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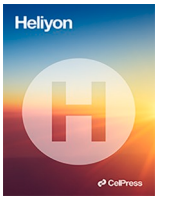

Review article

# Aspirin treatment for unruptured intracranial aneurysms: Focusing on its anti-inflammatory role

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ABSTRACT

Intracranial aneurysms (IAs), as a common cerebrovascular disease, claims a worldwide morbidity rate of 3.2%. Inflammation, pivotal in the pathogenesis of IAs, influences their formation, growth, and rupture. This review investigates aspirin's modulation of inflammatory pathways within this context. With IAs carrying significant morbidity and mortality upon IAs rupture and current interventions limited to surgical clipping and endovascular coiling, the quest for pharmacological options is imperative. Aspirin's role in cardiovascular prevention, due to its anti-inflammatory effects, presents a potential therapeutic avenue for IAs. In this review, we examine aspirin's efficacy in experimental models and clinical settings, highlighting its impact on the progression and rupture risks of unruptured IAs. The underlying mechanisms of aspirin's impact on IAs are explored, with its ability examined to attenuate endothelial dysfunction and vascular injury. This review may provide a theoretical basis for the use of aspirin, suggesting a promising strategy for IAs management. However, the optimal dosing, safety, and long-term efficacy remain to be established. The implications of aspirin therapy are significant in light of current surgical and endovascular treatments. Further research is encouraged to refine aspirin's clinical application in the management of unruptured IAs, with the ultimate aim of reducing the incidence of aneurysms rupture.

## 1. Introduction

Intracranial aneurysms (IAs), as a common cerebrovascular disease, claims a worldwide morbidity rate of 3.2% [1]. Although most IAs remain asymptomatic for their lifetime, their rupture confers high morbidity and mortality. With the introduction and advancement of computed tomography angiography (CTA) and magnetic resonance angiography (MRA), unruptured intracranial aneurysms (UIAs) are being increasingly diagnosed. According to a cross-sectional epidemiological study in China, 7.0% of adults aged 35–70 years have UIAs, and this number increases with age [2]. As UIAs progress, a range of neurological symptoms manifest, including subarachnoid hemorrhage (SAH) and cerebral infarction, which can lead to approximately 30% mortality within the first 30 days of onset [3] and permanent cognitive impairment in 76% of those who survive [4].

Owing to limited knowledge of the natural history and the scarcity of randomized controlled trials (RCTs) on the current

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management of UIAs, the most effective therapy for UIAs remains a subject of debate [5].

Currently, invasive therapies for UIAs include microsurgical clipping, isolation, wrapping, endovascular coiling, and stenting with a flow diverter. Albeit that invasive treatment is necessary for ruptured aneurysms, whether it is beneficial in the long term for UIAs patients remains to be elucidated [6]. Numerous investigations have been performed to develop non-invasive treatments with a lower incidence of post-treatment complications and better prognosis [7]. Recent studies have revealed that the inflammatory responses in the aneurysmal wall have pivotal effects on UIAs formation, growth, and rupture and could thus serve as a potential therapeutic target [8]. Aspirin, a representative nonsteroidal drug, has significant anti-inflammatory effects on multiple central nervous system (CNS) diseases. Since aspirin was first reported in 2013 to be capable of delaying the progression and reducing the rupture risk of UIAs [9], nevertheless, its effects on UIAs remain controversial [10]. In this review, we outline the role of CNS inflammation in the progression of IAs, and examine the anti-inflammatory properties of aspirin and its potential as a therapeutic intervention for the management of UIAs, highlighting its role in mitigating aneurysm progression and rupture risk.

## 2. Arterial structures compromised by inflammatory factors

The normal intracranial arterial wall consists of three layers, including the intima, media, and adventitia. The intimal layer is composed of a single layer of vascular endothelial cells (VECs), fibrous basement membranes, and internal elastic lamina (IEL); the media layer is composed of elastin and vascular smooth muscle cells (VSMCs); and the adventitia is composed of a thin layer of type I collagen fibers, fibroblasts and nerve fibers [11]. Contemporary research suggests that disruption of the endothelia and IEL structure, triggered by abnormal hemodynamic stress, constitutes the first stage of UIAs formation. In subsequent stages, various pro-inflammatory cells are recruited, and plentiful inflammatory cytokines are secreted, which subsequently results in proliferation, apoptosis, and remodelling of VSMCs in the aneurysmal wall. The ongoing degradation of the aneurysmal wall can eventually lead to IAs rupture (Fig. 1) [12,13]. The rest of this section will dwell on arterial structures that are compromised by inflammatory factors.

### 2.1. *Vascular endothelial cells (VECs)*

VECs, connected with specialized connections between adjacent cells like tight junctions, adherent junctions, and/or gap junctions, play an important role in repairing injured tissues, maintaining vessel permeability, and inhibiting inflammatory cell infiltration [14,15]. Extensive evidence indicates that abnormal hemodynamic stress can trigger the disruption of vascular endothelial cells (VECs) and resultant inflammation, marking the earliest stages of IAs formation [7,16–18].

