Aliskiren Improves Nitric Oxide Bioavailability and Limits Atherosclerosis

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Inhibition of the renin-angiotensin system (RAS), with angiotensin-converting enzyme inhibitor- (ACEI) and angiotensin receptor blocker (ARB)—based treatment approaches, has emerged as the cornerstone of contemporary cardiovascular risk reduction. These therapies offer robust reductions in cardiovascular mortality in patients postmyocardial infarction, those with systolic heart failure, and in high-risk patients with atherosclerosis. Furthermore, interruption of the RAS system has emerged as a critical modulator of normal and aberrant renal physiology, and interruption of RAS signaling is linked to improved renal structure and function.

The RAS supports a series of complex enzymatic reactions that culminate in the generation of angiotensin (Ang) II, the main effector molecule. Despite the success with conventional strategies to limit Ang II production and/or action, these agents promote a reflex rise in plasma renin activity (PRA), which may serve to sustain ongoing RAS activation. Although the predictive value of PRA remains debatable, it does predict myocardial infarction in stroke survivors enrolled in the Perindopril Protection Against Recurrent Stroke Study (PROGRESS). As such, if PRA is predictive of risk in a population of patients with vascular disease, this may represent residual risk and serve as a novel target of therapy by agents that inhibit renin and neutralize the compensatory rise in PRA. Experimental and early clinical studies with aliskiren, the first commercially available direct renin inhibitor, suggest that it limits this negative feedback rise in PRA and Ang II that occurs during treatment with ACEI- or ARB-based therapies and, therefore, may allow for more complete blockade of the RAS. In addition to the presumed benefits of limiting PRA on Ang II bioactivity, renin inhibitors may limit the direct deleterious effects of renin to activate the (pro)renin receptor. It has been suggested that renin and prorenin may exert direct (receptor mediated, Ang II–independent) proinflammatory effects augmenting profibrotic pathways such as transforming growth factor-β1. Furthermore, prorenin activation of the pro(relin) receptor may promote cell surface Ang II production via nonproteolytic activation, which may contribute to local tissue damage. In addition, as reported by Nguyen et al., renin bound to the (pro)renin receptor gains markedly enhanced catalytic activity and in this fashion can dramatically magnify Ang II signaling.

The vascular benefits of conventional RAS blockers have been ascribed, in part, to their ability to improve endothelial function. ACEIs and ARBs have been shown to improve endothelial vasomotion in clinical and experimental studies and to limit endothelial cell activation in response to a variety of inflammatory stimuli. Although the benefits have been largely ascribed to a reduction in Ang II bioactivity, these therapies, through augmenting bradykinin and/or promoting Ang II type 2 signaling, have also been linked to improving NO release. Conventional blockers of RAS have been shown to limit atherosclerosis in various experimental models and in patients, and these effects may be pleiotropic in nature, related to improving endothelial and vascular smooth muscle homeostasis, and limiting endothelial-leukocyte interaction, as well as being attributable to reduced blood pressure.

An important question that remains unanswered is whether direct renin inhibition improves endothelial function and NO bioavailability. In addition to being the main determinant of basal vascular smooth muscle tone, NO acts to negate the actions of vasoconstrictors such as Ang II and endothelin-1. In addition, NO serves to inhibit platelet and leukocyte activation and to maintain the vascular smooth muscle in a nonproliferative state.

In the present issue of Hypertension, Imanishi et al. demonstrate, for the first time, that aliskiren augments both basal and acetylcholine-stimulated NO production in Watanabe heritable hyperlipidemic rabbits and improves endothelium-dependent vasorelaxation in thoracic aortic segments. Endothelial NO synthase (eNOS) bioavailability is regulated by 3 different mechanisms, including transcriptional upregulation of eNOS, posttranscriptional activation of eNOS, and reduction of reactive oxygen species–mediated breakdown of NO. In the present study, the authors propose that aliskiren improves NO bioactivity via 2 pathways. They suggest that aliskiren affects eNOS by increasing eNOS mRNA stability and posttranscriptional stimulation of eNOS mRNA. Because phosphorylation of Ser1177 within eNOS by Akt is critical for activation of eNOS, the authors investigated the effects of aliskiren in this regard. These studies provide supportive data to indicate that aliskiren activates protein kinase Akt, which leads to posttranscriptional activation of eNOS via phosphorylation. The authors suggest that aliskiren may restore eNOS uncoupling via...
augmenting tetrahydrobiopterin (BH4) levels, an essential cofactor for eNOS. This multidomain enzyme contains 2 functional regions: a flavin-containing reductase domain and a heme-containing oxygenase domain, which has binding sites for the triad of heme, L-arginine, and BH4. Between these 2 domains, there is a regulatory calmodulin-binding sequence. In the presence of calcium/calmodulin, an electron transfer from reduced nicotinamide-adenine dinucleotide phosphate to heme occurs, and with L-arginine present, electrons can flow to the heme moiety to reduce oxygen, which, in turn, is used to oxidize L-arginine to NO. BH4, functioning as both an allosteric and redox cofactor for eNOS, stabilizes eNOS and improves the binding affinity of L-arginine and the heme ligand for eNOS. Under physiological conditions, eNOS, in a homodimeric configuration, functions normally and become catalytically active in the presence of adequate amounts of BH4. Diminished levels of BH4 “uncouple” eNOS and prevent stable formation of its homodimeric configuration. This uncoupled enzyme now serves to produce poten free radicals, such as superoxide anions.

