Renin-angiotensin-aldosterone system inhibition: Can we do better? Focus on ARNI and angiotensinogen suppression

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Coexistence of hypertension, heart failure, diabetes mellitus and chronic kidney disease synergistically aggravates the risk of cardiovascular and renal morbidity and mortality. These high-risk, multi-morbid patient populations benefit less from currently available antihypertensive treatment. Simultaneous angiotensin II type 1 receptor blockade and neprilysin inhibition ('ARNI') with valsartan/sacubitril (LCZ696, Entresto) might potentiate the beneficial effects of renin-angiotensin-aldosterone system (RAAS) inhibition by reinforcing its endogenous counterbalance, the natriuretic peptide system. In animal models of hypertension, either alone or in combination with myocardial infarction or diabetes, ARNI consistently reduced heart weight and cardiac fibrosis in a blood pressure-independent manner. Moreover, LCZ696 treatment reduced proteinuria, focal segmental glomerulosclerosis and retinopathy, thus simultaneously demonstrating favourable effects on microvascular complications. These results were confirmed in patient populations.

An exciting novel approach to block the RAAS is angiotensinogen suppression by making use of angiotensinogen antisense oligonucleotide, targeted to the liver by covalent linkage of triantennary N-acetylgalactosamine. This approach has the advantage of requiring only a few injections per year, thus potentially annihilating the problem of non-adherence. Initial studies in animals support robust and durable blood pressure-lowering effects of angiotensinogen suppression, combined with renoprotection. How exactly this compares to other types of RAAS blockade (include the concomitant use of multiple RAAS blockers) still needs to be investigated.

This talk will critically discuss the latest developments regarding ARNI and angiotensinogen suppression, focusing on their potential application in hypertension, heart failure and chronic kidney disease.