which predominantly blocks phosphodiesterase-4, suppressed expression of endothelial leukocyte adhesion molecules and reduced migration of macrophages into the IA wall.[61] Inhibition of mast cell degranulation or depletion of monocytes likewise reduce chronic inflammation.[62,63]

Some have postulated that aspirin may decrease the incidence of IA with its inhibitory effects on inflammation: specifically, inhibiting MMP-2 and -9 and TNF-α in SMC; and reducing cell adhesion in EC by reduced NF-κβ activity.[64] However, causal connection has not yet been rigorously proved.[65] Tetracycline derivates have demonstrated anti-inflammatory effects (inhibition of MMPs, among others) and have reduced IA rupture rates in mice. Oxidative stress has been recognized as a major and critical mediator of the inflammatory cascade. Edaravone treatment, a free radical scavenger, reduced ROS production, inhibited macrophage invasion into IA wall, and decreased expression of the DNA-binding form of the NF-κβ p65 subunit, MCP-1, VCAM-1, and MMP-2.[66] ROS is produced through enzymatic reactions mainly by NADPH oxidase, HO-1, and iNOS.

Inhibition of extracellular matrix degradation

Selective inhibition of MMP-2, -9, and -12 (MMP-2 and -9 primarily secreted by macrophages) prevented the progression of existing IA in a rat model.[67] Inhibition of cysteine cathepsins (with elastolytic and collagenolytic properties) prevented ECM degradation and IA progression.[68] Similar to MMP-mediated degradation, the data suggests an active participation of macrophages in cathepsin-mediated ECM degradation. Inhibition of MMPs may be important not only in the progression of untreated IA, but potentially play a pivotal role in aneurysm remodeling after EVT. MMP-9 knockout mice showed significant reduction in recanalization and recurrence after carotid artery coiling compared to control mice.[69] These examples underline the importance of understanding IA wall biology for the design of novel EVT modalities.

Trends in translation

The development of novel EVT modalities faces a wide range of technical barriers that result from the need to pass through microcatheters, provide radiopacity, and combine low angiotoxicity with high biocompatibility. Despite promising initial experimental success - with exception of devices to bridge the intraluminal space - only 42 (7%) of 641 therapeutic approaches were resolutely pursued to clinical trials. Most of the novel therapies applied into clinical settings failed in early randomized trials compared with the standard of GDC treatment[70] or produced complications that dampened enthusiasm for their widespread use.[71]

One potential reason behind the failure of translation may have been related to the inadequacy of animal models.[72] Endovascular device research performed in animal models is riddled with bias that allow treatments to advance uncontrolled into human trials. For example, a novel treatment can achieve excellent occlusion rates in a swine model because of the animal's intrinsic capability of excellent and robust wound healing.[39] Considerations must include not only differences among species but the fact that each model within a species has its own characteristics. Additionally, true bifurcational hemodynamics are essential to determine a device's effectiveness.[73,74] Further unknown biases may arise from the use of extracranial arteries, non-physiological surroundings, and the inclusion of only healthy animals with "healthy" aneurysm grafts.

With regard to the differences in translational efforts for 36 (9%) of 400 lumen-oriented strategies and 6 (2%) of 241 wall-oriented strategies, two possible explanations can be considered. First, wall-oriented research began 15 years later than lumen-oriented research. The first translational attempts were launched

only recently. However, with increasing recognition of the important role of the vessel wall biology in IA healing, additional clinical trials on wall-oriented concepts can be expected. Moreover, newer techniques may target both, occlusion of the lumen and modification of the vessel wall biology. Second, from a regulatory point of view, administration of a clinical trial testing a new pharmaceutical drug faces many more obstacles than testing a new medical device, at least in Europe until recently. This may have favored a relatively low threshold in device development.

Despite our systematic approach, strictly adherence to PRISMA guidelines, and independent screening of the literature by two investigators, we may have omitted a preclinical study or clinical trial. Additionally, despite two recent publications of our earlier systematic reviews, we may have missed strategies that were used in rare aneurysm models in species other than mice, rat, rabbit, dog, or swine (3,4). We acknowledge a potential for omission of studies of preclinical treatment concepts that were published in non-English languages. Nonetheless, even in this case, a single study would be unlikely to influence the overall essence of this review.

Conclusion

In this systematic review of 641 studies in select animal models during a 57-year period, overall numbers of lumen-oriented strategies exceeded wall-oriented strategies for treatment of IAs. However, maximal mechanical lumen obstruction has substantially declined in recent years. With the increasing importance of vessel wall biology, the (diseased) aneurysm wall seems to be a promising venue to target with pharmaceutical substances. Therefore, newer techniques often aim to target both occlusion of the lumen and modification of the vessel wall biology. Among the plethora of suggested preclinical treatment strategies, only a small minority ever translated into clinically applicable concepts: that is 9% of lumen-oriented and 2% of wall-oriented preclinical concepts. The recently observed shift from lumen-oriented strategies to wall-oriented strategies in preclinical investigations signals that we are on the brink of translation to clinical trials.

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Authors' contribution

BEG and FvFC performed the data collection and analysis. BEG had the lead in writing the manuscript with critical feedback from all the authors. SM was in charge of the overall direction. All authors have read and approved the final version of this manuscript.

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Supplemental materials

Supplemental material for this article is available online on JCBFM website.

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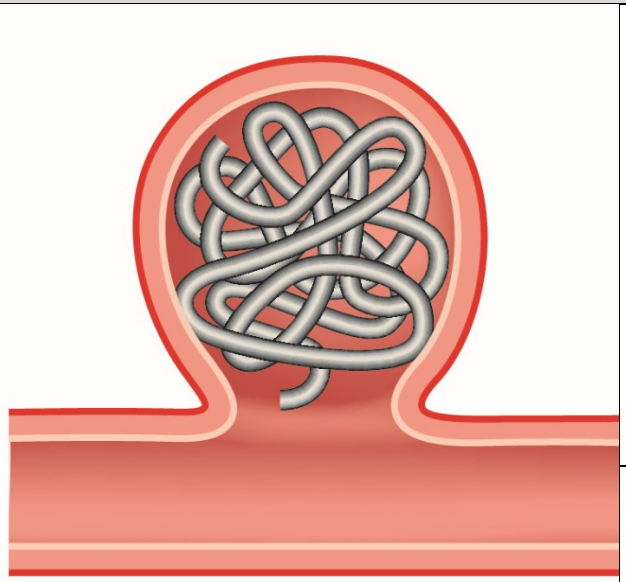
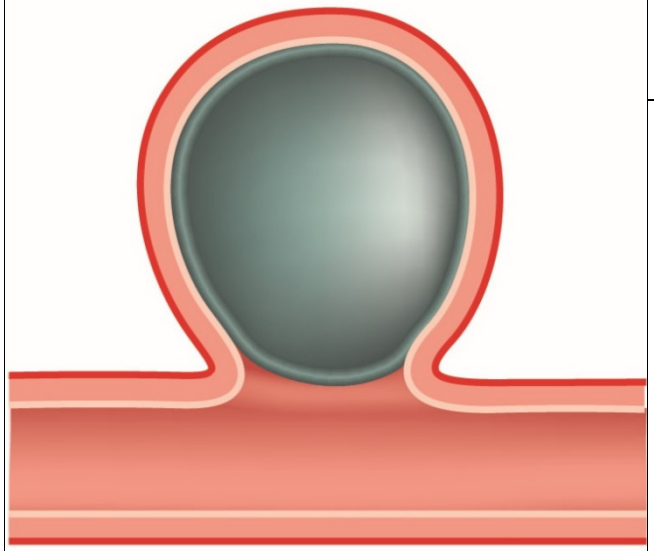
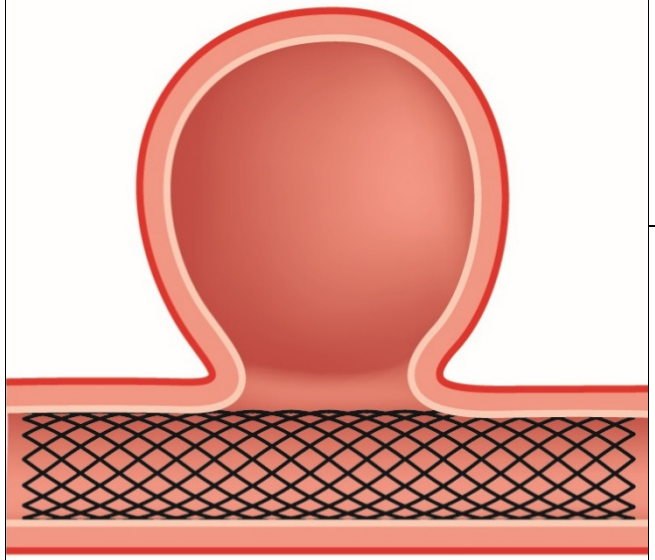
Lumen-oriented versus wall-oriented treatment strategies for intracranial aneurysms – a systematic review of suggested therapeutic concepts

Supplementary Materials

Supplementary Table 1: Lumen-oriented IA treatment approaches. Strategies tested in clinical trials are marked in bold.

