


# Recurrence of endovascularly and microsurgically treated intracranial aneurysms—review of the putative role of aneurysm wall biology

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**Abstract** Although endovascular therapy has been proven safe and has become in many centers the primary method of treatment for intracranial aneurysms, the long-term durability of endovascular embolization remains a concern; at least for some aneurysms despite initial good result. While healing after clipping relies on mechanical occlusion, restoration after endovascular occlusion mainly requires the induction of a biological response. Healing after embolization depends on the growth of new tissue over the thrombus formed by the embolization material, or alternatively, on the organization of thrombus into fibrous tissue. This review highlights the fundamental importance of aneurysm wall biology on the healing process and long-term occlusion after intracranial aneurysm (IA) treatment. It seems likely that the effect of luminal thrombus on the IA wall, as well as the IA wall condition at the time of thrombosis, determine if thrombus organizes into scar tissue (neointima formation by infiltration of cells originating from the IA wall) or if the wall undergoes continuous remodeling, which is primarily destructive (loss of mural cells). In the latter, intraluminal thrombus organization fails and the impaired healing increases the chance of recurrence.

Mechanisms underlying IA reopening, the influence of intraluminal thrombosis on the IA wall, and clinical implications of the IA wall condition are discussed in detail, along with how knowledge of IA wall biology can offer new solutions for IA treatment and affect the patient selection for and follow-up after endovascular treatment.

**Keywords** Intracranial aneurysm · Clipping · Coiling · Aneurysm wall biology · Thrombosis · Recurrence

## Introduction

Intracranial aneurysms (IA) must be isolated from the cerebral circulation to prevent rupture and subsequent devastating intracranial hemorrhage. This was originally performed by ligating the artery at the site where the aneurysm originated. With the development of microneurosurgical techniques, occlusion of the aneurysm neck with a microsurgical clip (clipping) became the golden standard for treatment. Later, due to safe catheterization techniques for cerebral vessels and surgical angiography, endovascular embolization with thrombogenic coils (coiling) evolved and eliminated the need for craniotomy and related manipulation of the brain itself. One-year results of the largest randomized controlled trial comparing clipping and coiling found less dependency or death for patients with ruptured small anterior circulation IA of good neurological grade [61]. Despite its criticism, the results of the study led to increased use of endovascular therapy and eventually surpassed clipping as the most popular therapeutic approach for IAs. Although endovascular therapy has been proven safe and effective, recurrence may occur even after perfect packing of the aneurysm with coils (Table 1). The variation in healing and long-term outcomes of embolized aneurysms may be explained by aneurysm wall biology,

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**Table 1** Recurrence in relation to IA rupture status

Authors (year)	Follow-up (months)	UIA <i>n/n</i> (% of recurrence)	Ruptured IA <i>n/n</i> (% of recurrence)
Cognard et al. [13] (1999)	3–48	4/54 (7)	16/94 (17)
Raymond et al. [74] (2003)	12 (mean)	52/190 (27)	76/191 (40)
Nguyen et al. [67] (2007)	20 (mean)	16/72 (22)	23/44 (52)
Tan et al. [91] (2011)	20–25 (mean)	10/49 (20)	19/47 (40)
Vanzin et al. [97] (2012)	21 (mean)	42/194 (22)	80/261 (31)
Abdihalim et al. [1] (2014)	9 (mean)	5/92 (5)	24/120 (20)

After EVT using mainly standard coils

which is fundamental to the healing of embolized aneurysms and long-term success of endovascular therapy. Regarding the term endovascular treatment (EVT), this review is mainly focused on standard coil embolization. Since, histological data of the healing response induced by more recent embolization devices is relatively scarce. The available published data, nevertheless, demonstrates a similar healing response after novel intrasaccular thrombogenic flow disruptive devices as after standard coil embolization [19, 52, 58, 60]. Moreover, clinical series demonstrate similar neck remnant and recanalization problems after application of intrasaccular flow disruptive devices, as after standard coil embolization [5, 74, 73, 88].