Hosaka et al. [12] found that aneurysm may occur at sites in human and animal cerebral vessels under high wall shear stress (WSS) [12], whereas under normal WSS, a low inflammatory environment may be triggered by downregulating nuclear factor-κB (NF-κB) and

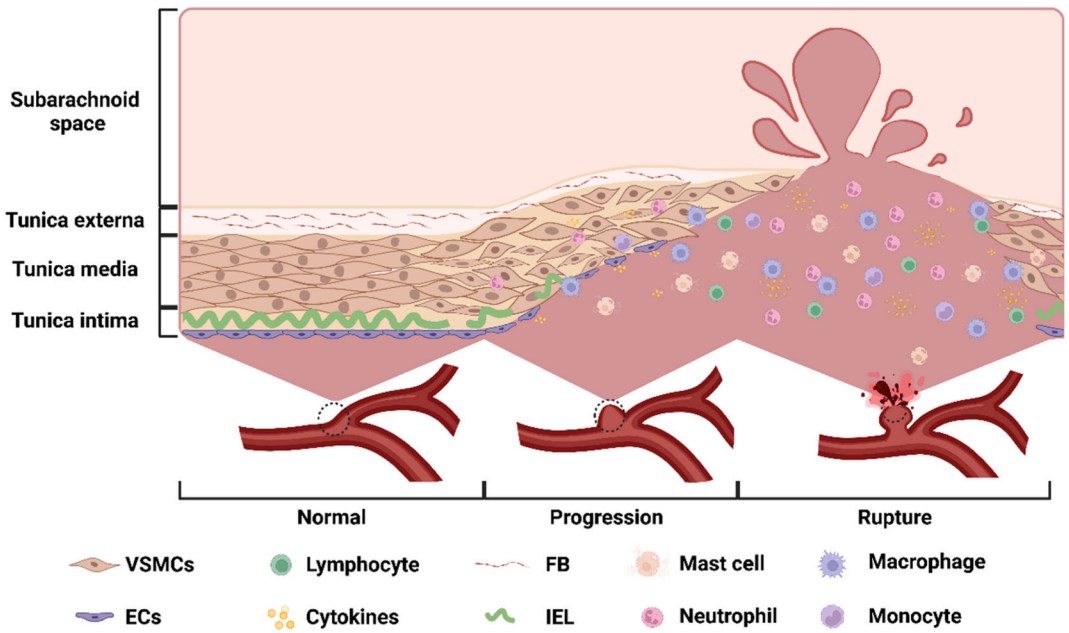


**Fig. 1. Schematic diagram of intracranial aneurysm occurrence, growth and rupture.** Abnormal hemodynamics leads to the structure dysfunction of artery blood vessels, mainly through the recruitment of inflammatory cells thus promoting the degeneration and fracture of IEL, and causing VSMCs proliferation and transition to a pro-inflammatory phenotype. The ECM degradation influenced by VSMCs apoptosis gradually resulted in IA formation, which in return cause further inflammation and the remodelling of vascular wall structure and ultimately induce IA rupture. VSMCs, vascular smooth muscle cells; FB: Fibrinogen; ECs, endothelial cells; IEL, internal elastic lamina.

epigenetic gene repression-related mechanisms [19]. The inflammatory environment also triggers hazardous nitric oxide synthase (NOS) activity and extensive oxidative stress, which can compromise the intercellular junctions of VECs, leading to the remodelling of vessel walls and ultimately the formation and growth of IAs [20]. However, adding to this nuanced understanding, Skodvin et al. [21] reported that a low WSS generated in the aneurysm dome may also contribute to IAs growth and rupture.

In addition to being attacked by pro-inflammatory factors, activated VECs promote the recruitment and infiltration of inflammatory cells into the intima, including monocytes, leukocytes, and T-lymphocytes. They also secrete inflammatory cytokines and chemokines [22], which in turn leads to VECs degradation and compromises endothelial integrity [23].

### 2.2. Vascular smooth muscle cells (VSMCs)

VSMCs, as the most important type of cells responsible for the adaptive remodelling of the arterial wall of UIAs, participate in the synthesis of the extracellular matrix (ECM), which serves as the foundational structure of the vessel walls [24]. In the pathological processes of IAs, the exposure of subendothelial collagen facilitates the apoptosis of VSMCs and induces aberrant activation of systemic immune responses as well as the recruitment of inflammatory cells and chemokines, further damaging the arterial middle membrane [19].

During IAs pathogenesis, VSMCs demonstrate plasticity by transitioning from a mature contractile phenotype to a hypo-differentiated synthetic phenotype [25]. Certain pro-inflammatory cytokines, like tumor necrosis factor (TNF), can induce a phenotype switch in VSMCs, which is characterized by increased expression of monocyte chemotactic protein-1 (MCP-1) and matrix metalloproteinases (MMPs). Then, these synthetic VSMCs continuously migrate from the injured media layer to the tunica intima of the arterial wall [26].

Increased WSS can induce apoptosis of VSMCs, while the loss of VSMCs and replacement of the low-strength transparent matrix can pare the arterial middle membrane, which in turn promotes the formation of IAs [7]. Moreover, Hosaka and Tulamo et al. [8,12] found that inflammation could aggravate these processes, weaken the strength and elasticity of the aneurysm wall, and eventually induce IAs rupture.

