Selective inhibition of the C-domain of angiotensin-converting enzyme (ACE) combined with inhibition of neprilysin

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Combined inhibition of NEP (neutral endopeptidase) and ACE (angiotensin-converting enzyme), without unwanted effects, remains an attractive therapeutic strategy in cardiovascular medicine. Omapatrilat, a dual NEP inhibitor–ACE inhibitor, was a promising antihypertensive drug but failed in trials due to angioedema, an effect possibly caused by inhibition of both the N- and C-domains of ACE. Here, we aimed to determine whether lisinopril-tryptophan (lis-Trp), a C-domain specific ACE inhibitor that preserves the N-domain catalytic activity, together with sacubitril (NEP inhibitor), differentially influences cardiovascular function and vascular permeability in hypertension compared with omapatrilat and lisinopril+sacubitril which inhibits both the ACE C- and N-domains. Ang II (angiotensin II)–dependent hypertensive mice (transgenic mice expressing active human renin in the liver [also known as LinA3]) received vehicle, sacubitril, lis-Trp, lisinopril, lisinopril+sacubitril, or l lis-Trp +sacubitril for 4 weeks. Systolic blood pressure was increased in LinA3 mice, along with cardiac hypertrophy/dysfunction, impaired endothelium- dependent vasorelaxation, hypercontractile responses, vascular remodeling, and renal inflammation. Lis-Trp +sacubitril, lisinopril+sacubitril, and omapatrilat reduced systolic bloodpressure and normalized cardiovascular remodeling and vascular hypercontractile responsesin LinA3 mice. Although lisinopril+sacubitril and omapatrilat improved Ach-induced vasorelaxation, lisW-S+sacubitril had no effect. Endothelial permeability was increased in omapatrilat but not in lis-Trp +sacubitril–treated mice. In conclusion, lisW-S combined with sacubitril reduced systolic blood pressure and improved cardiac dysfunction in LinA3 mice, similar to omapatrilat but without effects on endotheliumdependent vasorelaxation.
Moreover, increased vascular leakage (plasma extravasation) induced by omapatrilat was not evident in mice treated with lis-Trp +sacubitril. Targeting ACE C-domain and NEP as a combination therapy may be as effective as omapatrilat in lowering systolic blood pressure, but without inducing vascular permeability and endothelial injury.