Review Article

JCBFM

Journal of Cerebral Blood Flow & Metabolism
2022, Vol. 42(9) 1568–1578

DOI: 10.1177/0271678X211057498
journals.sagepub.com/home/jcbfm


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

Received 9 August 2021; Revised 13 October 2021; Accepted 16 October 2021

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)

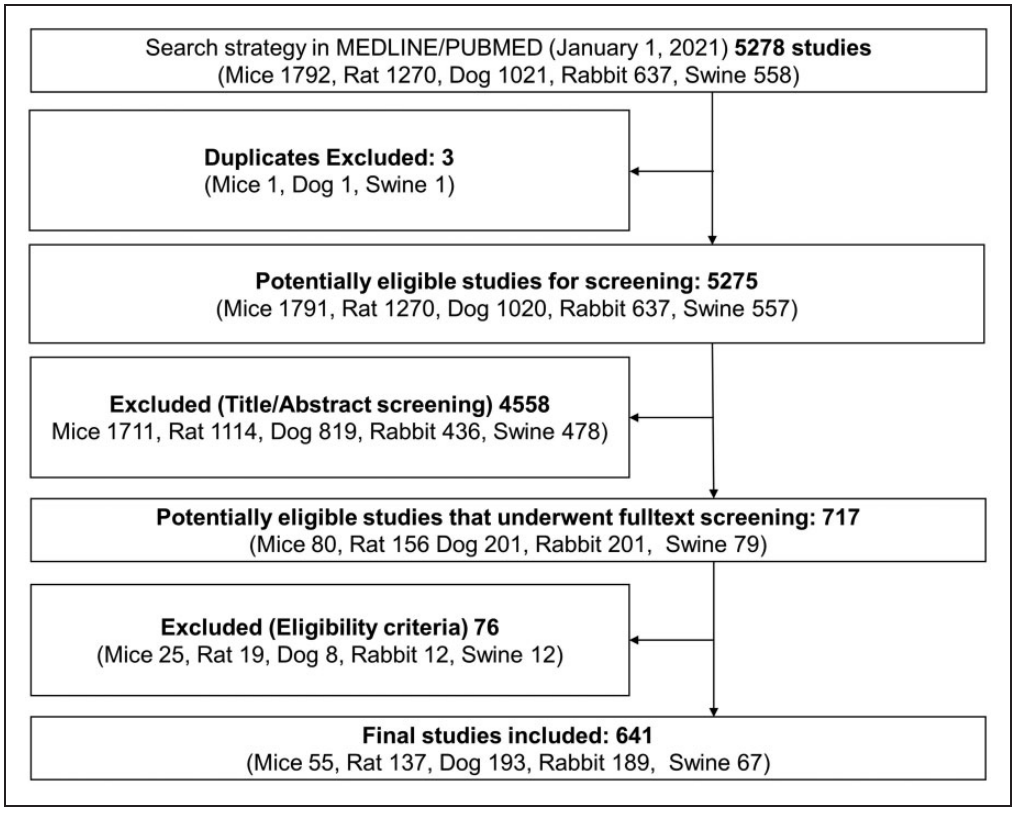

Figure 1. PRISMA Flow chart for study selection and exclusion.

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).

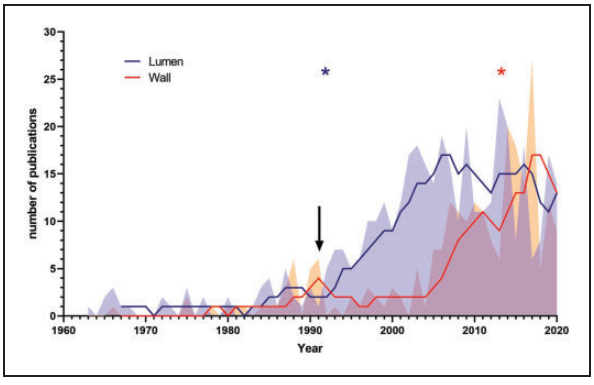

Figure 2. Comparison of lumen-oriented and wall-oriented therapies per year. Line shows the five-year average for lumen-oriented (blue) and wall-oriented (red) therapies, and the corresponding shadow shows the number of publications for each strategy per year. For most years, publications of lumen-oriented 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