## 3. Cells related to inflammation in intracranial aneurysms

UIAs-related inflammation is characterized by the aggregation and infiltration of various inflammatory cells, including macrophages, neutrophils, and T-lymphocytes [12]. The rest of this section will discuss the various cells that are related to inflammation in IAs.

### 3.1. Macrophages and monocytes

Macrophages, consisting of colonizing macrophages in the brain and recruited monocytes, constitute the predominant group of inflammatory cells in UIAs across human and animal models, playing a pivotal role in the IAs formation and progression. A pilot study involving UIAs patients utilized ferumoxytol-enhanced magnetic resonance imaging (Fe-MRI) to directly visualize macrophages accumulating in the aneurysm wall, and thereby provided visual evidence of inflammatory activity during UIAs formation [27]. Alejandra et al. [28] performed a single-cell transcriptome analysis of mouse elastase cerebral aneurysm and found that IAs resulted in a significant expansion of the total macrophage population, which was further amplified following the IAs rupture. Macrophages in hypertension-induced IAs models are considered the first type of inflammatory cells that infiltrate the aneurysm wall after ECs injury [29]. These macrophages secrete MMP-2 and -9, transforming growth factor-β (TGF-β), and platelet-derived growth factor B [30], all of which are critical mediators in the inflammatory process.

MMPs are proteolytic enzymes that can degrade the majority of ECM proteins, including elastin and collagen types I and III, and lead to degeneration of the IAs wall [31]. In addition, a study of surgical samples from 36 IAs patients revealed that the number of infiltrated macrophages was positively correlated with Cyclooxygenase-2 (COX-2) and prostaglandin E receptor subtype 2 (EP2) in the IAs wall [32]. Consequently, it was found that EP2 and prostaglandins (PGs), including $PGE_2$, $PGD_2$, and $PGI_2$, directly activated NF-κB [33]. NF-κB has been identified as the principal transcription factor that regulates inflammation-related genes, including nitric oxide synthase (NOS) and interleukin (IL)-1β, and stimulates the secretion of MCP-1. MCP-1, as a key chemoattractant molecule that recruits macrophages, has been detected in human blood samples from the aneurysmal lumen of patients with UIAs [34]. In MCP-1 deficient mice, a decrease in macrophage infiltration in the arterial wall was observed, which was found to be associated with both a reduced formation and inhibition of rupture in UIAs [30,35,36].

Moreover, it has been reported that pharmacological depletion of macrophages can reduce the incidence of aneurysmal rupture in a mice model [37]. Reduced macrophage infiltration following eicosapentaenoic acid (EPA) treatment suppresses media degeneration in a rat IAs model [38]. An aneurysmal model of macrophage/monocyte-specific toll-like receptor 4 knockout mice exhibited a lower risk of rupture and a decrease in the inflammatory cytokine level compared to control littermate mice [39]. These findings suggest that macrophages play a vital role in inflammatory responses during IAs formation and rupture.

Macrophages can polarize into two distinct subsets: classically activated (M1-like) and alternatively activated (M2-like) macrophages, with the former playing a pro-inflammatory role while the latter facilitating the attenuation of inflammation. Xing et al. [40] reported that both M1 and M2 macrophages were enriched in human aneurysmal tissues. A histopathological study of clinical blood blister-like aneurysms samples indicated that macrophages were the most infiltrated inflammatory cells in the wall of the aneurysm and that reduced M2 macrophages were associated with structural deterioration of aneurysms [41]. David et al. [42] analysed a cohort

of 10 UIAs patients and found that the M1/M2 imbalance contributed to aneurysm rupture, which was consistent with the findings in a mouse model in which the M1/M2 ratio increased in IAs over time [43]. However, Stratilová et al. [44] analysed a cohort of 41 patients with saccular IAs and found that a shift in macrophages towards M2 in the aneurysm wall were prone to rupture. Therefore, given the complexity of macrophages, further studies are needed to gain a more in-depth and comprehensive knowledge of the role of macrophages in different pathological stages of UIAs.

### 3.2. Neutrophils

In early arterial wall injury, neutrophils usually migrate to the damaged sites and create an inflammatory microenvironment by producing numerous proinflammatory factors, thereby promoting the rupture of IAs [45]. Clinical and pre-clinical research on the potential roles of neutrophils in IAs has been focused on aneurysmal subarachnoid hemorrhage (aSAH). Compared with patients with unruptured IAs, more neutrophil infiltration was observed in patients with ruptured IAs [46]. In blood and tissue samples of aSAH, genes related to neutrophil responses were enriched, and neutrophils were significantly increased [47]. Neutrophil counts could serve as an independent predictor of the prognosis of aSAH, while higher neutrophil counts are associated with increased mortality and hospital-acquired infections [48,49]. In addition, the ratio of neutrophils to other blood inflammatory cells, including lymphocytes and monocytes, could serve as a promising marker of IAs prognosis. In a clinical study that enrolled 532 patients, elevated neutrophil-to-lymphocyte ratio (NLR) was proven to be associated with the size of UIAs and poor prognosis [50]. A large cohort study indicated that a lower platelet-to-neutrophil ratio (PNR) was associated with a higher rupture rate [51]. Poppenberg et al. [52] constructed a predictive model based on circulating neutrophil transcription that can detects IAs formation with an accuracy of 90%.