#### Initial occlusion does not guarantee long-term healing—a problem of embolized aneurysms

The long-term success of any current therapy used to prevent IA rupture is dependent on permanent occlusion of the IA from the circulation. Embolized IA recur relatively frequently despite good initial treatment results (Tables 1 and 2; Supplementary Table 1). Many factors affect the risk of IA recurrence after embolization [13, 65, 72, 78], and the natural

history of IA recurrence after embolization is poorly known. However, it is clear that IA recurrence after embolization is associated with a risk of rupture (although very low) and necessitates a higher rate of retreatment [9, 48, 63, 71]—or at the minimum, additional follow-up that is prone to cause anxiety in the patient [24].

Angiographic occlusion after EVT or after clipping is not to be equated with biological healing [3, 50, 76, 80, 92, 93]. In a long-term digital subtraction angiography study after coiling, over 40% of patients with adequate IA occlusion at short-term follow-up (< 36 months) demonstrated IA recurrence and 26% of these patients required retreatment [10]. Recurrence and retreatment rates are even higher for patients with known recurrence at short-term follow-up, 67 and 49%, respectively [10].

Animal studies revealed significant discrepancy between angiographic and histological findings resulting in overrated radiologic occlusion after coil embolization [50, 80, 89]. Human histopathological studies confirmed these results and demonstrated that half of IA deemed completely occluded on angiography show tiny open spaces between the coils at the neck [3]. When reviewing all published literature on human

**Table 2** Recurrence in relation to IA size

Authors (year)	Follow-up (months)	Small IA < 10 mm <i>n/n</i> (% of recurrence)	Large IA > 10 to ≤ 25 mm <i>n/n</i> (% of recurrence)	Giant IA > 25 mm <i>n/n</i> (% of recurrence)
Byrne et al. [7] (1999)	6–12	24/176 (14)	12/81 (15)	2/2 (100)
Tateshima et al. [92] (2000)	19 (mean)	2/24 (8)	4/10 (40)	4/8 (50)
Raymond et al. [74] (2003)	12 (mean)	47/221 (21)	81/160 (51)	–
Murayama et al. [62] (2003)	6–12	66/579 (11)	70/198 (35)	43/73 (59)
Standhardt et al. [86] (2008) <sup>a</sup>	35 (mean)	22/163 (14)	5/20 (25)	9/19 (45)
Plowman et al. [70] (2011)	6	88/345 (26)	27/97 (28)	4/10 (40)
Gao et al. [32] (2012) <sup>b</sup>	38 (mean)	–	6/53 (11)	10/28 (36)
Dorfer et al. [19] (2012)	6–18	61/403 (15)	66/173 (38)	–
Chalouhi et al. [11] (2014) <sup>c</sup>	6–60	62/177 (35)	29/62 (47)	11/21 (52)

After EVT using mainly standard coils

<sup>a</sup> Small (< 12 mm) and large (13–24 mm) angiographic FU were available for 76% of all aneurysms

<sup>b</sup> Large (15–25 mm)

<sup>c</sup> Small (10–14 mm) and large (15–24 mm)

histopathology after EVT, it can be concluded that transformation of intraluminal thrombosis into scar formation and re-endothelialization of the luminal surface after EVT seems to be the exception rather than the rule (Supplementary Table 2).

### Recurrence after clipping—are problems with long-term durability also associated with clipping?

In general, the reopening rate is lower in clipped than in coiled IA [63, 90]. The largest study to date with the longest follow-up data (mean,  $7.2 \pm 4.7$  years) found that the risk of recurrence after clip ligation is 0.14% (1/699) and 13.6% (8/59) in IA without residual and with residual neck on postoperative imaging [6]. Previous series on long-term angiographic follow-up (mean,  $4.4 \pm 1.6$  years) found comparable increase of IA recurrence with increase of residual aneurysm, 1.5% (2/135), 25% (2/8), and 75% (3/4) in completely clipped IA, known dog-ear, and broad-based remnant, respectively [16]. When a significant portion of the aneurysm wall is incorporated into the reconstructed vessel segment, the chance of delayed recurrence is as high as 30% [102]. Drake and Vanderlinden reported 0% (0/45), 17% (2/12), and 23% (3/13) late rebleeding after surgical IA treatment with complete obliteration, small remnant, or large remnant on postoperative angiography [21].

Histological analysis of clipped human IA demonstrated that complete re-endothelialization and neointima formation across the aneurysm neck occurred only in those IA with 100% exclusion of the diseased vessel wall (Supplementary Table 2) [46]. This data demonstrates that IA clipping shares many of the challenges of IA coiling. If microsurgical clipping fails to realign normal arterial tissue, recurrence rate is similar that found after endovascular coiling.

