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Editorial

'Mind the (Gender) Gap': Aspirin's paradoxical acceleration of aneurysm growth in women

Aortic aneurysms remain a significant health concern with complex pathophysiology and limited pharmacological management options. Despite advancements in surgical techniques, the search for effective medical therapies to slow aneurysm growth has been challenging. In this context, the use of antiplatelet agents—particularly aspirin—is intuitively preventive given the recognized association between aneurysm progression and the presence of a mural thrombus [1].

Despite intensive clinical investigation, evidence for a net benefit of preventive aspirin and the biologic interplay between platelets and aneurysm progression remain elusive. Using an innovative artificial intelligence-driven approach to extract aortic diameter measurements from electronic health records, Mohammadmoradi et al. in this issue of *Atherosclerosis* (link) provide intriguing insights into sex-specific responses to antiplatelet therapy, revealing findings that challenge conventional understanding about vascular disease treatment.

1. Sex differences in aneurysm biology

The most striking finding from Mohammadmoradi et al. [2] is the sex-specific response to aspirin preventive therapy. Their data reveal that female patients with small abdominal aortic aneurysms (AAAs <50 mm) experienced accelerated aneurysm growth when treated with aspirin, while males showed no significant effect. This observation adds to evidence that cardiovascular diseases and their treatments may manifest differently between sexes [3], yet therapeutic approaches rarely reflect these differences.

This sex-specific vulnerability concur with Kang et al.'s study [4] of spontaneous isolated abdominal aortic dissection, which was significantly associated with higher aorta-related mortality in female patients. Their comprehensive analysis revealed that while most patients could be managed conservatively, female patients required more proactive management due to worse outcomes. These findings parallel the observations from Mohammadmoradi et al., suggesting that female patients have different aortic wall biology and repair mechanisms that influence their response to both the disease process and treatment interventions.

2. Platelets: double agents in aneurysm pathophysiology

To understand this paradoxical effect, we must reconsider the dual role of platelets in aneurysm progression. Mohammadmoradi et al. [2] observe that platelet counts are significantly lower in patients with aortic aneurysms compared to controls—though not reaching thrombocytopenic levels—aligning with the factual association with mural thrombus layering. However, platelets are also key mediators of vascular wall integrity, with roles extending beyond hemostasis and thrombosis [5,6].

As first responders to vascular injury, platelets initiate the wound healing cascade. When activated, platelets release growth factors, chemokines, cytokines, and adhesion proteins that recruit inflammatory cells, stimulate fibroblast proliferation, and promote angiogenesis—essential components of effective tissue repair [7,8].

The work by Trachet et al. [9] in the angiotensin II-induced mouse model has demonstrated that aneurysm formation involves a complex process of microdissections and intramural hematomas rather than simple luminal dilatation. These microdissections create entry points for blood components into the vessel wall. Platelets functioning properly at these sites of injury guide physiologic healing; when this process is impaired, these microdissections become sites of chronic inflammation [10] and eventually expand, leading to progressive aortic dilatation and aneurysm formation.

The correct sequence of wound healing, with platelets initiating a cascade that must evolve toward resolution through macrophage phenotype switching, determines the fate of these microdissections. In this process, platelets not only form the initial hemostatic plug but also secrete factors that influence subsequent steps of arterial wound healing.

3. The female vessel wall: distinct biological characteristics

Several mechanisms may explain why women respond differently to antiplatelet therapy. Women's platelets demonstrate different activation profiles and responses to antiplatelet therapy compared to men's [11]. Friede et al. [12] documented that female platelets show different patterns of inhibition with aspirin therapy, a biological difference rarely considered in clinical dosing strategies.

Hormonal factors, particularly estrogen deficiency in postmenopausal women (who constitute the majority of female AAA patients), may influence vascular wall integrity and repair mechanisms. The differential expression of matrix metalloproteinases and inflammatory mediators between sexes could contribute to disparate responses to antiplatelet therapy [13]. The macrophage phenotype switching required for the healing of dissecting aneurysms [14] may be less efficient in women, potentially explaining their increased vulnerability when platelet function is compromised by aspirin.

Additionally, biomechanical forces exerted by past pregnancies could serve as a trigger for accelerated AAA progression in females. Pregnancy induces substantial cardiovascular adaptations, including increased blood volume and cardiac output that exert heightened mechanical forces on aortic walls [15]. These hemodynamic changes coincide with hormonal fluctuations that alter aortic architecture, as

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estrogen influences collagen and elastin metabolism in vascular tissues [16]. Histologic studies demonstrate that pregnancy leads to fragmentation of reticulum fibers and reduced mucopolysaccharide levels in the aortic extracellular matrix, creating lasting alterations in vascular strength [17].

Some of these cardiovascular changes, including increased aortic diameter, can persist beyond the postpartum period, suggesting that pregnancy's impact on vascular health extends far beyond gestation. The observation that women with larger abdominal aortic aneurysms tend to reach menopause earlier points to complex hormonal interactions in aneurysm development [18]. This constellation of pregnancy-related vascular changes may create a unique biological substrate in female patients that interacts differently with antiplatelet therapy, potentially explaining the sex-specific acceleration of aneurysmal disease with aspirin treatment.