In addition, neutrophils are considered the main source of neutrophil gelatinase-associated lipocalin (NGAL) and myeloperoxidase (MPO), which promote extracellular matrix and endothelial degeneration [53]. In human aneurysms specimens, MPO and NGAL levels in the aneurysms wall are high, and these proteins can also exacerbate oxidative stress-induced injuries and inflammatory responses [20,52]. In a study of 36 patients with saccular IAs, MPO was found to be strongly associated with inflammatory cell infiltration and may potentially serve as a biomarker of rupture-prone saccular IAs [48]. Neutrophils also secrete neutrophil extracellular traps (NETs), networks of unravelled chromatin, and associated proteins, which consist of a variety of enzymes, such as gasdermin D, MPO, and elastase. Recently, Korai et al. [54] have explored the role of NETs in IAs and found that blocking NETs formation could decrease the number of proinflammatory cytokines in cerebral arteries, including IL-1β, MCP-1, and TNF, and thus reduce the incidence of IAs rupture in a mouse model.

### 3.3. T-cells

T-lymphocytes in the CNS, originating mainly in the peripheral blood, are responsible for modulating myeloid cells, preventing pathogens from invading the CNS, and orchestrating the inflammatory environment [55]. T-cells of various types detected in the aneurysm walls contribute to the increase in pro-inflammatory cytokines in both IAs patients [46,56] and elastase-induced mouse IAs models [57]. Moschetti et al. [56] explored T-cell heterogeneity in a pediatric IA case and reported that, $CD4^+$ and $CD8^+$ T-cells proliferated significantly in the aneurysm wall, while naïve T-cells and canonical memory T-cells were confined to the peripheral blood. Additionally, these active polyfunctional T-cells exhibited elevated expressions of IFN-γ, TNF, and IL-2. During the first 72 h after IAs rupture, the ratio of $CD4^+/CD8^+$ T-cells was lower than that in the chronic stages and showed a concomitant increase compared with a relatively healthy cohort [58]. Since $CD8^+$ and $CD4^+$ T-cells express T-cell immunoglobulin and mucin protein 3 (Tim-3), they can prevent IAs from rupturing by negatively regulating TNF [59]. Sun et al. [60] observed an imbalance between T helper (Th) 17 and regulatory T (Treg) cell ratios in the aneurysm wall of IAs patients, which is probably responsible for a significant elevation in the expressions of IL-17, IFN-γ, IL-17a, MCP-1, TNF, and IL-6.

Th17 cells were found to promote IL-17A expression and encourage macrophage infiltration in the aneurysms wall, eventually leading to the formation and rupture of aneurysms in both mouse and human IAs, especially in estrogen-deficient conditions [61]. In addition, IAs patients' peripheral blood exhibits excessive Th1 and Th17 activities, with Th2 and Treg activities being underrepresented. Such an imbalance leads to an increased production of IFN-γ, TNF, and IL-17 and a decreased production of IL-10 [62].

Altogether, T cells in both the CNS and the peripheral immune system have profound effects on the pathological processes of IAs.

### 3.4. Other inflammatory cell types

In addition to the immune cells mentioned above, several other types of proinflammatory cells also contribute to the pathological processes of IAs. Ollikainen et al. [63], for example, found that the presence of mast cells (MCs) in human IAs walls was associated with increased T-cells and macrophage infiltration, higher iron deposition, and higher neovessel density, thus proposing that MCs also contribute to the remodelling and degeneration of the aneurysm wall. In a rat model of IAs, the use of MCs degranulation inhibitors was found to significantly reduce the enlargement and medial layer thinning of the aneurysms, which was attributed to suppressing NF-κB activation, macrophage infiltration, MCP-1, MMPs, and IL-1β [64]. However, activation of MCs in mouse models markedly increased the incidence of IAs rupture without affecting aneurysm formation [65]. By stabilizing MCs, intravenous injection of mesenchymal stem cells (MSCs) exerted a protective effect against IAs rupture and TNF production in mice [66].

To be brief, administrating mast cell degranulation inhibitors can help delay macrophage infiltration and inhibit IAs progression [65].

## 4. The renin-angiotensin system (RAS) and intracranial aneurysms

The renin-angiotensin system (RAS), as a peptidergic hormonal system activated by the release of renin, plays an essential role in the hemostasis of the cardio-cerebral vascular system [67]. In recent years, there have been studies proposing that RAS is involved in the inflammatory response associated with various arterial diseases such as atherosclerosis and abdominal aortic aneurysms [68]. Upregulated local RAS is believed to cause VSMCs proliferation and subsequent VECs degeneration, which are the main factors conducive for aneurysms formation [69]. Nevertheless, reports have surfaced of paradoxical findings in patients with IAs. Compared to the arterial walls of healthy subjects, those of patients with IAs exhibit significantly fewer classical RAS molecules, such as angiotensin-converting enzyme (ACE), angiotensin (Ang) II receptor type 1 ($AT_1$), platelet-derived growth factor-AA (PDGF-AA), and tissue inhibitor of metalloproteinase kinase-1 (TIMP-1), especially in walls of ruptured aneurysms [69,70]. Since decreased RAS activity typically occurs in the later stage of IAs progression, it remains unclear whether this reduction is a cause or a consequence of IAs rupture, necessitating further investigation.