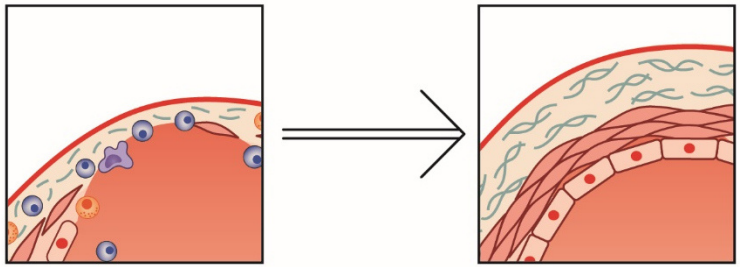
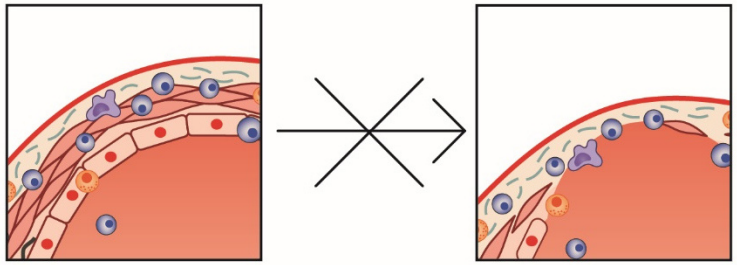
Enhanced intraluminal healing		
	Coil coating	• Silk (1), → **clinical trial nylon (2), dacron (3)** • Fiber coils; Polyurethanes (4), Gold (5) • ECM (types I and IV collagen (6-9), fibronection (10), laminin (10), vitronectin (10), and tenascin-C (11)) • SEK-1005 (drug that promotes wound healing through inducing transforming growth factor b (TGF-b) (12) • Simvastatin (13) • Polyglycolide endovascular coils (PGA) (14), bioabsorbable polymeric coils (PGLA) (15, 16) Matrix2 coils (17) → clinical trial (18, 19), Cerecyte (20) • Gellan sulfate core platinum coil with tenascin-C (21, 22) • Osteopontin and interleukin-10 (23, 24) • Silk fibroin, consisting of stromal cell-derived factor-1α (SDF-1α) (25) • Shape memory polymer foam-coated coils (26)
	Growth factor stimulation	• bFGF (mediated by cells (27), hydrogel (28-30), PVA core (31, 32), microcoil (33) • TGF-β, coil mediated (34), added to gelatin sponges (35) • VEGF, mounted on coils (34, 36, 37) or VEGF coupled to a pH-responsive chitosan polymer (38) • rhSDF-1α (recombinant human stromal cell-derived factor 1alpha) (39, 40)
	Tissue allograft transplantation	• Fibroblasts, coil mediated (41, 42) and collagen-gel coil mediated (43), gelation or gel polymer (44)) • Modified fibroblasts (bFGF (27), BMP-13 (45)) • Endothelial progenitor cells seeded in fibrin polymer (46) • Mesenchymal stem cells (47-50)
		• In situ beta radiation (51-53) → **clinical trial (32P-coil) (54)**
		• Chemokine MCP-1 (55, 56)
Enhanced intraluminal packing		
	Expandable coils	• Hydrogel filaments (57, 58) • Hydrogel coils (59) → **clinical trial (60)** • Electro-responsive hydrogel (61)

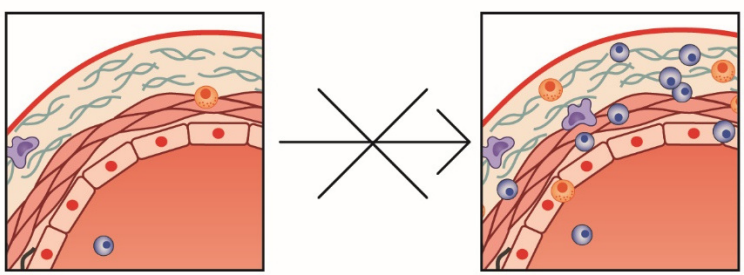
	Complex shaped coils	• Complex-coil → **clinical trial (62, 63)** • 360°-coil → **clinical trial (64)** • 3D-coil system → **clinical trial (65, 66)** • Coil-in-shell (67)
	Liquid embolique agents	• Iron acrylic (68) • Fibrin sealant (69, 70) • Celluloseacetate polymer (71-73) -> **clinical trial (74)** • Cyanoacrylate (75-78), alginate (79, 80) and chitosan (38, 81-83) • Ethylene-vinyl alcohol copolymer (84) -> **clinical trial (ONYX) (85)** • n-butyl cyanoacrylate, Lipiodol, and ethanol (balloon assisted) (86) / n-butyl cyanoacrylate-lipiodol-Iopamidol (87) • PHIL 35 (fast precipitating, non-adhesive liquid embolic agent), FRED assisted (88) • Thermoreversible gelatin polymer (89, 90) • PPODA-QT (a liquid-to-solid gelling polymer system that is poly propylene glycol) diacrylate and pentaerythritol tetrakis (3-mercaptopropionate) (91, 92) • Shape memory polymer/polyurethane foam (93) • Liquid to solid dual-gelling poly(N-isopropylacrylamide)-based polymer systems (94) • Liquid urethane (95) • Gel-in-shell (67) • Chitosan-doxycycline hydrogel (96)
		• Cellulose porous beads (97)
		• Flow-diverter assisted microsphere embolization (98)
Bridging the intraluminal space		
	Stent systems	• Neuroform (99) → **clinical trial (100)** • Enterprise (101) → **clinical trial (101)** • Leo → **clinical trial (99, 102-105)**, • Honeycomb microporous covered stent (106) → **clinical trial (107)** • Accero (braided stent with porosity) (108) → **clinical trial (109)**
	Flow diverter	• Pipeline → **clinical trial (110, 111)** • Silk → **clinical trial** (**112, 113)** • Surpass → **clinical trial (114, 115)**

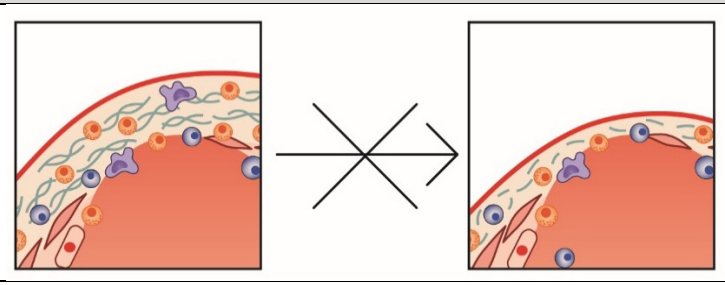
		• FRED (Flow Re-direction Endoluminal Device) (116) → **clinical trial (117)** • Penumbra Liberty (118) → **clinical trial NCT01753388** • Derivo (119) → **clinical trial (120)** • FD Stent (121) • TFN (thin film nitinol) (122, 123) • FD compaction (124) • FloWise (125) → **clinical trial (126)**
	3D-devices/Flow disrupters	• WEB (127, 128) → **clinical trial (129)** • eCLIPs (bridges aneurysm neck, allows coil retention, disrupts flow away from the aneurysm, leaves main vessel and side branches unencumbered by intraluminal metal, and serves as platform for endothelial growth across the neck, excluding the aneurysm from the circulation) (130, 131) → **clinical trial (132)** • Pulsar Vascular Aneurysm Neck Reconstruction Device (PVANRD) (133) → **clinical trial (134) NCT03383666** • Luna AES (self-expanding ovoid braided implant) (135) → **clinical trial (136)** • TriSpan (neck bridging device) (137) → **clinical trial (138)** • Embolic-containing device (ECD, neck bridging detachable device) (139) → **clinical trial (140-142)** • pCONus (stent-like self-expanding nitinol implant) → **clinical trial (143, 144)**
	Biodegradable stent	• Aliphatic polyesters (e.g. poly-lactic acid) (145) → **clinical trial (146)** • Magnesium alloy covered stent (147-149)
	Modified/coated stent and flow diverter	• Phosphorilcholine modified flow diverter (150) • VEGF loaded Poly(L-lactide-co-caprolactone) Nanofiber Covered Stent-Graft (151) • Condroitin sulfate and EGF bioactive-coated stent (152) • Stent releasing basic fibroblast growth factor and argatroban (153) • Rosuvastatin- and heparin-loaded poly (l-lactide- co-caprolactone) nanofiber stent (154) • Electrospun fiber-covered stent with programmable dual drug release (155) • Stents with antithrombogenic hydrophilic polymer coating (156)

	Combined procedures	• Comaneci neck bridging device (157) → **clinical trial (158)** • Flow diversion combined with jailed branch occlusion using coils and/or Onyx (159)
Alternative concepts		
	Endothelial denudation	• Mechanical (160, 161) • Radiofrequency ablation (162)
		• Intra-arterial magnetic microparticles navigated by external magnetic field (163)
		• Focused ultrasound (FUS) (164)
		• Gamma knife radiosurgery (165)