### Clipping vs. coiling—mechanical vs. biological healing

There is a fundamental difference in the way clipping and coiling prevent IA rupture. Aneurysm clips exclude the

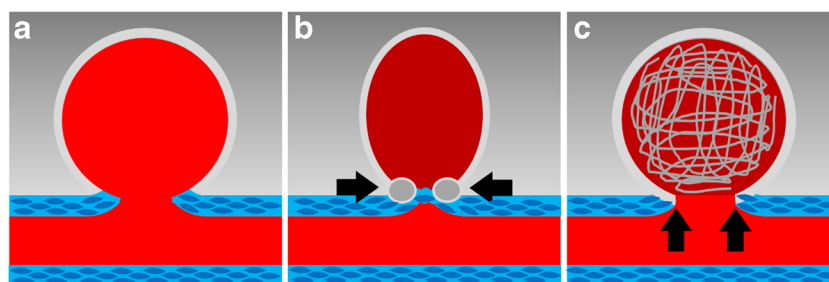
diseased vessel segment, close the aneurysm neck and realign healthy arterial walls (Fig. 1). When successful, the clip blades pull the opposing healthy vessel walls towards each other (if the parent artery segment is not diseased), immediately reconstituting the affected vessel segment. Conventional histological and electron microscopy results after experimental clipping show a completely reconstructed normal vessel wall, with endothelialization across the aneurysm neck directly below the clip blades [50]. However, in clipped human IA, the effectiveness of treatment is mainly related to the mechanics of vessel reconstruction rather than the slow biological healing process (endothelialization and neointima formation) [46].

In embolization, the aneurysm sac is filled with material that will induce thrombosis but – at least initially – keeps the aneurysm neck open, separates adjacent healthy tissue and prevents realignment of the endothelium of the diseased arterial segment (Fig. 1). Healing after embolization requires the growth of new tissue over the thrombus, or the organization of the thrombus into fibrous tissue (Supplementary Table 2). In summary, healing after clipping relies on mechanical occlusion, whereas healing after coiling mainly requires the induction of a biological response.

### Mechanisms for recurrence of embolized aneurysms—a mechanical or biological problem?

The mechanisms underlying reopening are poorly understood. Most hypotheses are based on subjective interpretation of morphological IA changes. IA volume-oriented mechanisms include coil compaction, coil migration into intraluminal thrombus, and resorption of pre-existing intraluminal thrombus [8, 42, 50, 100].

Human histopathological studies after Guglielmi detachable coil (GDC) embolization revealed that the unorganized intraluminal thrombus organizes itself by creating granulation tissue; first at the aneurysm wall, followed by the expansion of the endothelial cell lining over the granulation tissue at the aneurysm neck [3]. Based upon these findings and the



**Fig. 1** Aneurysm healing after clipping vs. after coiling. **a** Schematic illustration of an IA with healthy parent arteries (*blue vessel wall*) and diseased bulging segment (*thinner gray aneurysm wall*). **b** Aneurysm clips exclude the diseased segment, close the aneurysm neck, realign healthy arterial walls (*black arrows*), and exclude the thrombosed IA lumen from the circulation. **c** In IA coiling, the healthy

transition zone at the neck is not realigned (*black arrows*). The coils hold the neck open, induce intraluminal thrombosis, and prevent exclusion of the diseased arterial segment until neointima forms over the aneurysm orifice or the thrombus organizes into fibrous tissue. In summary, healing after clipping requires mechanical occlusion while healing after coiling mainly depends on the induction of a biological response

confirmation of the healing processes in experimental settings, deficient fibrosis, insufficient neointima, and lack of endothelialization may tentatively be seen as mechanisms of IA recurrence [14, 15, 17, 50, 79].

Based on extensive experience with canine carotid bifurcation aneurysm models, Raymond et al. found that, following GDC occlusion, thrombus organization, endothelialization, and neointima formation take place at the same time as IA recurrence. They presented an alternative concept and proposed that connective tissue contraction leads to fibrosed cavity shrinkage [76]. This results in displacement towards the fundus, the opening of recurring space, progressive enlargement, and coil compaction. Cognard et al. [13] found regrowth after subtotal occlusion to be more frequent than true recurrences and emphasized that aneurysm growth might be an important factor for IA recurrence. They hypothesized that IA growth is related to coil compaction in that regrowth may produce changes in the coil mesh, or conversely, that round coil compaction could lead to recanalization of the neck and restart the IA growth process.