The Ang II-$AT_1$ axis is a pivotal mediator of RAS signaling that induces an inflammatory cascade in the arterial walls by activating transcription activity of NF-κB [3]. In an elastase-induced IAs mouse model, Ang II increased the expression of TNF, integrin alpha M (itgam, a marker of macrophage infiltration), and microsomal prostaglandin E2 synthase-1 (mPGES-1, a pro-inflammatory enzyme) in cerebral arteries, while Ang 1–7, an inhibitor of Ang II, downregulated MMP-9 and COX-2 expression and reduced the aneurysmal rupture ratio but had negligible impact on the above pro-inflammatory factors [71]. Similarly, in a rat model, the $AT_1$ blocker valsartan failed to suppress inflammation in the cerebral aneurysmal walls at a dosage that left systemic blood pressure unaffected [3]. In a surgical IAs rat model, the ACE inhibitor imidapril suppresses IAs formation in an MMP-9-dependent manner rather than in an ACE-dependent manner [72]. By reviewing the database of 3044 hypertensive patients with IAs from 20 medical centers in China, Zhong et al. [73] established that blocking the activation of $AT_1$ lowered the level of inflammation in the aneurysmal wall and reduced the likelihood of rupture.

The controversial role of RAS in IAs progression may be attributed to the significance of genetic polymorphisms. In a Cerebral Aneurysm Renin-Angiotensin System (CARAS) study that enrolled 149 patients with aSAH, the G allele of the $AT_2$ G/A single-nucleotide polymorphism (SNP) was found to contribute to aSAH, while downregulating the local RAS was proposed to be conducive for the formation and subsequent rupture of IAs [70]. In a prospective case-control study by Slowik et al. [74], the I/D polymorphism analysis of ACE in patients with IAs demonstrated that type II genotype of ACE gene constituted an independent risk factor for rupture. However, the link between RAS polymorphisms and inflammatory responses in IAs remains poorly understood.

## 5. Gastrointestinal microorganisms and intracranial aneurysms

Gastrointestinal microorganisms, as environmental factors, play a vital role in IAs progression by modulating arterial

**Table 1**
Summary of animal studies assessing the impact of aspirin on IA models.

| Authors | Year | Model | Animal and Number | Statistical results |
|---|---|---|---|---|
| Li et al. [81] | 2015 | Ligation left common carotid artery and posterior branches of bilateral renal arteries, followed by high-salt diet (8 % sodium chloride) for 2 months. | 7-week-old male Sprague-Dawley mice<br>Control: Aspirin = 20:20 | Media thickness,<br>Control vs Aspirin = 0.46 ± 0.06 vs 0.62 ± 0.12 μm, $P < 0.01$;<br>Aneurysm size,<br>Control vs Aspirin = 58.2 ± 8.8 vs 43.9 ± 6.7 μm, $P < 0.01$ |
| Peña Silva et al. [91] | 2015 | Deoxycorticosterone acetate-salt-induced hypertension and intracranial injection of elastase in the basal cistern. | Wild type and mPGES-1 knockout C57BL/6 mice<br>Control: Aspirin = 12:13 | SAH rate,<br>Control vs Aspirin = 75% vs 46%, $P = 0.07$ |
| Chalouhi et al. [87] | 2016 | Deoxycorticosterone acetate-salt-induced hypertension and intracranial injection of elastase in the basal cistern. | Wild type and COX-1 knockout C57BL/6 mice<br>Control: Aspirin: COX-1 inhibitor: COX-2 inhibitor = 14:14:14:14 | Aneurysm rupture rate,<br>Control vs Aspirin = 100% vs 42.9%, $P < 0.05$<br>Control vs COX-2 inhibitor = 100% vs 33.3%, $P < 0.05$ |
| Suzuki et al. [84] | 2018 | deoxycorticosterone acetate-salt and a single injection of elastase into the cerebrospinal fluid | 8- to 10-week-old male mice C57BL/6 mice<br>Control: Aspirin = 26:25 | Aneurysm rupture rate,<br>Control vs Aspirin = 80% vs 31%, $P < 0.05$ |
| Ho et al. [82] | 2021 | Injecting elastase into the origin of the right common carotid artery to induce aneurysm | New Zealand white rabbits<br>Female: Male = 12:12 then assigned to control and aspirin group (n = 6) | Histopathologic analysis and vessel wall imaging patterns,<br>No appreciable differences were seen in histology or imaging when comparing gender or treatment with aspirin. |
| Wanderer et al. [83] | 2022 | Anastomose the right common carotid artery (CCA) with the distal side of the left common carotid artery and insert it into the arterial pocket to form a bifurcation aneurysm | 16-week-old female New Zealand white rabbits<br>Vital: Decellularized: Elastase-degraded = 12:12:12, then assigned to control and aspirin group (n = 6) | Periadventitial inflammation, control vs Aspirin ($P < 0.01$)<br>Aneurysm wall inflammation control vs Aspirin (vital group: $P < 0.01$; decellularized group: $P < 0.05$; elastase group: $P < 0.01$) |