In addition, beyond its abilities as a cofactor, BH4 is also a potent reducing agent that rapidly reacts with superoxide. This reaction rapidly depletes intracellular levels of BH4 and further augments the uncoupling of eNOS. Superoxide anions are generated from the oxygenase domain of eNOS by the dissociation of the ferrous-dioxygen complex, in the absence of adequate amounts of BH4. In the present report, aliskiren exhibited a marked effect to augment vascular BH4 content in Watanabe heritable hyperlipidemic rabbits. Furthermore, the authors evaluated the state of eNOS uncoupling by treatment with L-NNA. Coincubation of thoracic aortic segments from aliskiren-treated rabbits with L-NNA resulted in a more, the authors evaluated the state of eNOS uncoupling by treatment with L-NNA. Coincubation of thoracic aortic segments from aliskiren-treated rabbits with L-NNA resulted in a reduced production of superoxide, suggesting that therapy attenuates eNOS uncoupling. In keeping with an effect to improve NO bioactivity and stabilize eNOS, aliskiren treatment reduced markers of inflammation and endothelial activation and attenuated the development of spontaneous atherosclerotic plaque formation in Watanabe heritable hyperlipidemic rabbits.

Although this is the first study to demonstrate an effect of aliskiren on improving eNOS bioactivity and basal NO release, previous studies have demonstrated an effect of aliskiren on limiting atherosclerosis. In a recent article, Nussberger et al demonstrated that aliskiren treatment reduced atherosclerosis volume and vulnerability in 2-kidney, 1-clip apolipoprotein E−/− mice, and this effect was at least partially independent of changes in blood pressure. Likewise, Lu et al demonstrated that aliskiren profoundly reduced atherosclerosis in the LDLr−/− mice fed a fat-enriched diet.

The reduction in atherosclerosis noted in the LDLr−/− mice with aliskiren appears to be quantitatively greater than that reported with Ang II type 1 receptor blockers or ACEIs in similar models, across different studies. However, the 2 studies wherein direct comparisons between aliskiren and ARBs on atherosclerosis have been made, including the article by Imanishi et al in this issue of Hypertension, do not suggest a superiority of renin inhibition over conventional blockade with ARBs on atherosclerosis volume, vulnerabil-

ity, or endothelial NO release. Some critics have suggested that, because renin inhibition prevents the formation of all of the angiotensin peptides (both beneficial and harmful), while also augmenting renin concentration (with the potential of untoward effects through the renin receptor), aliskiren would be inferior to ACEI or ARB with respect to atherosclerosis and endothelial dysfunction. The available data, however, indicate that, at least in animal models, aliskiren exhibits antiatherosclerotic effects. Importantly, it appears that renin deficiency in bone marrow–derived cells decreases atherosclerosis via the inhibition of monocyte adhesion to endothelial cells in the vascular wall, invoking a prominent role for macrophage-derived renin in atherosclerosis.

Another notable feature in the article by Imanishi et al relates to the benefits of combination therapy with aliskiren and valsartan. Combination therapy had an additive effect on endothelial function, BH4 content, NO release, and plaque volume. These data suggest that combination therapy of an ACEI/ARB with aliskiren may be a superior strategy with respect to vascular protection. It is our contention that, whereas aliskiren may be similar to conventional RAS blockers in monotherapy situations, it offers unique benefits in combination therapy that are superior to the addition of an ACEI to ARB or vice versa. Recent data suggest that the addition of an ARB to an ACEI does not promote an additional vascular benefit in patients with atherosclerosis.

We believe that the ability of aliskiren to neutralize the rise in PRA in ACEI- or ARB-treated patients translates into a reduction in Ang II production and action that exceeds what can be achieved by combination therapy with either agent alone. This may explain in part the hemodynamic superiority of combining valsartan and aliskiren in hypertension, the beyond blood pressure–mediated renal benefits noted in patients with diabetic nephropathy (Aliskiren in the Evaluation of Proteinuria in Diabetes [AVOID] Trial), and the profound reductions in brain natriuretic peptide noted in ACEI/ARB-treated patients with heart failure.

As we eagerly await the results of larger clinical trials with aliskiren in secondary prevention (ASPIRE-HIGHER Program), experimental data like those presented by Imanishi et al suggest that renin inhibition should also be evaluated in high-risk primary prevention cohorts to reduce atherosclerotic vascular events.

Disclosures

None.

References


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