Rigorous three-dimensional image analysis of IA reopening revealed that not only coil compaction but also aneurysm growth is an important mechanism for recurrence of initially complete or near-complete obliteration [35]. Comparison of coil mass and the area surrounding aneurysm sacs in 29 patients with significant IA recurrence (24/29 patients with ruptured IA status) points to IA growth as the leading cause in more than half of the cases (62%; 18 patients) [1]. A study minimizing image analysis bias by using non-recurrence control subjects and automated image analysis protocols demonstrated that aneurysm sac growth is the predominant etiology of IA recurrence after coil embolization [39]. The fact that recurrence in patients with multiple aneurysm is higher than the subpopulation of patients with single IA supports the hypotheses that biological processes are responsible for IA recurrence after EVT using standard coils [101].

### **The fundamental difference between ruptured and unruptured IA**

Raymond et al. studied IA recurrence after embolization and was not able to explain the significant difference in recurrence between unruptured and ruptured IA based on factors such as aneurysm size, neck width, or quality of initial angiographic results [78]. They therefore assumed that biological differences must exist. The difference in recurrence rate after EVT between ruptured and unruptured IAs is a solid finding (Table 1) [1, 13, 70, 78, 95, 101]. Analysis of a matched (aneurysm location, diameter, and neck size) cohort demonstrated not only an overall higher risk of recanalization in ruptured IA but also shorter period and higher degrees of recanalization and a higher percentage of retreatment when compared with unruptured IA [95]. It is increasingly

recognized that the need of retreatment after GDC embolization are more common in ruptured than unruptured IA [20, 38, 64, 71, 72].

Ruptured and unruptured IAs most likely represent different biological entities. Human histopathological series clearly demonstrate underlying differences in aneurysm morphology between ruptured and unruptured IA. Ruptured aneurysms are associated with wall degeneration and some exhibit extremely thin thrombosis-lined hypo- to acellular walls, with degenerated extracellular matrix and loss of endothelial cells [29, 44]. We hypothesize that this type of IAs with loss of smooth muscle cells (SMC) are not only prone to growth and rupture [27] but also lack the capacity to organize thrombus, which could explain the significantly higher recurrence rate after embolization of ruptured IA.

### **Intraluminal thrombosis destabilizes the IA wall and influence healing**

Acute thrombus induction has been linked to mural destabilization not only in experimental aneurysms [4, 56, 57, 77] but also in clinical settings after endovascular therapy [23, 34, 51, 66]. Various degrees of inflammation may exist depending on both the volume of induced thrombus and the IA wall condition at the time of EVT (wall enhancement is less common in ruptured than unruptured IA) [23]. Aneurysm wall enhancement is found in 32–64% after EVT and may not be pathological per se but rather part of a normal healing response [23, 91]. Increased aneurysm size and the associated large thrombus volume after GDC embolization is an independent predictor of IA wall enhancement [23, 40, 91]. Aneurysm wall and perianeurysmal inflammation is frequently encountered in partially thrombosed aneurysms which provide further evidence that intraluminal thrombosis contributes significantly to IA wall inflammation [23, 49].