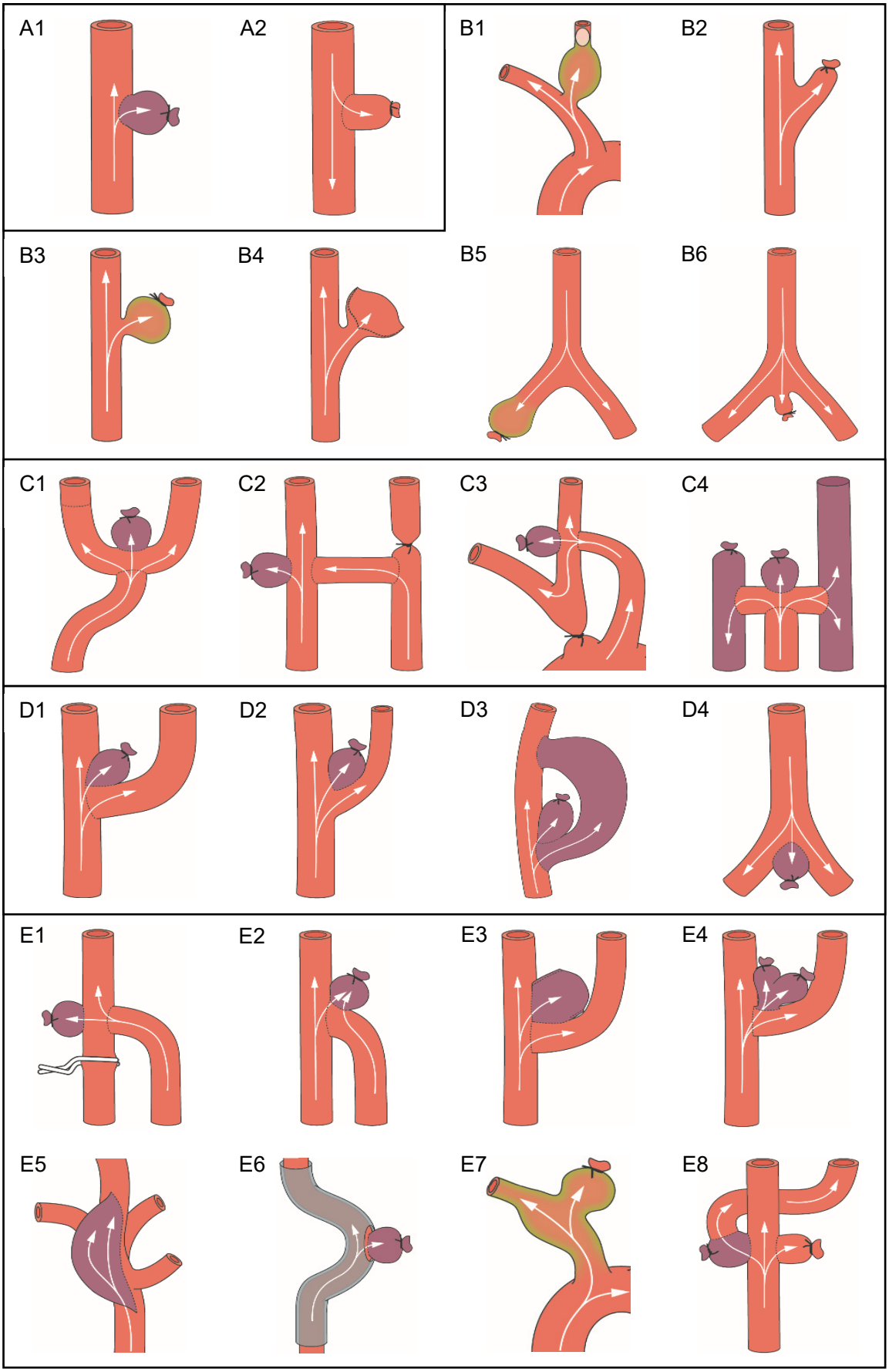
Supplementary Table 2. Wall-oriented IA treatment modalities. Strategies tested in clinical trials appear in bold.

Exogenous stimulation of proliferative response	
	• Blood coagulation factor XIII (166) • Intravenous factor VIII (166-168); • Basic fibroblast growth factor (169) • AMD3100 (promotion of EPCs into the peripheral blood) (170) • Osteoprotegerin (promoting collagen biosynthesis and vascular smooth muscle cell proliferation) (171) • Angiopoietin-1 (Ang-1) (enhances tube formation, migration, and proliferation ability of endothelial progenitor cells) (172) • MiR-17-5p (promotes re-endothelialization via endothelial progenitor cells) (173) • miR-31a-5p agomir (stimulation of endothelial progenitor cells) (174) • Nrf-2 activation (modulating vascular smooth muscle cell phenotype and function) (175) • Gene therapy (delivery of transgenes to modify cells in the arterial wall) (176) • SRPK1 gene silencing (promotes vascular smooth muscle cell proliferation and vascular remodeling via inhibition of the PI3K/Akt signaling pathway) (177)
Prevention of EC and SMC injury	
	• Aminoguanidine (NOS inhibition) (178) iNOS -/- (prevents apoptosis in SMC) (179) • Batroxobin (defibrinogenic agent) (178) reduces of wall shear stress by reduction of blood viscosity • Estrogen (beneficial effect on EC function and growth) (180-182) → **clinical trial NCT01895881 (withdrawn)** • Bazedoxifene (estrogen receptor modulator) (183) • IL-1β -/- (prevents apoptosis in SMC probably by non-activation of iNOS) (184) • Endothelin B receptor blockage (e.g. K-8794) reduced SMC apoptosis (185) • Fasudil (rho-kinase inhibitor; suppress inflammation, and reduces endothelial • dysfunction) (186) • EPO (increased EPC count which maintains endothelial integrity) (187, 188) • ARB, valsartan (189), olmesartan (190)) • Statins (193) → **clinical series (191, 192)** (simvastatin (194, 195), pravastatin (190, 195), rosuvastatin (196) atorvastatin (197)) → **clinical trial NCT04149483 // (198)**

	• Metformin (regulating vascular smooth muscle cell phenotype switching via the ampk/acc pathway) (199) • Sitagliptin (stimulates endothelial progenitor cells to induce endothelialization) (200) • ASP4058 (sphingosine-1-phosphate receptor type 1 agonist, promoting endothelial integrity and blocking macrophage transmigration) (201) • miR-133a-3p (restrains endothelial cell damage via suppressing the gsk3β/β-catenin pathway) (202)
Inhibition of inflammation and oxidative stress	
	• Vitamin C (203) NF-κβ decoy oligodeoxynucleotide (inhibits transcriptional activity of NF-κβ) (204-206) • Nifedipine (inhibits DNA binding of NF-κβ) (207) • Pitavastatin (inhibits NF-kappaB pathway) (208) • Prostaglandin E receptor antagonist (suppresses NF-κβ-mediated chronic inflammation) (209, 210) • Ets-1 decoy oligodeoxynucleotides (reduces MCP-1 expression in SMC) (206, 211) • Anti-MCP-1 gene therapy (decreases monocytes/macrophage recruitment) (212) • Ibudilast, (predominantly blocks phosphodiesterase-4) decreases macrophage migration (213) • Clodronate liposomes (depletion of monocytes) (214, 215) • Tranilast, emedastine difumarate (inhibits mast cell degranulation, reduces chronic inflammation) (216) • Aspirin (inhibits several inflammatory mediators) (217-221) → **Clinical Trial (217)** • Doxycycline and minocycline (tetracycline derivates, anti-inflammatory effects) (222) • TNF-α inhibition (prevents induction of proinflammatory/matrix remodeling genes) (223) • TNF receptor (TNFR1)-depletion (suppress inflammatory IA wall responses) (224) • Edaravone, a free radical scavenger (reduces production of ROS) (225) • Eplerenone, mineralocorticoid receptor blocker (inhibits oxidative stress) (226, 227) → **Clinical Trial (228)** • Apocynine (NADPH oxidase inhibitor) (227) • Pioglitazone (PPARγ agonist) (229, 230) • Angiotensin-(1-7) (231) • Mesenchymal Stem Cell-Derived Microvesicles (Suppression of Mast Cell Activation) (232) • Nr1h2 (liver X receptor β) (glucose-sensing nuclear receptor inhibiting macrophage activation) (233) • Curcumin (inhibition ROS and apoptosis) (234)

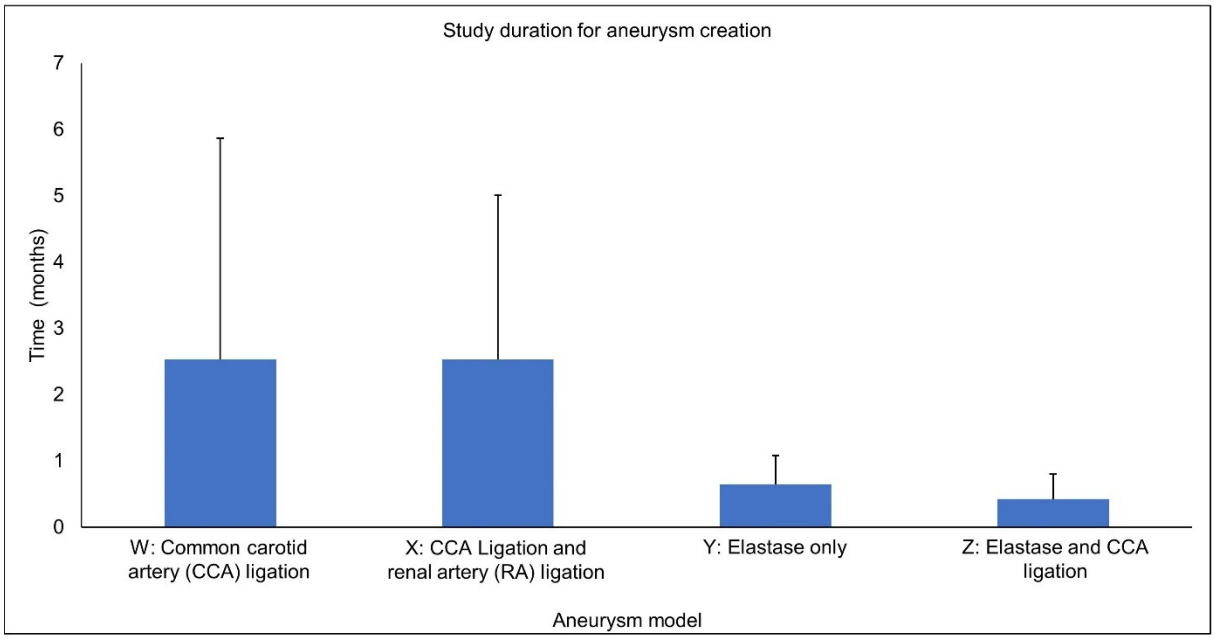
	• Anagliptin (Sipeptidyl Peptidase-4 inhibitor, suppression of macrophage infiltration/activation) (235) • Inhibitors of tPA (neuroserpin and PAI-1) or indirect inhibitors (eg, tranexamic acid via inhibition of plasmin) (236) • Vagus nerve stimulation (237) • Eicosapentaenoic acid (reduces degenerative changes in the media and macrophage infiltration) (238) • Tanshinone IIA (Tan IIA) (inhibiting the NF-κB-mediated inflammatory response) (239) • Adenomatous polyposis coli (Apc) siRNA (regulating the NF-κB signaling pathway mediated inflammatory response) inhibiting the NF-κB signaling pathway mediated inflammatory response (240) • β-sitosterol (suppressing TNF-α-mediated mechanism) (241) • miR-448-3p (regulating klf5 expression) (242) • Paroxetin (disruption of P2X4 purinoceptor) (243) • Dimethyl fumarate activation of nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, which reduces oxidative stress by inducing the antioxidant response element (244) • Cilostazol (antiplatlet) (245)
Inhibition of ECM degradation	
	• Imidapril (MMP-9 inhibition) (246) • Tolylsam (selective inhibitor for MMP-2, -9, -12) (247) • SB-3CT (selective inhibitor of MMP-2 and -9) (222) • NC-2300 (selective inhibitor for cysteine cathepsins) (248) • PHA 680623, Rapamycin, and Forskolin (stabiizlation of primary cilia) (249)

Supplementary Figure 1 – Extracranial aneurysm models classified according to Marbacher et al. 2020 (modified form J Cereb Blood Flow. 2020 May;40(5):922-938.)