inflammation. A decrease in the genus *Hungatella hathewayi* and an increase in *Campylobacter* constitute the principal changes in gastrointestinal microorganisms that influence the IAs formation, progression, and rupture [25]. Studies demonstrate that supplementation with *H. hathewayi* can slow down the inflammatory process by increasing the plasma taurine concentration [75], whereas *Campylobacter* can enhance cytokine secretion, neutrophil-mediated proteolysis, and oxidative stress, promote the remodelling of aneurysmal wall, and eventually lead to IAs rupture [76]. Depletion of gastrointestinal microbiota in a mouse model reduced IAs formation by suppressing macrophage infiltration, mRNA levels of IL-1β, IL-6, and iNOS in the arterial wall but leaving TNF unaffected [77].

## 6. Administration of aspirin for intracranial aneurysms

Aspirin, as a nonsteroidal anti-inflammatory agent, is endowed with significant antipyretic, analgesic, and antiplatelet properties. It can irreversibly inhibit COX-1 and COX-2, which catalyzes arachidonic acid (AA) into prostaglandin $H_2$ ($PGH_2$) and is then converted into thromboxane $A_2$ ($TXA_2$) in activated platelets by thromboxane synthase [78]. Emerging evidence suggests promising benefits of aspirin for treating IAs, including a reduced rupture incidence, shorter hospital stay, and lower rate of nonroutine discharge [79].

### 6.1. Pre-clinal trials

Aspirin's anti-inflammatory effects and their mechanism have been investigated in numerous animal aneurysm models [80–84] (Table 1).

It is widely accepted that low doses of aspirin can inhibit COX-1 in platelets and block TXA2 formation, whereas high doses of aspirin can suppress COX-2 expression associated with inflammation and pain [85]. Smyth et al. [86], for example, found that in inflammatory diseases, such as abdominal aortic aneurysm and atherosclerosis, COX-1 possibly mediated the initial stage of an acute inflammatory responses, while COX-2 upregulation occurring within several hours. Moreover, Chalouhi and Starke et al. [78,87] found that the use of COX-1 inhibitors (SC560) or genetic COX-1 knockout in mice didn't affect the incidence of UIAs formation or rupture, whereas the incidence of rupture decreased with the use of selective COX-2 inhibitors (Celebrex) or genetic COX-2 knockout in mice. The expression of COX-2 and downstream enzymes like mPGES-1 was found to be higher in the walls of ruptured IAs than in those of UIAs [88,89]. Separately, aspirin has been shown to decrease the expression of these enzymes in a rat IAs model [90]. Surprisingly, Peña et al. [91] found that vascular mPGES-1 plays a protective role in blood vessels and attenuates rupture of IAs. In contrast to effects on abdominal aneurysms, mPGES-1 deficiency is associated with an increased IAs rupture morbidity and mortality in a mouse model, which, however, can be alleviated by low-dose aspirin.

Furthermore, based on a rabbit bifurcation aneurysm model, Wanderer et al. [83] found that daily intake of aspirin for 28 days mitigated inflammation in both the periadventitial tissues and aneurysm walls but failed to affect neutrophil infiltration. However, the markers they employed to quantify inflammation lacked specificity and the aspirin dosage was not clearly given in their study [83]. In a rat IAs model, aspirin exhibited an extraordinary effect on the attenuation of IEL degradation, medial layer thinning, and macrophage infiltration with reduced IAs size and lowered MMP-2/9, NF-κB, MCP-1, and VCAM-1 expression in the aneurysmal walls [81].

In addition, pathophysiologically, aspirin exhibits anti-inflammatory properties in various stages in IAs, including the inhibition of MMP-2/9 and TNF expression in VSMCs and reduced inflammatory cell adhesion in ECs by reducing NF-κB activity [92]. To sum up,

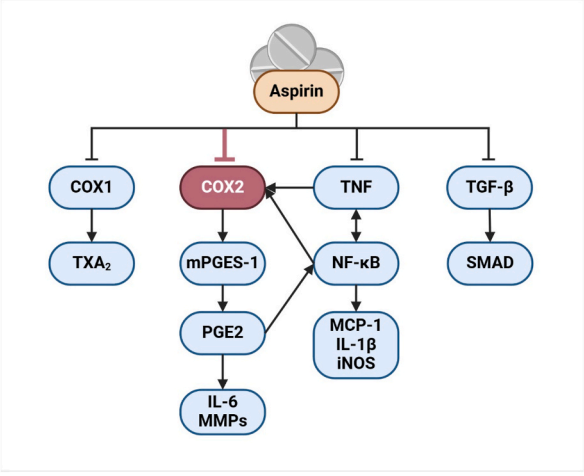


**Fig. 2. Mechanism of aspirin-medication treating intracranial aneurysms.** Aspirin exerts anti-inflammatory effects not only through the COX-dependent pathways, but also attenuate inflammation through TNF and TGF- β signal pathways. COX1, cyclooxygenase 1; COX2, cyclooxygenase 2; IL-6, interleukin-6; IL-1β, interleukin-1β; mPGES-1, microsomal prostaglandin E2 synthase-1; MMPs, matrix metalloproteinase; MCP-1, monocyte chemotactic protein-1; NF-κB, nuclear factor-kappa B; PGE2, prostaglandin E2; SMAD, small mother against decapentaplegic; TNF, tumor necrosis factor; TGF-β, transforming growth factor-β; TXA2, thromboxane A2; iNOS, inducible nitric oxide synthase.

