MAYO CLINIC

Making a Case for the Anti-inflammatory Effects of ACE Inhibitors and Angiotensin II Receptor Blockers: Evidence From Randomized Controlled Trials

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In this issue of *Mayo Clinic Proceedings*, Awad and colleagues[1] present a meta-analysis of randomized controlled trials evaluating the effects of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) as anti-inflammatory agents. Their findings support the beneficial role of ACEIs and ARBs in reducing blood levels of inflammatory markers but reveal potential differences in their anti-inflammatory effects. However, regardless of the class of medications used, the implications of the results merit the need to better understand the inflammation-alleviating effects of renin-angiotensin-aldosterone system (RAAS) inhibition. Moreover, the abundance of data supporting the benefit of RAAS blockade in reducing cardiovascular events and slowing the progression of proteinuric kidney disease independent of the antihypertensive effects suggests that the pleiotropic anti-inflammatory effects deserve more in-depth analysis.

In light of our current understanding of the effect of ACEIs and ARBs as potential anti-inflammatory agents, it is essential to highlight the role of angiotensin II (AngII) as an inflammatory and oxidative stress mediator. When the RAAS is activated, renin stimulates the release of angiotensin I, which is converted to AngII through the action of the angiotensin-converting enzyme secreted in endothelial cells. Data continue to accumulate on the role of local RAAS in vascular wall pathophysiology. Both local and circulating AngII exert their activities by binding to AngII type 1 (AT1) or type 2 (AT2) receptors. AT1 receptors are widely expressed in different cell types involved in atherosclerogenesis.[2] AT2 receptors are not abundant in healthy adults but are up-regulated in stressful conditions, such as myocardial infarction, heart failure, and vascular injury. When bound to the AT1 receptor on the vasculature, AngII initiates vasoconstriction and stimulates oxidative stress. In contrast, it elicits nitric oxide–mediated vasodilation, reduces platelet aggregation, and facilitates the action of insulin through binding to the endothelium-located AT2 receptors.[3] In addition, AngII is a mitogenic stimulus for vascular smooth muscle cells. By these myriad proinflammatory mechanisms, AngII causes a host of deleterious vascular effects, including endothelial damage associated with atherosclerosis. By targeting AngII, ACEIs and ARBs are believed to exert potent antiatherosclerotic effects, not only through their antihypertensive pathway but also through anti-inflammatory, antiproliferative, and antioxidant properties.[3]

Awad et al[1] provide an important contribution to the literature. Leveraging data from 32 randomized controlled trials, the authors conducted their meta-analysis by investigating the effects of RAAS blockade on blood levels of the primary inflammatory mediators C-reactive protein (CRP), interleukin 6, and tumor necrosis factor α. Although there was substantial heterogeneity of the included trials, several subgroups and drug class analyses were presented. Interestingly, there was no association between use of ARBs and reduction in levels of tumor necrosis factor α and CRP. Moreover, the insignificant impact of ARBs on CRP levels was retained irrespective of individual drug type, study duration, or primary disease. Surprisingly, the influence of

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RAAS blockade is different by ACEI and ARB therapy. The mechanistic pathways implicated in the different anti-inflammatory effects of ACEIs and ARBs led the authors to postulate that the effects of ACEIs and ARBs on bradykinin differ. Contrary to ARBs, ACEIs reduce bradykinin degradation, leading to increased nitric oxide levels and vasoactive prostaglandins.[4] Indeed, the bradykinin pathway deserves more in-depth study. Moreover, previously published studies suggested that because ARBs block AT1 receptors and not AT2 receptors, higher levels of AngII stimulate the already markedly up-regulated AT2 receptors and cause more vascular damage in atheromatous plaques.[5] One would also speculate that the differential anti-inflammatory effects of ACEIs and ARBs could be related to their different downstream ability to abrogate aldosterone secretion. Aldosterone is widely known to have a deleterious role in vascular injury, inflammation, and fibrosis.[6,7] It is plausible that ARBs are not as efficient as ACEIs in suppressing aldosterone. In other words, the higher levels of aldosterone suppression afforded by ACEIs over ARBs may hold the key to the apparently more potent effects of ACEIs on CRP reduction described in this study. As part of this meta-analysis, Awad et al[1] reported that the lowering effect of ACEIs on CRP levels was mainly manifested when they were used for less than 24 weeks. This study corroborates previous findings: ACEIs do not completely abrogate AngII production in the body. AngII synthesis can still occur through alternative ACE-independent tissue-based enzymatic pathways, such as chymase and other proteases.[8] These alternative pathways can become up-regulated on prolonged use of ACEIs, resulting in less efficacy over time.[8]