Supplementary Figure 2 – Creation time for intracranial aneurysm models classified according to Strange et al. 2020 (modified from Brain Sci. 2020 Feb 27;10(3):134.)

W: Common carotid artery (CCA) ligation only
X: CCA Ligation and renal artery (RA) ligation
Y: Elastase only
Z: Elastase and CCA ligation



Supplementary Table 3 – Study details (including species used, experimental model, main results and conclusion) of preclinical concepts to improve the treatment of intracranial aneurysms.
*Models are classified according to Supplementary Figure 1 for extracranial aneurysm models (A1-E8) and Supplementary Figure 2 for intracranial aneurysm models (W-Z).

Ref No.	Name	Year	Species	Model*	Conclusion
1	Graves, et al.	1990	Dog	A1	Flower petal coils with silk fibers were effective in producing thrombosis of the aneurysms, suggesting that coils of appropriate design may be useful in the endovascular treatment of aneurysms. Other coil designs evaluated, those with simple and complex curves without silk fibers, demonstrated insufficient thrombogenicity and spatial stability.
4	Ahuja, et al.	1993	Rabbit	B2	Authors investigated a modification of the Gugliemi detachable coil (GDC). They developed a rabbit model and coating technique to test differences in thrombogenicity of platinum coils with a variety of polyurethanes.
5	Whitlow, et al.	2009	Rat	B2	Ultrathin coatings of gold provoked a neointimal response and degree of luminal occlusion greater than that of plain platinum aneurysm coils in a rat arterial occlusion model.
6	Dawson, et al.	1995	Swine	A1	Aneurysms treated with collagen microcoils were completely obliterated with a collagen-rich fibrous scar with no histological evidence of residual thrombus or recanalization. After treatment of experimental aneurysms with collagen microcoils, re-endothelialization across the former aneurysm neck was seen. In contrast, aneurysms embolized with dacron-fibered microcoils contained persistent thrombus surrounded by a relatively immature scar with residual aneurysmal lumen and lack of endothelium.
7	Dawson, et al.	1996	Swine	A1	Local fibroblast proliferation and collagen production were stimulated by heterologous cross-linked collagen embedded in micro-coils in this experimental model. Such biologic stimulation holds promise for improving the endovascular cure rate of aneurysms in humans.
8	Murayama, et al.	1997	Swine	A1	Ion implantation combined with protein coating of GDCs improved cellular adhesion and proliferation. Future application of this technology may provide early wound healing at the necks of embolized, wide-necked, cerebral aneurysms.

9	Tamatani, et al.	1999	Dog	B2	Collagen-coated platinum coils can produce rapid and stable occlusion of embolized vessels.
10	Murayama, et al.	1999	Swine	A1	GDC-Is indicated a more intense inflammatory response in the aneurysm body and dome and faster re-endothelial coverage of the aneurysm neck. This accelerated histologic response may decrease the chances of coil compaction and aneurysm recanalization. This technology may improve anatomic and clinical outcomes in patients harboring intracranial aneurysms.
11	Toma, et al.	2005	Rat	B2	Placement of TNC-coated coils can remarkably accelerate organization of luminal cavities and reduce their volume, providing improved efficacy of these coils for endovascular embolization.
12	Sano, et al.	2010	Rat	B2	SCs accelerated intra-aneurysmal organization in our rat aneurysm model suggesting that platinum coils coated with the novel cyclic peptide SEK-1005 may prevent recanalization and improve the clinical outcome in patients treated by coil embolization.
13	Kodama, et al.	2013	Rat	B2	Organized tissues that formed around the coils coated with simvastatin were characterized by an accumulation of cells positive for alphaSMA and collagen connective matrix. Tissues also were accompanied by marked formation of endothelium at the orifice of the ECA sac. We suggest that coating coils with simvastatin effectively accelerated organization within the aneurysms and endothelialization over the coil.
14	Abrahams, et al.	2001	Rat	B2	BPCs enhanced the vascular response of CCA segments compared with GDCs, and were also suitable for local protein delivery to the vessel lumen, under conditions of stasis and arterial pressurization of vascular cells.
15	Murayama, et al.	2003	Swine	A1	Matrix accelerated aneurysm fibrosis and neointima formation without parent artery stenosis. The Matrix system might prevent aneurysmal recanalization after endovascular treatment of cerebral aneurysms.
16	Murayama, et al.	2001	Swine	A1	BPM/GDCs accelerated aneurysm fibrosis and intensified neck neointima formation without causing parent artery stenosis or thrombosis. Use of BPM/GDCs may improve long-term anatomical outcomes by decreasing aneurysm recanalization due to stronger in situ anchoring of coils by organized fibrous tissue. Retraction of this scar tissue may also decrease the size of aneurysms and clinical manifestations of mass effect observed in large or giant aneurysms.

17	Mitome-Mishima, et al.	2016	Swine	A1	Aneurysms embolized with Matrix2 coils build thicker scaffolds for endothelialization, but this is not necessarily evidence of earlier tissue proliferation and maturation than those embolized with BP coils. Matrix2 coils may not be superior to BP coils for preventing aneurysmal recanalization after endovascular treatment of cerebral aneurysms.
21	Hamada, et al.	2014	Rat	B2	A newly developed coil, GSCC-TNC, may be effective for improving intra-aneurysmal organization after coil embolization.
22	Miura, et al.	2016	Rabbit	B3	GSCC-TNCs promote intra-aneurysmal clot organization in simulated clinical settings using Rabbit possibly through the TGF-beta and MMP-9 upregulation.
23	Chen, et al.	2016	Rat	B2	Possible application of OPN and IL-10 coated coils in aneurysm treatment to overcome the recurrence.
24	Hosaka, et al.	2017	Mouse	B1	IL-6 and OPN are key downstream mediators of MCP-1-mediated intra-aneurysmal healing.
25	Gao, et al.	2016	Rat	B2	SDF-1alpha-coated coils with MSC or EPC transplantation may be beneficial in the aneurysm healing and endothelialization at the orifice of embolized aneurysm.
26	Jessen, et al.	2020	Rabbit	B1	When considering cell types and extracellular matrix composition, the overall host response scores were significantly better in FCC-treated aneurysms at the later time point. Based on results of these metrics, the FCC device may lead to an advanced tissue remodeling response over BPC occlusion devices.
28	Hatano, et al.	2003	Rabbit	A1	Local, controlled release of sufficient amounts of bFGF with polyethylene terephthalate fiber coils coated with gelatin hydrogel accelerated the organization of aneurysms.
29	Hong, et al.	2001	Rabbit	A1	Local controlled release of bFGF stimulated the formation of in vivo fibrosis, resulting in obliteration of the aneurysm. Long-term results of the fibrous organization remain speculative.
30	Kawakami, et al.	2006	Rabbit	A1	Local, controlled release of bFGF from the hollow fibers combined with gelatin hydrogel incorporating bFGF accelerated the aneurysm healing by tissue organization.
31	Matsumoto, et al.	2003	Rat	B2	FGF-core coils may be effective in inducing fibrotic changes inside aneurysms. These coils may be used as an embolic material to cure cerebral aneurysms
32	Tsumoto, et al.	2007	Rabbit	B1	Implantation of the PVA-core coil containing bFGF accelerated tissue growth at the neck as well as in the dome of aneurysms induced by elastase in Rabbit. These

					results suggested that PVA-core coils could prevent the recanalization of embolized aneurysms.
33	de Gast, et al.	2001	Rabbit	B1	TGFbeta-coated platinum coils undergo earlier cellular coverage than standard platinum coils, but differences in coverage between coated and control coils are no longer present at later time points. These data suggest that improvements in intra-aneurysmal cellular proliferation resulting from coil modifications, although significant in the early postembolization phase, may dissipate over time.
34	Agrawal	2013	Rat	B2	The coated GDC with TGF-beta or VEGF appears beneficial in promoting endothelization, clot organization, and cellular tissue integration of the coils.
35	Raymond, et al.	2003	Swine and Dog	B1, C1	Growth factor delivery can be performed with alginate, but formulation changes and improved endovascular control are necessary before contemplating its use in intracranial aneurysms.
36	Abrahams, et al.	2001	Rat	B2	rhVEGF may be beneficial in promoting endothelialization, clot organization, and tissue integration of the coils. This is the first study to hypothesize that rhVEGF may be useful as a surface modification to GDCs for enhancing their therapeutic effects in the treatment of cerebral aneurysms.
37	Ohyama, et al.	2004	Rat	B2	Platinum microcoils coated with immobilized rhVEGF may be effective for the obliteration of aneurysms.
38	Pan, et al.	2010	Rat	B2	Chitosan with a bioactive agent, such as rhVEGF, showed excellent results in occluding aneurysms in a rat model.
39	Li, et al.	2017	Rabbit	B1	Study reveals an important role of rhSDF-1α in inducing aneurysm occlusion and suggests that it achieves its function through modulating the reendothelialization.
41	Marx, et al.	2001	Rabbit	B2	Fibroblast allografts remain viable and proliferate in the vascular space in a rabbit model. ~~Furthermore, T~~These same fibroblasts, after seeding onto platinum coils in culture, remain protected within the lumen of the coils and retained within the coil lumen even after prolonged exposure to arterial blood flow. Coils can be used to deliver viable fibroblasts directly into experimental aneurysms successfully. These findings indicate that coil-mediated cell implantation is feasible and may be a potential method of increasing the biological activity of embolic coils.
42	Dai, et al. 2007	2007	Rabbit	B3	FBC coils can accelerate early histological healing compared with control coils in the rabbit aneurysm model.
44	Dobashi, et al.	2012	Rat	B5	TGP mixed with both dermal fibroblasts and bFGF induced the most advanced thrombus organization in the experimental aneurysms followed by TGP mixed only