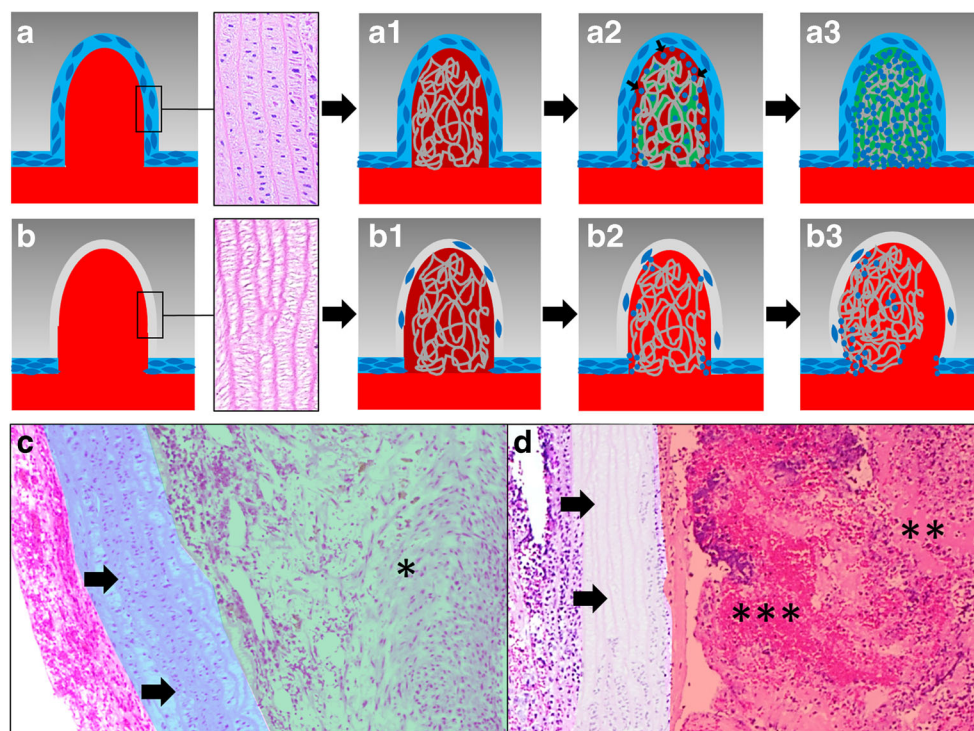
Approximately 70% of aneurysm volume is filled with thrombus following coil embolization [12, 83, 94]. Recanalization has been linked to a packing volume with higher recurrence rates in aneurysms in over 80% of intraluminal thrombus [41, 45, 53, 81, 86, 94, 97, 100]. Increasing packing volumes is more difficult to achieve in larger aneurysms. Packing density is inversely related to aneurysm volume with higher amounts of thrombus in larger aneurysms [47, 86, 98]. In experimental aneurysms, volume was negatively correlated with packing density, and histological healing was negatively correlated with aneurysm size [18]. Both thrombus organization and neointima formation were superior in aneurysms with less thrombus. Small aneurysm size was found to be associated with stable long-term results after coiling, irrespective of IA location [87]. Histologically, confirmed complete healing after coiling tends to be found only in small IA (Supplementary Table 2).

Coil packing density is particularly poor in large and giant aneurysms which leads to >95% of intraluminal thrombus and recurrence rates of >50% [7, 11, 25, 62, 85, 96, 99]. Overall, recurrence rates for small aneurysms (4–10 mm) are reported to be 5–20%, depending on neck size [65]. This increases to 35–50% in large (10–25 mm) and 60–90% in giant aneurysms (Table 2) [32, 33, 65, 78]. The presence of intraluminal thrombosis alone is a possible risk factor for a coiled IA reopening [25, 69, 71, 72, 96, 100, 102]. Large aneurysm size is not only a risk factor for IA recurrence but also raises the need for retreatment after EVT [9, 71, 72].

Overall, it seems likely that the effect of luminal thrombus on the IA wall as well as the IA wall condition at the time of thrombosis determine if thrombus organizes into scar tissue (neointima formation by infiltration of SMC or myofibroblasts) or if the wall will undergo continuous remodeling (driven by inflammatory processes which are primarily destructive). In the latter case, intraluminal thrombus organization fails and impaired healing makes the IA more susceptible to recurrence.

### Implications of wall pathology on aneurysm healing—an explanation for posttreatment recurrence?

In experimental models of saccular aneurysm, most thrombus organizing neointima cells are derived from the aneurysm wall—with a possible negligible contribution from circulating bone marrow cells [28, 37]. The finding that intraluminal unorganized thrombus is mainly organized by IA wall cells is in line with human histological studies after GDC embolization which found that granulation tissue response starts at the periphery of the luminal clot adjacent to the aneurysm wall (Supplementary Table 2) [2, 3, 62, 68, 84]. However, many processes of aneurysm healing are not well understood and remain controversial. Recent studies suggest that also bone marrow-derived endothelial progenitor and not only parent artery endothelial cells contribute to re-endothelialization at the aneurysm neck [54, 103]. Furthermore, in a murine elastase saccular model, monocyte chemotactic protein-1-coated coils were capable to recruit bone marrow-derived fibroblasts and macrophages via macrophage inflammatory protein-dependent pathways [36].



