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Sex-Specific Blood Pressure Responses to RAAS Inhibitors versus Non-RAAS Antihypertensives: A Systematic Review and Meta-Analysis

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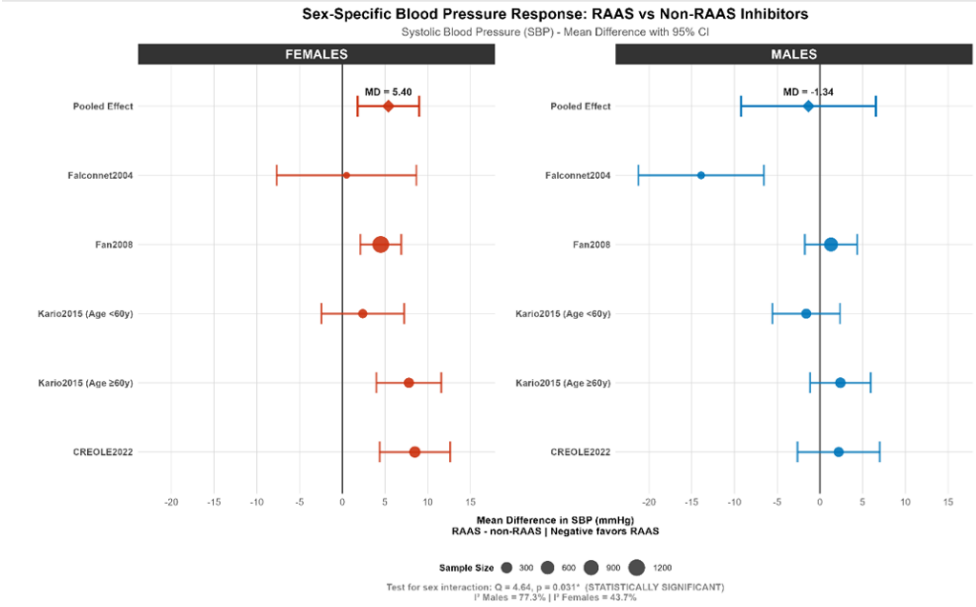
Objectives : Despite equivalent treatment intensity, women achieve poorer blood pressure control than men, contributing to persistent sex disparities in cardiovascular outcomes. The renin-angiotensin-aldosterone system exhibits pronounced sexual dimorphism, with estrogen suppressing renin activity and angiotensin II production while upregulating protective ACE2-Ang-(1-7)-MasR pathways. These biological differences suggest sex-specific antihypertensive responses may exist, particularly for RAAS-targeting therapies. This study aimed to investigate sex-specific differences in antihypertensive efficacy by comparing blood pressure responses to RAAS-targeting agents and non-RAAS therapies, and to explore the potential modifying effects of sex and menopausal status through meta-analytic interaction testing.
Methods : We systematically searched MEDLINE (PubMed), Scopus, and ScienceDirect through November 2025 for studies comparing blood pressure responses to RAAS inhibitors (ACE inhibitors/ARBs) versus non-RAAS antihypertensives (calcium channel blockers, diuretics) with sex-stratified data. The primary outcome was the change in systolic blood pressure. A random-effects meta-analysis with interaction testing was used to evaluate sex-specific treatment effects. Menopausal status stratification was performed where available.
Results : Four studies (5 comparisons, n=5,033 participants) met inclusion criteria. In females, RAAS inhibitors reduced systolic blood pressure 5.40 mmHg less than non-RAAS agents (MD 5.40, 95% CI 1.79-9.01, p=0.014), with significant sex × treatment interaction (p=0.031). Males showed no differential response (MD -1.34 mmHg, p=0.66). Sensitivity analysis restricted to monotherapy confirmed robustness (MD 4.68 mmHg, p=0.037). Age-stratified data from one study demonstrated larger effects in women ≥60 years (MD 7.8 mmHg). Subgroup analysis suggested greater female benefit from calcium channel blockers (MD 7.03 mmHg, p=0.08) versus diuretics.
Conclusions : RAAS inhibitors demonstrate inferior systolic blood pressure reduction in females compared with males. These findings suggest potential sex-specific differences in response to RAAS versus non-RAAS antihypertensives, with women showing numerically greater BP reductions with CCBs or diuretics. These hypothesis-generating results require validation in adequately powered prospective trials before informing guideline modifications.

Figure 4. Forest Plot. Sex-Specific Systolic Blood Pressure Response to RAAS vs Non-RAAS Inhibitors.png



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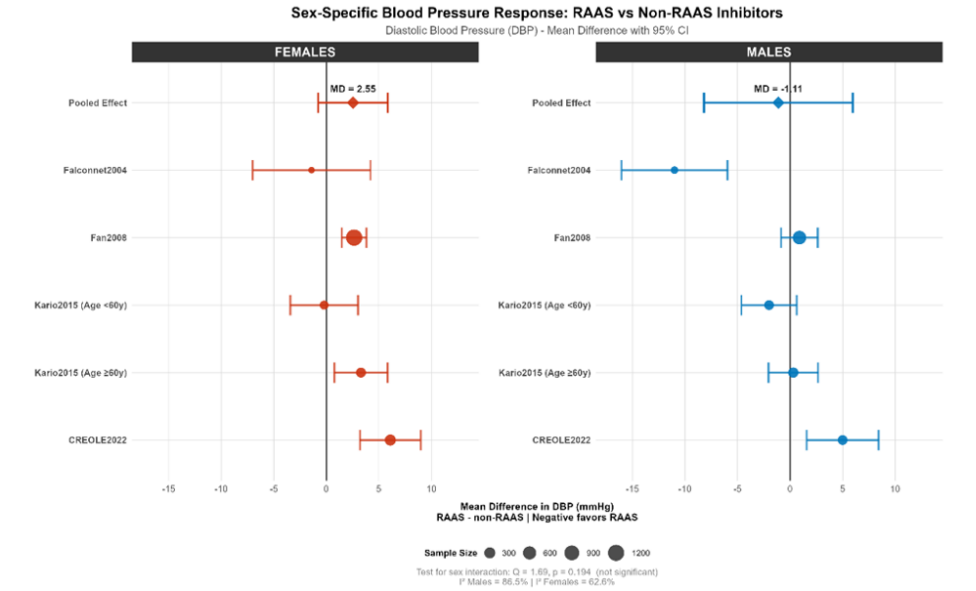

Figure 5. Forest Plot: Sex-Specific Diastolic Blood Pressure Response