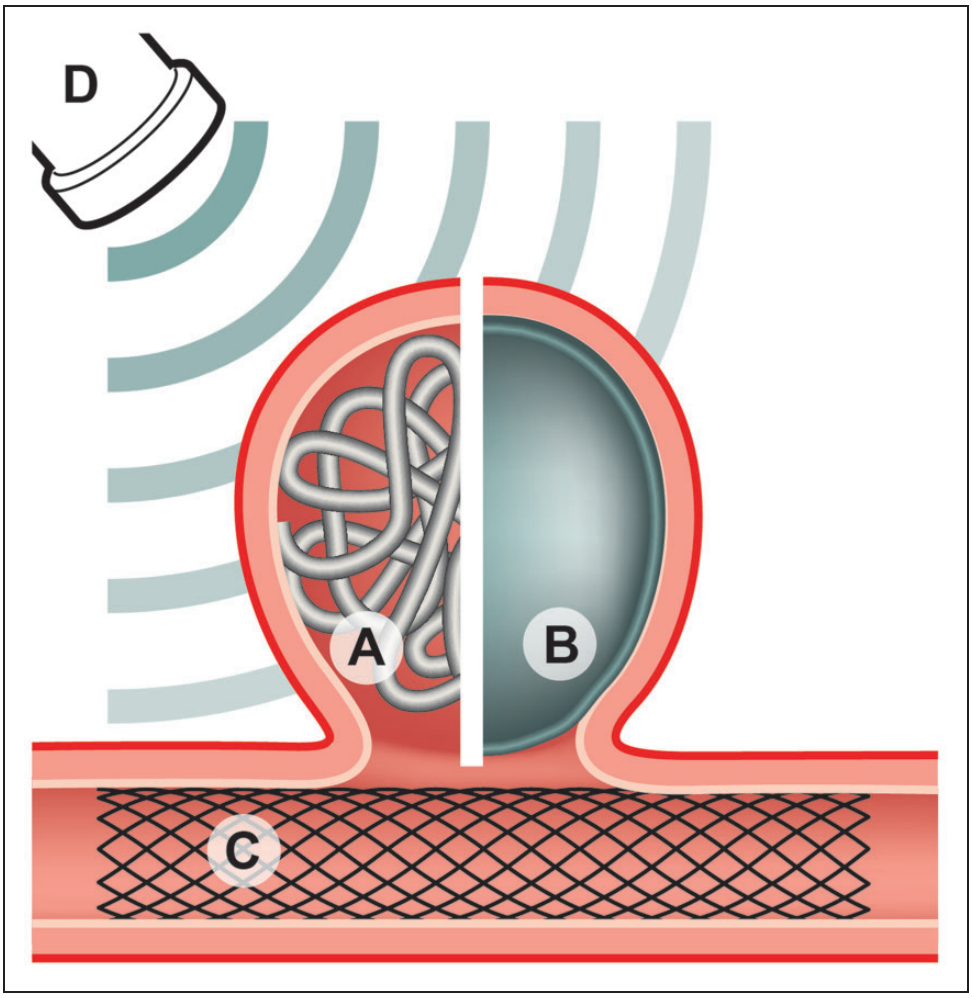

Figure 3. Lumen-oriented treatment strategies are grouped into four types with the following aims: (a) enhance intraluminal thrombus organization; (b) enhance intraluminal packing; (c) bridge the intraluminal space; and (d) alternative concepts (i.e., other strategies for endothelial denudation, navigation 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]

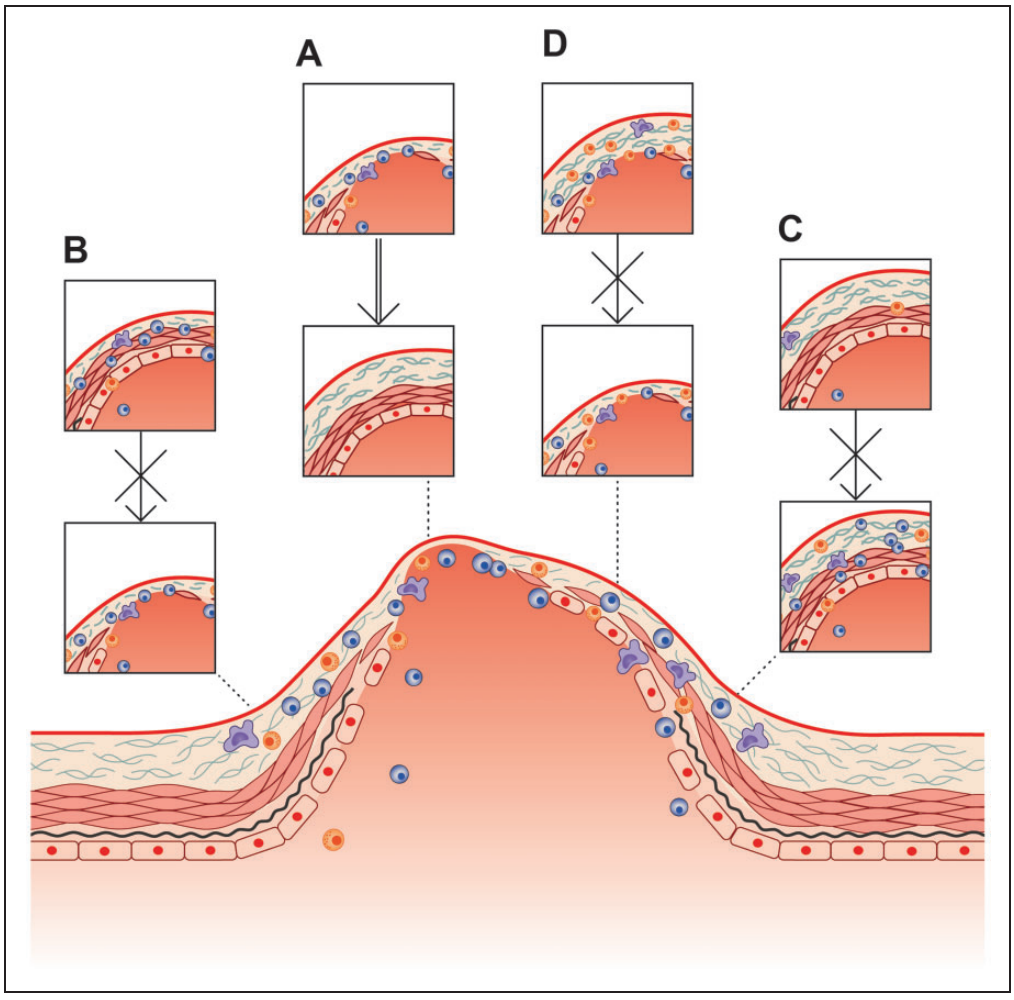

Figure 4. Wall-oriented treatment strategies. Strategies were categorized with to aim to stimulate the proliferative response (a), prevent aneurysm wall cell injury (b), inhibit the inflammation and oxidative stress (c), and inhibit the extracellular matrix degradation (d).

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.

Funding

Dr Marbacher reports a grant from the Swiss National Science Foundation (310030_182450). No other financial support was received.

Acknowledgements

We thank Mary Kemper (Glia Media) for medical editing and express our gratitude to Ruth Angliker for illustrations.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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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