**Fig. 2** The natural course of aneurysm healing after coiling is not solely dictated by the angioarchitecture of the aneurysm; it is largely determined by the condition of the aneurysm wall. Schematic illustration comparing healing after coiling in IA with many functioning SMC (**a**, thick blue aneurysm wall) and IA with highly degenerated walls and loss of SMC (**b**, thin gray aneurysm wall). In healthy wall IA, coiling induces intraluminal thrombosis (**a1**, dark red areas), SMC undergo phenotypic modulation, migrate into the thrombus (**a2**, blue dots), and transform it into scar tissue (**a3**, green areas). EVT also induces intraluminal thrombosis in IAs with a degenerated wall (**b1**, dark red areas).

Missing mural cells, however, prevent thrombus organization and recanalization (**b2**, red areas) and may further damage the aneurysm wall which potentially cause progression of the disease (**b3**, enlargement and recurrence). **c** Histology of a healed rat sidewall aneurysm (green area with intraluminal connective tissue formation (asterisk)) with a vital wall full of SMCs (black arrows). **d** Unorganized thrombus (red area with fibrin mesh (double asterisks) and red blood cells (triple asterisks)) in an experimental aneurysm with missing mural cells (black arrows)

Many IA walls lack the SMCs that are meant to organize the thrombus induced by embolization and thus permanently heal the embolized aneurysm [27, 29, 44]. This loss of SMCs slows thrombus organization, causing the embolized IA to remain in an unstable state of continuous coagulation cascade—with subsequent activation of clot lysis pathways. This can eventually lead to clot lysis, recanalization, and IA recurrence. Moreover, experimental models have demonstrated that continuous exposure of the unorganized thrombus to the circulation can promote recruitment of neutrophils and inflammatory cells [55, 57], which increase proteolytic injury to the IA wall [30]. Unruptured IAs tend to have more viable SMCs in their walls, providing unruptured IAs increased opportunity to heal after embolization. This could explain why unruptured IAs have lower rebleeding rates [20, 75], necessitate less retreatment [20, 31, 38, 71, 72, 82], and are more stable after GCD embolization than ruptured IAs [1, 13, 26, 43, 70–72, 78, 95, 101].

We demonstrated in an experimental aneurysm model how the loss of SMCs from the aneurysm wall leads to growth and rupture, with concomitant wall inflammation and neutrophil recruitment [57], as well as how thrombus organization and prevention of aneurysm growth and rupture is significantly dependent on the presence of healthy SMCs in the aneurysm wall [55]. The contribution of bone marrow-derived cells to intra-aneurysmal tissue healing might vary in relation to the aneurysm wall condition (loss of mural cells).

The experimental data confirms the importance of aneurysm wall SMCs and—together with histopathological data from human IAs—strongly suggests that loss of this particular cell population could explain the failure of EVT in patients. IAs with a decellularized wall are less likely to heal properly after EVT as they lack the capacity for thrombus organization (Fig. 2).

### Why knowledge of aneurysm wall biology can offer new solutions

The biology of the aneurysm wall determines the risk of rupture as well as the biological potential for healing. Although risk factors influencing IA recurrence and the need for retreatment have been identified [71, 72], it remains difficult to determine which IA will reopen after EVT and which will not. A growing body of evidence emphasizes the paramount importance of the aneurysm wall condition in IA growth and recurrence after EVT.

IA walls can be imaged with modern MRI techniques already available for clinical use [22, 59, 67]. This enables us to study different aspects of their biology and condition in patients in a clinical setting. Gadolinium uptake on T1 was more frequently observed in unstable IA [22] and has been associated with major recurrence after embolization [23].

Other MRI techniques able to identify IA walls with mural SMC loss have considerable potential as diagnostic tools to help designate patients for endovascular or microsurgical intervention. In cases where endovascular intervention has been selected, they could help identify which embolized IAs are likely to recur and necessitate retreatment. The development of MRI or other imaging methods to identify decellularized IA walls with loss of SMCs is urgently needed.

### Compliance with ethical standards

**Ethical statement** We hereby confirm that no funds were received for this work. Ethical approval and informed consent are not applicable for this review.

**Conflict of interest** The authors declare that they have no conflict of interest.

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