					with dermal fibroblasts. TGP may be useful as a delivery device to deploy fibroblasts and cytokines into aneurysms.
45	Dai, et al.	2008	Rabbit	B1	Ad-BMP-13-coated coils can improve neck coverage and dome fibrosis in the rabbit model, even in the absence of observed differences in angiographic outcome.
46	Aronson, et al.	2012	Rabbit	B3	This novel technique may address reasons for the limited durability of standard coil embolization and provides further avenues to develop improved devices for the care of patients with aneurysms.
47	Rouchaud, et al.	2013	Rabbit	B1	Percutaneous seeding of BMSCs may colonize and heal the arterial wall thus limiting aneurysm expansion.
48	Adibi, et al.	2017	Rabbit	B3	Proof-of-concept study shows that adjuvant MSC therapy for intracranial aneurysms is feasible and may enhance histological improvement of coiled aneurysms at 4 weeks post-treatment.
49	Kuwabara, et al.	2017	Mouse	Y	Intravenous administration of MSCs after aneurysm formation prevented aneurysmal rupture in mice. Protective effect of MSCs against the development of aneurysm rupture appears to be mediated in part by the stabilization of mast cells by MSCs.
50	Avery, et al.	2019	Rabbit	B3	While aneurysm morphometric comparisons revealed no differences, significant cytokine alterations were observed in vitro and in vivo, suggesting both anti-inflammatory and proinflammatory processes occurred in the presence of MSCs. Histological analyses suggested that tunica intima hyperplasia was inhibited in the presence of MSCs.
52	Levesque, et al.	2004	Dog	arteries	Radioactive coils can be produced by using the binding properties of a ^{32}P-oligodeoxynucleotide to platinum. Use of these coils in an animal model was effective in preventing recanalization. This method could be performed on site to provide coils tailored to each intervention.
53	Raymond, et al.	2006	Dog	B2, C1	beta-Radiation can prevent recanalization after coil occlusion. We could not demonstrate any deleterious effects of radioactivity on nervous structure or on neointima formation. Delayed organization of thrombus provides a rational basis to establish an upper limit for 32P.
55	Hoh, et al.	2011	Mouse	Z	MCP-1 has a critical role in promoting inflammatory intra-aneurysmal tissue healing in an MIP-1alpha- and MIP-2-dependent pathway
57	Killer, et al.	2009	Rabbit	B1, D1	Embolization of experimental aneurysms with hydrogel filaments resulted in durable angiographic and histologic occlusion from 2 to 26 weeks. With improvements, hydrogel filaments free from metallic coils show promise for endovascular use.

58	Killer, et al.	2011	Rabbit	A1, D1	Loading hydrogel filaments with SPIO in an effort to provide adequate visualisation for use in MR-guided interventions.
59	Kallmes, et al.	2002	Rabbit	B1	Distinct from previous devices aimed at speeding the organization of thrombus, the new device ~~has been~~ was designed to entirely fill the aneurysm cavity, with complete or near-complete exclusion of thrombus. Unlike thrombus, the hydrogel material is stable and unaffected by natural thrombolytic processes and thus may diminish observed rates of aneurysm recanalization. We report the angiographic and histologic findings of the new, hybrid device used to treat experimental aneurysms in Rabbit.
67	Moftakhar, et al.	2015	Swine and Dog	A1	AIOD tested in this study showed promise in terms of acute and chronic occlusion of aneurysms. Our findings suggest that these devices have the potential to promote robust tissue healing at the aneurysm neck, which may minimize aneurysm recurrence. Although proof of principle has been shown, further work is needed to deliver this device through an endovascular route.
68	Alksne, et al.	1977	Dog	B2	~~A new iron-acrylic compound~~ Developed for stereotaxic thrombosis of intracranial aneurysms, this new iron-acrylic compound ~~The compound~~ polymerizes rapidly, does not fragment, and is nontoxic. It has been used in a series of experimental animals and in initial clinical cases with good results. Use of this material simplifies and increases the safety of stereotaxic aneurysm treatment.
69	Moringlane, et al.	1987	Rabbit	A1	Microscopic examination showed complete resorption of the fibrin clot and formation of dense granulation tissue within the aneurysm, which was covered with a layer of endothelial cells after 2 weeks. Results are ~~only~~ tentative and require further experimental studies.
70	Moringlane, et al. 1988.	1988	Rabbit	A1	Complete resorption of the fibrin sealant was observed. The aneurysm cavity was filled with a dense connective tissue covered by a layer of newly formed endothelial cells.
71	Mandai, et al.	1992	Dog	A1, D1	It rapidly hardened in the shape of the aneurysms, completely obliterating them but preserving the parent vessels in all cases. No distal migration of the polymer was seen. Good results of this experimental trial led to a clinical study using a cellulose acetate polymer.
72	Macdonald, et al.	1998	Dog	A1, C1	Complete packing of aneurysms with GDC obliterates the aneurysm, but endothelialization does not always occur within 2 months. There are substantial problems with CAP: it is thrombogenic and carries a higher risk of causing arterial

					thrombosis. Even if aneurysm is successfully obliterated initially with CAP, the CAP may disappear, leaving the aneurysm completely untreated.
73	Yang, et al.	2001	Rat and Dog	A1, B2, D1	CAP is not an ideal embolic material for intracranial aneurysms. Further tests and improvements are needed before it can be widely used clinically.
75	Debrun, et al.	1984	Dog	E5	The Silastic balloon was ~~found to be~~ much more effective than the latex balloon in preventing spillage of IBCA into the lumen.
76	Kerber, et al.	1985	Dog	A1	Although the results are encouraging, we believe that it would be prudent to broaden the animal experimentation rather than begin human use. Because no experimental aneurysm models are yet physiological, apply our results cautiously to human intracranial aneurysms.
77	Raymond, et al.	2002	Dog	A1	Cyanoacrylate embolization is currently difficult to control. Although has the potential to decrease recurrences after endovacular treatment of aneurysms, a safe method for endovascular delivery has yet to be developed.
78	Suh, et al.	2003	Rabbit	A1	Effective glue embolization into the aneurysmal sac is technically feasible. Microcatheter position within the aneurysm, concentration of glue, and direction of the aneurysmal neck angle all must be considered. With a coil framework, glue injection was more complete, without deformity or spillage of the glue from the aneurysm.
79	Becker, et al.	2007	Swine	A1	Calcium alginate was an effective endovascular occlusion material that filled the aneurysm and provided an effective template for tissue growth across the aneurysm neck after 30 days and up to 90 days. Complete filling of the aneurysm with calcium alginate ensures stability, biocompatibility, and optimal healing for up to 90 days in Swine. in swine model?
81	Chabrot, et al.	2012	Rabbit	Auricular artery	Viscosity obtained with chitosan and 3% STS permits better control during injection and longer vascular occlusion. These findings, combined with the intravascular neovascularization observed with CH0, led to preferred combination with STS.
82	Fatimi, et al.	2012	Dog	E5/E6	Chitosan/STS hydrogels have great potential as embolizing and sclerosing agents for EVAR and possibly other endovascular therapies.
83	Nakai, et al.	2004	Rabbit	A1	At 30 days, most of aneurysm lumen was replaced with inflammatory cells, and the remaining chitosan was not observed. Severe complications (eg, anaphylaxis) did not occur after the embolization with chitosan. Thus photocrosslinkable chitosan might be a candidate for an embolization material for endovascular treatment of cerebral aneurysms.

84	Raymond, et al.	2003	Dog	C1	HCEVOH embolization of aneurysms without neck protection is feasible. It does not, however, eliminate recurrences in an experimental wide-necked aneurysm model.
86	Tanaka, et al.	2015	Swine	A1	Although at a preliminary stage, balloon-assisted lipiodol and ethanol injection is feasible for packing a wide-neck aneurysm.
87	Higashino, et al.	2020	Swine	A1	Configuration of NLI changed at each ratio. NLI231 is a feasible and safe liquid embolic material for balloon-assisted embolization of wide-necked aneurysms in Swine.
88	Berenstein, et al.	2016	Dog	A1, C1	We developed a new treatment for cerebral aneurysms by combining a retrievable stent and a new liquid embolic agent.
89	Takao, et al.	2006	Swine	A1	We successfully embolized experimentally produced wide-necked lateral wall aneurysms using TGP, a novel embolic agent. Long-term and pathological evaluations are necessary. By taking advantage of the features of this polymer, such as the capacity to deliver drugs or cultured cells, TGP may also prove useful for the treatment of arteriovenous (AV) malformations, AV fistulas, and tumors.
90	Takao, et al.	2009	Swine	A1	Experimental aneurysms were safely embolized using TGP. Further modifications related to mechanical stability and long-term safety evaluation results are necessary before clinical application.
91	Brennecka, et al.	2013	Dog	A1	Study compared neointimal tissue overgrowth in the ostium of experimental aneurysms embolized with PPODA-QT, PPODA-QT plus a framing coil, or coils alone. The coils-only and coil+PPODA-QT groups showed rough and discontinuous ostial surfaces, which hindered neointimal tissue coverage. The PPODA-QT aneurysms consistently produced smooth ostial surfaces that facilitated more complete neointimal tissue coverage over aneurysm necks.
92	Brennecka, et al.	2012	Swine	A1	This small-scale pilot study highlighted first-time in vivo use of PPODA-QT as an embolic agent for aneurysm treatment. Filling aneurysms to 80% to 90% capacity proved to be a safe and effective delivery strategy, and PPODA-QT showed excellent biocompatibility. ~~This study indicates tha~~ Future investigation of PPODA-QT for aneurysm embolization is warranted, as it may prove to be a viable alternative to current embolic materials.
93	Rodriguez, et al.	2013	Swine	A1	Clotting was initiated within the SMP foam at time 0 (<1 h exposure to blood before euthanization), partial healing was observed at 30 days, and almost complete healing had occurred at 90 days in vivo, with minimal inflammatory responsel