4. Clinical implications

The sex-specific findings have immediate implications for clinical practice. Given that women with AAAs already face higher rupture risks at smaller diameters compared to men [19], the potential for aspirin to accelerate aneurysm growth in this population is concerning. In smaller aneurysms (<50 mm), where wall stress is lower and repair mechanisms might still be functional, impairing platelet function could tip the balance toward progression by compromising the healing of microdissections.

Clinicians should exercise caution when prescribing aspirin for primary prevention in female patients with small AAAs, carefully weighing the potential cardiovascular benefits against the possible risk of accelerated aneurysm progression. This is particularly relevant in postmenopausal women, where estrogen deficiency may already compromise vascular repair mechanisms.

The finding that aspirin may accelerate aneurysm growth in some patients corresponds with the concept that inhibiting platelet function in this complex inflammatory environment could further compromise healing of microdissections by interfering with the platelet-macrophage crosstalk needed for effective repair. This paradoxical effect—an allegedly protective therapy potentially causing harm—highlights the risks of applying non-sex-specific approaches to complex vascular pathologies.

5. Future directions

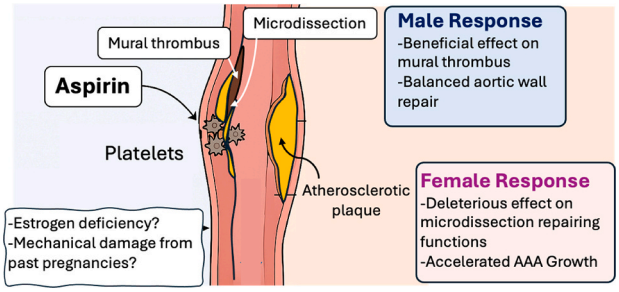
Several research priorities emerge from these findings. Large-scale prospective studies evaluating sex differences in response to antiplatelet therapy are urgently needed, particularly comparing pre-menopausal women, post-menopausal women with and without hormone replacement therapy, and men. This hormonal status stratification could reveal whether estrogen levels directly influence the paradoxical response to aspirin in female patients with AAAs. Investigation into molecular mechanisms underlying these differences may identify new therapeutic targets. Additionally, developing personalized risk assessment tools that incorporate sex, hormonal status, aneurysm size, and biomarkers of platelet activity and vascular repair capacity could help guide individualized treatment decisions. Alternative antithrombotic strategies might offer cardiovascular benefits without compromising critical platelet functions needed for aortic wall repair. The innovative AI-based methodology employed by Mohammadmoradi et al. [2] represents a promising approach for mining existing datasets to identify previously unrecognized sex-specific patterns in disease progression.

6. Conclusion

The study by Mohammadmoradi et al. [2] demonstrates that even well-established medications like aspirin may have context-dependent and sex-specific effects. Their findings highlight the need to consider sex differences in our approach to vascular disease management, recognizing that women's cardiovascular biology may differ fundamentally from the predominantly male-derived models upon which much of clinical practice is based.

As we continue to unravel the complex pathophysiology of aortic aneurysms, with better understanding of microdissections, intramural hematomas, and sex-specific inflammatory responses, this study serves as an important step toward more personalized management strategies. The paradoxical acceleration of aneurysm growth with aspirin therapy in women indicates that the traditional "one-size-fits-all" approach is not only inadequate but potentially harmful in this heterogeneous disease.

The time has come to develop truly sex-specific approaches to vascular disease management, moving beyond assumptions that therapeutic interventions will affect women and men identically. Only through deliberate attention to sex-specific biology can we hope to provide optimal care for all patients with aortic aneurysms.



Sex-Specific Responses to Aspirin Therapy in Progression of Small Aortic Aneurysms

Schematic illustration of the contrasting effects of aspirin therapy on small abdominal aortic aneurysms (<50 mm) between male and female patients. In males (upper right), aspirin shows no significant effect on aneurysm growth, likely due to a balanced relationship between its beneficial effects on mural thrombus reduction and preservation of repair mechanisms. In contrast, female patients (lower panel) experience accelerated AAA growth when treated with aspirin. This paradoxical response may be attributed to sex-specific deleterious effects of aspirin on platelet repair function, leading to impaired healing of microdissections and intramural hematomas. Potential contributing factors to this sex-specific vulnerability include estrogen deficiency in postmenopausal women and vascular remodeling in response to mechanical damage from past pregnancies, which may create lasting alterations in aortic wall architecture and repair capacity. These findings suggest caution when prescribing antiplatelet therapy to female patients with small AAAs, as traditional therapeutic paradigms may have unintended consequences depending on sex-specific vascular biology.

Declaration of competing interest

I, Giuseppina Caligiuri, declare that I have no conflicts of interest in connection with the editorial entitled "**"Mind the (Gender) Gap': Aspirin's Paradoxical Acceleration of Aneurysm Growth in Women**" submitted to Atherosclerosis.

I have no financial, personal, or professional relationships that could inappropriately influence or bias this work.

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