The paper by Awad et al[1] also builds on carefully selected randomized clinical trials that captured only placebo-controlled trials. Whereas placebo-controlled trials are the most rigorous method of assessing treatment efficacy, several aspects of this work deserve further discussion. First, there was a lack of homogeneity of the included randomized controlled trials regarding the measured inflammatory markers. The primary end point set by the authors was reduction of CRP plasma levels; however, not all the included randomized studies looked at measured CRP levels. Second, there is a vast difference in the duration of treatment with ACEIs or ARBs, which lasted from 4 weeks up to 24 months. Third, the lack of information about medication-specific dose effects remains an issue because the dose of the medications used could directly influence the studied outcomes (ie, circulating inflammatory marker levels herein). Finally, there is mounting evidence that certain ARBs might be superior clinically and pharmacologically to others in the same class.[9] The reason may lie in the degree of selectivity of different ARBs in binding to AT1 receptors and the degree of adrenal aldosterone suppression.

Taken together, the associations described in this study by Awad et al[1] provide added insights into the broad but differential anti-inflammatory effects of ACEIs and ARBs. How should we interpret the principal findings of this study on the difference in reduction of various inflammatory mediators between ACEIs and ARBs? In other words, are ACEIs better anti-inflammatory agents than ARBs? Does the reduction of blood levels of the anti-inflammatory markers by RAAS blockade translate into better cardiovascular outcomes? Although this meta-analysis corroborates the ACEI-ARB paradox of the presumed superiority of ACEIs over ARBs, the much-debated differences in outcomes between ACEIs and ARBs may have originated from a generational gap in clinical trials performed early on with ACEIs. ACEIs have been traditionally recommended as first-line therapy by most guidelines as the ACEIs trials were conducted a decade earlier than the ARBs trials. In a meta-analysis of 106 randomized trials of 254,301 patients without heart failure, Bangalore et al[10] reported that ARBs are as efficacious and as safe as ACEIs for all clinical outcomes. Moreover, sensitivity analysis restricted to trials published after 2000 (to control for the generational gap) revealed similar outcomes with ACEIs vs placebo and ARBs vs placebo. Recent studies found better cardiovascular outcomes with

ARBs over ACEIs. In clinical practice, the major impediments in choosing one of these agents over another are cost, adverse effects (ie, cough, angioedema with ACEIs), and clinicians' familiarity with various generic and brand-name medications. Although the study by Awad et al[1] categorized individual drugs, regardless of the possible mechanistic anti-inflammatory and clinical benefit of ACEIs over ARBs or vice versa, numerous trials have established the beneficial effects of both ACEIs and ARBs on cardiovascular and renal end points.[11-13]

In a broader sense, the results of Awad et al[1] emphasize the need to determine whether the direct reduction of blood levels of the inflammatory markers by RAAS blockade causes better long-term clinical cardiovascular outcomes. Moreover, the study can potentially extrapolate the role of RAAS inhibition not only in disease states but also in the primary and secondary prevention of diseases mediated by inflammatory processes. For example, RAAS inhibition may be used to prevent cardiovascular diseases in healthy middle-aged individuals, irrespective of the antihypertensive effects. Another promising use could be prevention of metabolic syndrome and insulin resistance in patients with obesity. Nevertheless, the take-home message from this paper is that within the limitations discussed, RAAS blockade is associated with lower levels of the main circulating inflammation markers. Furthermore, this study should serve as a stimulus for the design of larger randomized trials to study the effects of reduction of inflammatory markers by RAAS blockade, focusing more on clinically relevant outcomes.

POTENTIAL COMPETING INTERESTS

The author reports no competing interests.

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