94	Bearat, et al.	2013	Swine	A1	With the possibility to engineer hydrogels bottom-up for particular applications, these studies show properties that need to be optimized for dual-gelling polymer systems to serve as liquid-to-solid embolic agents for aneurysm treatment.
96	Zehtabi, et al.	2017	Swine	Renal artery	An injectable embolizing chitosan hydrogel releasing doxycycline (DOX) was developed as the first multi-faceted approach for occlusion of blood vessels. It combines occlusive properties with DOX sclerosing and MMP inhibition properties, respectively known to prevent recanalization process and to counteract underlying pathophysiology of vessel wall degradation and aneurysm progression. After drug release, the biocompatible scaffold can be invaded by cells and slowly degrade. Local DOX delivery requires lower drug amount and decreases risks of side effects compared to systemic administration. This new gel could be used for prevention or treatment of endoleaks after endovascular aneurysm repair, and the embolization of other blood vessels such as venous or vascular malformations
97	Hasegawa, et al.:	2020	Rat	B2	CPBs may be promising as embolic materials that can induce stable vessel wall regeneration at the neck orifice of an aneurysm without surrounding inflammatory reactions.
99	Fiorella, et al.	2004	Dog	A1	Neuroform stent is a useful device for treatment of patients with aneurysms that may not otherwise be amenable to endovascular therapy. In the majority of cases, the stent can be deployed accurately, even within the most tortuous segments of the cerebral vasculature. Although delivery and deployment may be technically challenging, clinically significant complications are uncommon.
106	Nakayama, et al.	2016	Dog, Rabbit	A1	Excellent embolization performance of the honeycomb microporous covered stents without disturbing branching flow was confirmed at the aneurysms in this proof-of-concept study.
108	Mühl-Benninghaus, et al.	2019	Rabbit	Subclavian artery	Study showed flow remodelling properties of the device prototype with progredient aneurysm occlusion. A larger in vivo study with induced aneurysm should be done to confirm these results.
116	Ding, et al. 2015	2015	Rabbit	A1	The Flow-Redirection Endoluminal Device in experimental aneurysms demonstrated high rates of progressive and complete aneurysm occlusion while preserving the patency of branch vessels.
118	Chavan, et al.	2015	Rabbit	B1	Animal study demonstrated promising results with the novel Liberty stent system. The Liberty showed consistent precise positioning and accurate deployment. Stent revealed good compatibility with embolic coiling procedures, while morbidity and

					mortality were negligible. In addition, persistent occlusion of aneurysms without recanalization or in-stent stenosis was observed at the 180 day follow-up.
119	Ley, et al.	2015	Rabbit	B1	Derivo Embolization Device provides excellent occlusion of elastase-induced aneurysms while preserving branch arteries.
121	Ma, et al.	2015	Rabbit	B3	New device exhibits high radial stiffness compared to interwoven FD stents and superior longitudinal flexibility. Results from on-going in-vivo experiments and CFD simulations also demonstrated the efficacy of the new device as a FD stent.
122	Ding, et al.	2016	Rabbit	B1	In this rabbit model, the thin film nitinol flow diverter achieved high rates of aneurysm occlusion and promoted tissue in-growth and aneurysm neck healing, even early after implantation.
123	Chen, et al.	2016	Swine	A2	The TFN can be conformally deployed in the curved blood vessel of a swine model without any significant complications or abnormalities.
124	Gentric, et al.	2016	Dog	A1	Compaction of FDs can improve angiographic occlusion of experimental wide-necked aneurysms.
125	Kim, et al.	2016	Rabbit	B1	Newly developed, partially retrievable flow-diverter seems to be a safe and effective tool of aneurysm occlusion, as evaluated in the rabbit aneurysm model.
127	Ding, et al.	2011	Rabbit	B1	WEB device in experimental aneurysms demonstrated promising rates of immediate and long-term aneurysm occlusion.
128	Ding, et al.	2016	Rabbit	B1	Histologic evaluation showed progressive thrombus organization within aneurysm lumen from 1 to 12 months. Results indicated that the WEB II device can achieve high rates of aneurysm occlusion over time in experimental aneurysms.
130	Marotta, et al.	2008	Swine	A1	Aneurysm occlusion with a single extrasaccular endovascular device has potential advantages. The authors believe that eCLIPs may prove to be a useful tool in the endovascular treatment of cerebral aneurysms. The system should reduce risks associated with coiling, procedure time, costs, and radiation exposure. Device satisfactorily occluded 8 experimental sidewall aneurysms. Observed healing pattern was similar to that seen after microsurgical clipping.
131	Marotta, et al.	2017	Rabbit	D1	eCLIPs device permits physiological remodeling of the bifurcation.
133	Turk, et al.	2013	Dog	C1	PVANRD is a novel bifurcation stent that facilitates treatment of wide-necked bifurcation aneurysms compared with currently available adjunctive devices.
135	Kwon, et al.	2011	Rabbit	B1	Luna AES achieved high rates of complete angiographic occlusion and showed promising histologic findings in the rabbit aneurysm model.

137	Turk, et al.	2001	Dog	A1, C1	TriSpan coil in conjunction with standard GDCs can be used safely and effectively for treatment of wide-necked aneurysms in this canine model. Positioning and deployment of the neck bridge in aneurysms having an acute angle with the long axis of their parent artery are difficult or impossible. ~~It is likely that t~~This device, used in conjunction with the standard GDC, will likely allow treatment of some wide-necked aneurysms that are not treatable with the GDC alone.
139	Berenstein, et al.	2009	Dog	A1, C1	Within the limitations of this experimental study, treatment of large, wide-necked aneurysms with the ECD and LEA may be feasible. Suboptimal technique and ECD geometry can cause leakage of LEA into the parent vessel or incomplete apposition of the ECD/glue to the aneurysm wall. However, the ECD and glue injection technique did achieve complete occlusion in 1 aneurysm that persisted 1 year later. Histopathological findings in this instance are moderately encouraging. Further investigations of an ECD with N-butyl cyanoacrylate or another LEA are warranted.
145	Wang, et al.	2013	Rabbit	B1	PGA-FD was an effective device for the treatment of aneurysms and was safe for side branches at 3-month follow-up.
147	Wang, et al.	2016	Rabbit	A1	Magnesium-alloy-covered stents proved to be an effective approach for occlusion of lateral aneurysm in the rabbit CCA; it provides distinct advantages that are comparable to that obtained with the Willis covered stent.
148	Cui, et al.	2017	Rabbit	A1	MACS is effective for occlusion of lateral aneurysms and is superior to WCS in growth of the stented CCA and endothelialization. Further work is needed to make this device available for human use.
149	Nevzati, et al.	2017	Rat	A2	Feasibility of standardized stent occlusion of saccular sidewall aneurysms in Rat - with low rates of morbidity and mortality. This stent embolization procedure combines the opportunity to study novel concepts of stent- or flow-diverter based devices as well as molecular aspects of healing.
150	Marosfoi, et al.	2017	Rabbit	B1	In the rabbit model, phosphorilcholine surface-modified flow diverters are associated with less thrombus formation on the device surface.
151	Wang, et al.	2015	Rabbit	B1	The heparin and VEGF loaded nanofiber could provide an approach to fabricate covered stent-graft with properties of anticoagulation and induction of rapid endothelialization.
152	Lequoy, et al.	2016	Dog	E5	The bioactive coating promoted in vitro cell survival, displayed good durability, and was successfully transferred onto a commercial SG. Preliminary in vivo results suggest improved healing around bioactive Stent grafts.

153	Arai, et al.	2019	Rabbit	B1	Most of the aneurysm cavity is occupied by loose connective tissues in the group treated with drug-coated stents, whereas extensive massive hematomas are observed in the group treated with drug-free stents. Occurrence rate of in-stent thrombus is small in the drug-coated stents. Stent incorporating bFGF and PLGA microspheres containing argatroban is an effective device for cerebral aneurysm treatment.
154	Liu, et al.	2018	Rabbit	B1	Rosuvastatin- and heparin-loaded PLCL-covered stents show favorable anticoagulation and pro-endothelialization properties in vitro and in vivo in a rabbit aneurysm model. VEGF-A elevation played a crucial role in rosuvastatin-promoted endothelialization. This work provides an additional option for treating cerebral aneurysms with covered stents.
155	Zhang, et al.	2019	Dog	A1	Study yields new method to improve the biosafety of covered stent insertion for the treatment of intracranial aneurysms.
156	Martínez Moreno, et al.	2019	Dog	C1	HPC-coated p64 FDSs appeared to be biocompatible, without acute inflammation.
157	Gupta, et al.	2016	Rabbit	B3	Comaneci device is a new adjuvant treatment for bridging of wide necked aneurysms with the advantage of averting flow arrest during deployment. No evidence of significant endothelial damage during deployment in preclinical studies.
159	Fahed, et al.	2017	Dog	D2	Treatment failures after flow diversion of bifurcation aneurysms can be caused by persistent flow to the jailed branch. Branch occlusion combined with flow diversion may improve angiographic occlusion scores of a canine bifurcation aneurysm model.
160	Raymond, et al.	2004	Dog	B2, C1	Endothelial denudation can prevent recanalization after coil embolization.
161	Darsaut, et al.	2007	Dog	C1	Stenting led to suboptimal results in the presence of an intact endothelial layer. Endothelial denudation can promote aneurysm occlusion when combined with stenting.
162	Raymond, et al.	2010	Dog	Maxillary and vertebral arteries	RF ablation can prevent recanalization after coil occlusion-at least in the arterial model. Modifications of coils, dedicated neurovascular electrodes, and technique optimization remain necessary before considering a clinical application.
163	Oechtering, et al.	2011	Rabbit	B2	MMPs can be magnetically directed into aneurysms, allowing short-term obliteration. Although the method has yet to show reliable long-term stability, these experiments provide proof of concept, encouraging further investigation of intravascular magnetic compounds.