these studies suggest that aspirin may play a role in hindering the pathological progression and rupture of IAs via anti-inflammatory mechanisms (Fig. 2).

### 6.2. Clinical evidences

Multiple clinical trials have confirmed that aspirin can inhibit IAs progression and rupture [79,93–102] (Table 2). Jabbarli et al. [102], for example, matched IAs cohort with a healthy population (1:1) and found that the administration of aspirin was associated with a lower risk of IAs formation [0.23, 95% CI (0.13–0.43)] and rupture [0.55, 95% CI (0.41–0.75)]. According to a retrospective evaluation of 271 cases (58 ruptured and 213 unruptured) from the International Study of Unruptured Intracranial Aneurysms (ISUIA), patients taking aspirin at least three times a week had fewer incidents of IAs rupture during a 5-year follow-up period [93]. In a prospective cohort study involving 315 patients with UIAs (<7 mm) and concurrent cerebral ischemia, aspirin users experienced a lower risk of aneurysms growth during the first 5-year follow-up period [94]. The same research group pointed out that aspirin users exhibited a low incidence of IAs rupture in a subsequent multicenter study that enrolled 1866 IAs patients [95]. A similar result was obtained through a multivariate analysis involving a large cohort of 1729 ruptured IAs and 605 UIAs patients, indicating an inversed association between aspirin use and aSAH [96].

Moreover, it is noteworthy that the protective effects of aspirin on IAs are dependent on the dose, frequency, and duration of the regimen [103]. By reviewing the data of 271 patients with UIAs from ISUIA, Hasan et al. [93] found that patients who used aspirin three times weekly had a lower risk of hemorrhage compared to those who took aspirin less than twice weekly. The common

**Table 2**
Summary of clinical studies assessing the impact of aspirin on IA.

| Authors | Year | Study design | Number of cases | Dosage | Frequency of use | Primary endpoint | Statistical results |
|---|---|---|---|---|---|---|---|
| Hasan et al. [93] | 2011 | Case-control | 271 | 325mg/time | ≥3 times/ week | Aneurysm rupture | OR: 0.27<br>95% CI: 0.11–0.67<br>$P = 0.03$ |
| Hasan et al. [101] | 2013 | Prospective | 11 | 81 mg/day | 3 months | MRI signal changes in iron oxide nanoparticles, macrophage numbers, COX-2, mPGC-1 expression changes | $P < 0.05$ |
| García-Rodríguez et al. [97] | 2013 | Case-control | 1340 | – | >3 years | Aneurysm rupture | OR: O.63<br>95% CI: 0.45–0.90<br>$P < 0.05$ |
| | | | | 75 mg/day | – | aSAH incidence | OR: O.81<br>95% CI: 0.64–1.00 |
| | | | | 150 mg/day | – | aSAH incidence | OR: O.97<br>95% CI: 0.56–1.68 |
| | | | | 300 mg/day | – | aSAH incidence | OR: O.55<br>95% CI: 0.16–1.87 |
| Gross et al. [98] | 2014 | Retrospective | 747 | 81 or 305 mg/ day | – | Aneurysm rupture | Control group: aspirin group = 40%: 28%<br>$P = 0.016$ |
| Serrone et al. [99] | 2016 | Retrospective | 192 | – | – | Increased growth/number of aneurysms | OR: 0.72<br>95% CI: 0.29–1.81<br>$P = 0.17$ |
| Hostettler et al. [96] | 2017 | Prospective | 2334 | – | – | Aneurysm rupture | OR: O.28<br>95% CI: 0.20–0.40 |
| Can et al. [79] | 2018 | Case-control | 4701 | 81 mg/day (n = 310)<br>162 mg/day (n = 7)<br>325 mg/day (n = 117)<br>Indeterminate (n = 83) | – | Aneurysm rupture | 81 mg: 162 mg: 325 mg = 21.4%: 14.3%: 9.4%<br>OR: 0.60<br>95% CI: 0.45–0.80<br>$P < 0.01$ |
| Zanaty et al. [100] | 2019 | Retrospective | 146 | ≥81 mg/day | – | Aneurysm rupture | OR: 0.19<br>95% CI: 0.05–0.63<br>$P = 0.007$ |
| Weng et al. [94] | 2020 | Prospective | 315 | 325 or 70–100mg/dose | ≥3 times/ week | Aneurysm growth | HR: 0.29<br>95% CI: 0.11–0.77<br>$P = 0.013$ |
| Weng et al. [95] | 2021 | Prospective | 1866 | 325 or 70–100mg/dose | ≥3 times/ week | Aneurysm rupture | HR: 0.11<br>95% CI: 0.01–0.86<br>$P = 0.035$ |
| Jabbarli et al. [102] | 2023 | Retrospective | 1960 | – | – | Aneurysm rupture | OR: 0.23<br>95% CI: 0.13–0.43<br>$P = 0.03$ |