164	Coluccia, et al.	2014	Rabbit	D1	Presented rabbit model proved suitable and capable of being extended to acquire data on the effect of HIFU on aneurysms and larger vessels. Fact that HIFU led to alteration of aneurysm without inducing rupture encourages further investigations.
165	Meadowcroft, et al.	2018	Rabbit	B1	Data indicate that GKRS targeted to saccular aneurysms is associated with histopathological changes and linear reduction of aneurysm size over time. Results suggest that GKRS may be a viable, minimally invasive treatment option for intracranial aneurysm obliteration.
166	Kang, et al	1990	Rat	W	Proliferative response at the sites of aneurysm development was modified by exogenous Factor XIII.
167	Hino, et al.	2001	Swine	B2	Administration of factor XIII may contribute to more effective aneurysm obliteration during coil embolisation.
168	Hino, et al.	2004	Swine	B2	Administration of wound-healing ~~factor,~~ factor XIII would contribute rapid intimal proliferation and may be ~~effective to~~ facilitate complete obliteration of aneurysms after coil embolization.
169	Futami, et al.	1995	Rat	W	Results demonstrate that exogenous basic FGF induces the proliferative response of smooth muscle cells in aneurysmal lesions in Rat.
170	Li, et al.	2017	Rabbit	B1	Interval use of AMD3100 promotes the formation of neointima in rabbit saccular aneurysm and facilitates endothelialization of the neointima after FD treatment.
171	Miyata, et al.	2020	Rat	X	Osteoprotegerin suppressed the IA progression by a unique mechanism whereby collagen biosynthesis and VSMC proliferation were activated via TGF-β1 without altering proinflammatory gene expression. Osteoprotegerin may represent a novel therapeutic target for IAs.
172	Lu, et al.	2018	Rat	B2	Overexpression of Ang-1 enhanced the tube formation, migration, and proliferation ability of EPCs. Ang-1 gene-modified EPCs accelerated organization within the aneurysms and occlusion of aneurysm neck. Transplantation of Ang-1-transfected EPCs may be a new method for the treatment of aneurysm.
173	Tian, et al.	2020	Rat	A2	miR-17-5p overexpression promoted the vascular repair in aneurysm rat model and increased the level of EPCs in the aneurysm tissues and peripheral blood of the Rat.
174	Yu, et al.	2019	Rat	A2	Collectively, these results indicate that miR-31a-5p is an important regulator of EPC mobilization and endothelialization and may have a positive effect on aneurysm repair.
175	Shi, et al.	2019	Rat	Y	Results suggest that Nrf-2 exerts protective effects against IA development by preventing VSMCs from changing to a synthetic phenotype.

176	Abrahams, et al.	2002	Rat	B2	Catheter deployment of platinum or biodegradable gene delivery endovascular microcoils represents an interventional device–based gene therapy system that can serve as a suitable platform for either single or multiple gene therapy vectors.
177	Li, et al	2019	Rat	X	siRNA-mediated silencing of SRPK1 gene inhibits VSMC apoptosis, and increases VSMCs proliferation and vascular remodeling in IA via the PI3 K/Akt signaling pathway. Our findings provide a novel intervention target for the molecular treatment of IA.
178	Fukuda, et al.	2000	Rat	X	NO, particularly that derived from iNOS, is a key requirement for the development of cerebral aneurysm. iNOS induction may be caused by an increase in shear stress near the apex.
179	Sadamasa, et al.	2003	Mouse	X	Inducible NOS is not necessary for initiation of cerebral aneurysm. However, results of this study suggest that regulation of iNOS may have therapeutic potential in the prevention of the progression of cerebral aneurysms.
180	Jamous, et al.	2005	Rat	W	The cerebral aneurysm model was highly reproducible in Rat. Bilateral oophorectomy increased the susceptibility of Rat to aneurysm formation, indicating that hormones play a role in the pathogenesis of cerebral aneurysms.
181	Jamous, et al.	2005	Rat	W	Significant protective role of estrogen against the formation and progression of cerebral aneurysms. It appears to be related to the beneficial effects of estrogen on the function and growth of endothelial cells, which play a major role in preserving the integrity of the vascular wall.
182	Tamura, et al.	2009	Rat	X	A therapy targeted at the endothelium and management of hypertension may help to prevent cerebral aneurysms.
183	Maekawa, et al.	2017	Rat	X	Observation that bazedoxifene decreased the incidence of aneurysmal rupture in ovariectomized rats warrants further studies to validate this response in humans.
184	Moriwaki, et al.	2016	Mouse	X	IL-1beta is important for the progression of cerebral aneurysms in a mouse model. Disruption of the IL-1beta gene results in reduced incidence of mature experimental cerebral aneurysms.
185	Sadamasa, et al.	2007	Rat	X	Results suggest that ETBR might play a significant role in the progression of cerebral aneurysms and have the potential to improve prevention and treatment of cerebral aneurysms.
186	Eldawoody, et al.	2010	Rat	X	Fasudil attenuated induction of cerebral aneurysms in the rat model.
187	Xu, et al.	2011	Rat	X	EPCs may serve as a marker for CA progression and EPO a promising candidate for the clinical management of CA.

188	Liu, et al.	2016	Rat	A2	EPO enhanced the endothelialization of a coiled embolization aneurysm neck by stimulating EPCs via VEGF modulation. Thus, promotion of endothelialization with EPO provides an additional therapeutic option to prevent recurrence of aneurysms.
189	Aoki, et al.	2009	Rat	X	RAS might play a less important role in CA formation compared to aortic anuerysms or other vascular diseases. This suggests that there are different mechanisms between the pathogenesis of cereberal and aortic aneurysms.
190	Kimura, et al.	2010	Rat	X	Pravastatin reduced both stages III and II+III and olmesartan ameliorated stage III, implying that these may prevent aneurysmal formation by acting on different steps.
193	Brinjikji, et al.	2017	Rabbit	B1	Systemic statin administration after platinum coil embolization of unruptured aneurysms in a rabbit model does not improve aneurysm occlusion rates at 4 weeks.
194	Aoki, et al.	2008	Rat	X	Treatment with simvastatin suppresses the development of CAs by inhibiting inflammatory reactions in aneurysmal walls. Simvastatin also has a preventive effect on the progression of preexisting Cas and is a promising candidate of a novel medical treatment to prevent CA progression.
195	Tada, et al.	2011	Rat	X	Our results provide the first evidence that cerebral aneurysm growth is partly associated with apoptosis and issue a warning that statins exert bidirectional effects on cerebral aneurysms. Additional intensive research is necessary to understand better their mechanisms and to identify in which patients the administration of statins may elicit deleterious effects.
196	Liu, et al.	2016	Rat	A2	Rosuvastatin promoted endothelialization of the coiled aneurysm neck via induction of EPCs, suggesting that promoting endothelialization gives an additional therapeutic opportunity during vascular endothelium repair.
197	Qi, et al.	2018	Rat	SAH model (cisterna magna punctatio n)	Early treatment with atorvastatin effectively ameliorates EBI after SAH through anti-apoptotic effects and the effects might be associated inhibition of caspase-3 and endoplasmic reticulum (ER) stress related proteins CHOP and GRP78.
199	Li, et al.	2020	Rat	Z	Metformin protects against IA formation and rupture by inhibiting VSMC phenotype switching and proliferation, migration, and apoptosis. Thus, metformin has therapeutic potential for the prevention of IA.
200	Yu, et al.	2019	Rat	A2	Western blot assays showed that sitagliptin activated the expression of NRF2, which is dependent on the function of CXCR4. Furthermore, sitagliptin promoted progenitor

					endothelial cell migration, invasion and angiogenesis through the SDF-1/CXCR4/NRF2 signaling pathway. Progenitor endothelial cells expressed SDF-1 and VEGF. The promotion of endothelialization by sitagliptin provides an additional therapeutic option to prevent the recurrence of AN.
201	Yamamoto, et al.	2017	Rat	X	A selective $S1P_1$ agonist is a strong drug candidate for IA treatment. It promotes the endothelial cell barrier and suppresses the trans-endothelial migration of macrophages in IA lesions.
202	Jia, et al.	2020	Rat	X	Overexpression of miR-133a-3p or downregulation of PSAT1 restrains endothelial cell damage and advances endothelial cell proliferation via inhibiting the GSK3β/β-catenin pathway in IA. MiR-133a-3p might be a potential candidate marker and therapeutic target for IA
203	Dai, et al.	2013	Rabbit	B3	Vitamin C supplementation after platinum coil embolization did not demonstrate improvement of long term occlusion rates of aneurysms.
204	Aoki, et al.	2007	Rat	X	Our data indicate that NF-kappaB plays a crucial role as a key regulator in the initiation of CA development by inducing some inflammatory genes related to macrophage recruitment and activation. NF-kappaB may represent a therapeutic target of a novel medical treatment for CA.
205	Aoki, et al.	2009	Rat	X	Collagen biosynthesis was significantly inhibited at the transcriptional level and in the posttranscriptional enzymatic modification in CA walls through upregulated expression of IL-1beta and the NF-kappaB pathway. Reduced collagen biosynthesis may contribute to CA progression, and inhibition of this process may lead to the prevention of the progression and rupture of CAs.
206	Aoki, et al.	2012	Rat	X	Results suggest the possibility of a minimally invasive molecular therapy targeting the inhibition of NF-kappaB and ets-1 for IAs in humans.
207	Aoki, et al.	2008	Rat	X	Immunohistochemistry and gelatin zymography showed that the expression and activity of MMP-2 was also reduced by nifedipine. Furthermore, nifedipine significantly prevented the enlargement and degeneration of aneurysmal walls of preexisting CAs. Nifedipine may be useful as a medical drug for patients with CAs.
208	Aoki, et al.	2009	Rat	X	Pitavastatin has a suppressive effect on CA progression through the inhibition of NF-kappaB activation in aneurysmal walls. Moreover, pitavastatin treatment can cause the regression of degenerative changes in preexisting CA walls. Pitavastatin is a promising candidate as a novel preventive agent against subarachnoid hemorrhage.

209	Aoki, et al.	2011	Rat	X	Shear stress activated PGE_2-EP_2 pathway in ECs and amplified chronic inflammation via NF-κB. We propose EP_2 as a therapeutic target in cerebral aneurysm.
210	Aoki, et al.	2017	Rat, Mouse	X	Rats administered an EP2 antagonist had reduced macrophage infiltration and intracranial aneurysm formation and progression. This signaling pathway in macrophages thus facilitates intracranial aneurysm development by amplifying inflammation in intracranial arteries. Results indicate that EP2 antagonists may therefore be a therapeutic alternative to surgery.
211	Aoki, et al.	2010	Rat	X	Inhibition of DNA-binding activity of Ets-1 may lead to prevention of human CA enlargement and rupture. Results of this study will provide clues for a novel therapeutic strategy for CAs.
212	Aoki, et al.	2009	Rat, Mouse	X	MCP-1 plays a crucial role in CA formation as a major chemoattractant for monocyte/macrophage. MCP-1 expression in CA walls is induced through nuclear factor-kappa B activation. MCP-1 may be a novel therapeutic target of medical treatment preventing CA progression.
213	Yagi, et al.	2010	Rat	Y	Blocking of PDE4 is associated with reduction of inflammation-related molecules and macrophage migration, thereby reducing the progression of cerebral aneurysms. It may represent a new conservative therapy to treat patients with cerebral aneurysms.
214	Mandelbaum, et al.	2013	Rabbit	W	During aneurysm initiation triggered by hemodynamics, SMCs rather than macrophages are responsible for MMP production that is critical for aneurysmal lesion development. These SMCs exhibit proinflammatory behavior.
215	Kanematsu, et al.	2011	Mouse	Y	Data suggest critical roles of macrophages and proper macrophage functions in the formation of intracranial aneurysms in this model.
216	Ishibashi, et al.	2010	Rat	X	Mast cells contribute to the pathogenesis of CA by inducing inflammation and that inhibitors of mast cell degranulation can be therapeutic drugs for CA.
220	Li, et al.	2015	Rat	X	Evidence suggested that aspirin significantly reduced degeneration of aneurysm walls by inhibiting macrophages-mediated chronic inflammation and mobilizing EPCs.
221	Chalouhi, et al.	2016	Mouse	Y	15-Hydroxyprostaglandin dehydrogenase activation in females reduces the incidence of rupture and eliminates the sex-differential response to aspirin.
222	Makino, et al.	2012	Mouse	Y	Our data established the feasibility of using a mouse model of intracranial aneurysm to test pharmacological stabilization of aneurysms. Tetracycline derivatives could be potentially effective in preventing aneurysmal rupture.

223	Ali, et al.	2013	Rat	X	Results demonstrate a novel role for TNF-alpha in promoting a pro-inflammatory/matrix-remodeling phenotype. This has important implications for the mechanisms behind intracranial aneurysm formation.
224	Aoki, et al.	2014	Rat	X	In this study, using rodent models of IAs, we clarified the crucial role of TNF-alpha-TNFR1 signaling in the pathogenesis of IAs by inducing inflammatory responses, and propose this signaling as a potential therapeutic target for IA treatment.
225	Aoki, et al.	2009	Mouse	X	Cerebral aneurysm (CA) formation was markedly inhibited by p47phox deletion in mice and accompanied by decreased inflammation in aneurysmal walls. Data suggested the active participation of ROS and p47phox in CA formation and the therapeutic potential of an ROS-eliminating agent against CA formation.
226	Tada, et al.	2009	Rat	X	We demonstrate that mineralocorticoid receptor activation at least partly contributes to the pathogenesis of cerebral aneurysms.
227	Tada, et al.	2010	Rat	X	In rat, the destruction of tight junctions may facilitate macrophage migration and cerebral-aneurysm formation.
229	Hasan, et al.	2015	Mouse	Y	Endogenous PPARgamma, specifically smooth muscle PPARgamma, plays an important role in protecting from formation and rupture of experimental cerebral aneurysms in mice.
230	Shimada, et al.	2015	Mouse	Y	Activation of macrophage PPARγ protects against the development of aneurysmal rupture. PPARγ in inflammatory cells may be a potential therapeutic target for the prevention of aneurysmal rupture.
231	Shimada, et al.	2015	Mouse	Y	Findings indicate that Ang-(1-7) can protect against the development of aneurysmal rupture in an AT2R-dependent manner.
232	Liu, et al.	2016	Mouse	Y	Human MSC-derived MVs prevented the rupture of intracranial aneurysm, in part due to their anti-inflammatory effect on mast cells, which was mediated by PGE2 production and EP4 activation.
233	Tanaka, et al.	2016	Mouse	$CaCl_2$	Hyperglycemia suppresses macrophage activation and aneurysmal degeneration through the activation of Nr1h2. Although further validation of the underlying pathway is necessary, targeting Nr1h2 is a potential therapeutic approach
234	Bo, et al.	2017	Mouse	$CaCl_2$	All these data taken together may suggest that curcumin could significantly reduce the $CaCl_2$-induced cerebral aneurysm through the inhibition of cell apoptosis in the cells.
235	Ikedo, et al.	2017	Rat	X	A DPP-4 inhibitor, anagliptin, prevents the growth of IAs via its anti-inflammatory effects on macrophages.

236	Labeyrie, et al.	2017	Mouse	Y	Overall, this preclinical study demonstrates that the tPA present in the blood stream is a key player of the formation of IAs. Thus, tPA should be considered as a possible new target for the prevention of IAs formation and rupture.
237	Suzuki, et al.	2019	Mouse	Y	VNS can reduce aneurysm rupture rates and improve the outcome from ruptured aneurysms.
238	Abekura, et al.	2020	Rat	W	Results suggest the potential of the medical therapy targeting GPR120 or using EPA to prevent the progression of IAs.
239	Ma, et al.	2019	Rat	X	Tan IIA can suppress CA formation by inhibiting inflammatory responses in macrophages.
240	Lai, et al.	2019	Rat	X	Apc has the potential role to attenuate IA formation and rupture by inhibiting inflammatory response through repressing the activation of the NF-κB signaling pathway.
241	Yang, et al.	2019	Rat	Z	Treatment with β-sitosterol suppresses the development of CA by inhibiting inflammatory reactions including TNF-α and thus β-sitosterol can be a suggestive candidate for the prevention of CA treatment and progression.
242	Zhang, et al.	2018	Rat	X	The expression levels of KLF5, MMP2, and MMP9 levels were elevated by LPS, and were attenuated by miR-448-3p. These data suggest that miR-448-3p plays the inhibitory role in IA progression, indicating that miR-448-3p overexpression is crucial for preventing the development of IA through downregulation of macrophage-mediated inflammation.
243	Fukuda, et al.	2019	Mouse and Rat	X	P2X4 is required for the inflammation that contributes to both cerebral aneurysm formation and growth. Enhanced shear stress-associated hemodynamic stress on the vascular endothelium may trigger cerebral aneurysm development. Paroxetine may have potential for the clinical treatment of cerebral aneurysms, given that this agent exhibits efficacy as a clinical antidepressant.
244	Pascale, et al.	2020	Mouse	Y	Dimethyl fumarate demonstrated a neuroprotective effect in mice with a resultant inhibition of oxidative stress, inflammation, and fibrosis in the cerebrovasculature. This suggests a potential role for DMF as a rescue therapy for patients at risk for formation and rupture of IAs.
245	Suzuki, et al.	2018	Mouse	Y	Aspirin prevented aneurysm rupture in a mouse intracranial aneurysm model, while cilostazol did not. Aspirin, the most frequently used drug for patients with ischemic myocardial and cerebral diseases, is also effective in preventing cerebral aneurysmal rupture.

246	Ishibashi, et al.	2012	Rat	X	Angiotensin-converting enzyme is not involved in the pathogenesis of CA formation. Imidapril suppresses CA formation in an ACE-independent and MMP-9-dependent manner.
247	Aoki, et al.	2007	Rat	X	Macrophage-derived MMP-2 and -9 may play an important role in the progression of cerebral aneurysms. The findings of this study will shed a new light into the pathogenesis of cerebral aneurysms and highlight the importance of inflammatory response causing the degeneration of extracellular matrix in the process of this disease.
248	Aoki, et al..	2008	Rat	X	Data obtained by using NC-2300 revealed an important role of cysteine cathepsins in the progression of CAs. Our findings strongly suggest that an imbalance between cysteine cathepsins and their inhibitor may cause the excessive breakdown of extracellular matrix in the arterial walls leading to the progression and rupture of CAs
249	Liu, et al.	2017	Mouse	Y	Study provides an important support for the role of primary cilia in development of intracranial aneurysms. The primary cilia stabilizing chemicals might be useful for preventing intracranial aneurysmal development.

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