therapeutic and prophylactic aspirin doses include the standard-dose (325 mg) and low-dose (75–100 mg), but there is a lack of medical evidence to support the difference between them. According to a recent study, the hemorrhagic incidence of the patients taking aspirin 81 mg/day was significantly lower than that of the patients taking aspirin 325 mg/day (28%: 40%, $P = 0.016$) [98]. In another retrospective case-control study involving 146 patients with 375 UIAs, patients taking aspirin >81 mg/day had a lower incidence of SAH than those taking other antiplatelet or anticoagulant drugs in a 5-year followed-up period [100]. Furthermore, aspirin had more benefits in the treatment of IAs when used in combination with other selective COX-2 inhibitors such as Celecoxib, as shown by less production of TXA2, reduced platelet aggregation, and lower incidence of adverse reactions including gastrointestinal discomfort [104].

The effects of aspirin also vary between males and females. According to another analysis of ISUIA data, aspirin decreased the risk of IAs rupture more significantly in men than in women [87]. Several studies have been performed to elucidate the possible causes of this. In a study of 20 female and 18 male IAs patients, higher 15-hydroxyprostaglandin dehydrogenase (15-PGDH) level was observed in the plasma of men than in that of women, which is recognized to be a key enzyme responsible for the inactivation of prostaglandins, which may explain why aspirin confers better protective effects in suppressing the inflammatory response in men [105].

Nevertheless, aspirin medication failed to show a protective effect on the prevention of de novo IAs formation in a cohort of 1419 IAs patients regardless of the frequency of aspirin use [106]. Several risk factors for UIAs growth or de novo aneurysm formation were assessed in 192 patients with 234 UIAs, Results of the study indicate that aspirin medication was not associated with UIAs growth [99]. A separate retrospective cohort study in Spain suggested that aspirin medication alone did not serve independently as a protective factor against UIAs, while a combined therapy of aspirin and statins proved to be protective against IAs [10]. In a large case-control study involving 6411 unruptured and ruptured saccular IAs, aspirin medication significantly decreased the risk of aneurysmal hemorrhage in a dose-dependent manner but increased the risk of re-rupture of untreated ruptured IAs [79]. Possibly, this is attributed to the fact that, in the early stages of IAs rupture, aspirin's inhibition of platelet aggregation impeded the repair of the aneurysm wall breach.

Therefore, although aspirin exhibits substantial protective effects against UIAs, further research is warranted to develop guidelines for its clinical application.

Owing to the lack of quantification of inflammation in IAs, the impact of aspirin on inflammation in patients is yet to be fully understood. Fe-MRI and gadolinium-enhanced high-resolution vessel wall imaging (HR-VWI) have enabled researchers to examine and observe vascular inflammation in vivo. Ferumoxytol, as an iron oxide nanoparticle coated by a carbohydrate shell, is primarily phagocytized by reticuloendothelial system macrophages, offering prolonged intravascular imaging and serving as an inflammatory marker [88].

In a small trial of 6 UIAs patients, a daily intake of aspirin (81 mg/day) for 3 months suppressed inflammation in the vessel walls in the patients, as evidenced by both immunostaining and Fe-MRI results, which demonstrated decreased COX-2 and mPGES-1 staining and MRI signal intensity, and less macrophage infiltration than patients not taking aspirin [101]. Another study on 74 patients with HR-VWI indicated that a daily intake of aspirin (≥81 mg/day) for >6 months ameliorated aneurysms inflammation [103]. These research findings offer corroborative indirect evidence of aspirin's anti-inflammatory impact on the UIAs walls.

## 7. Conclusion

Systemic and local inflammation observed in the pathological development of IAs is a complex interplay between the nervous and immune systems, ultimately leading to the degeneration of arterial wall structures.

While surgical clamping and endovascular coiling are established as promising and effective strategies for mitigating complications associated with IAs, the quest for an optimal management strategy for UIAs continues. Notwithstanding that previous studies have elucidated the benefits of aspirin for mitigating IAs progression and rupture, further in-depth research is warranted to obtain a comprehensive understanding of the specific mechanisms underlying inflammation in IAs. This should include exploring effective clinical strategies to manage the inflammatory response, particularly focusing on how aspirin influences key inflammatory pathways and cellular mechanisms involved in the progression and rupture of aneurysms.

## Data availability statement

No data was used for the research described in the article.

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## Ethics declarations

Review and/or approval by an ethics committee was not needed for this review.

## CRediT authorship contribution statement

**Yuan Feng:** Writing – original draft, Investigation. **Hongchen Zhang:** Visualization, Formal analysis. **Shuhui Dai:** Writing – review & editing. **Xia Li:** Writing – review & editing, Supervision, Funding acquisition.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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