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Pharmacotherapy of Endothelin Receptor Antagonists for patients with Chronic Kidney Disease: A Component Network Meta-analysis and Systemic Review

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Objectives : Endothelin receptor antagonists (ERA) along with dual endothelin and angiotensin receptor antagonist — sparsentan, are emerging medications. We performed a systematic review and component network meta-analysis (CNMA) to assess effects of newer drugs compared with current renoprotective medicines.

Methods : Eligible RCTs compared drugs of interest with RASi in CKD patients. Eligible trials had a follow-up of 52 weeks or longer. Certainty was assessed following the GRADE approach. The CNMA is a variant of the standard NMA that allows dissection of complex interventions and estimation of the interactive effects of each component within them. It is worth noting that we reported the effect estimates with 90% confidence interval (CI), as non-inferiority margin, on the outcomes of eGFR slope and ESRD.

Results : The analysis identified 10 eligible trials with 18368 patients, together evaluating four different drug classes. The interactive model of CNMA probed a significant interaction between SGLT2i and ERA that potentially compromise the sum efficiency of two drugs on reducing UACR at 3 month (Table.1). Although, the combination of SGLT2 inhibitors, ERA and RASi is identified as the most effective and followed by the other useful medications such as ERA+RAS, sparsentan and SGLT2i+RAS (Figure.2). ERA+RAS shows non-inferiority to RASi on eGFR slope and Sparsentan probably does (Figure.3). However, patients with ERA+RASi have a higher risk of hospitalization for heart failure compared to their counterparts with SGLT2i+RASi (Figure.4). The evidence is not robust, but there is a suggestion that Sparsentan may lead to an increase in adverse events compared to ARNI which provides significant benefits in reducing the risk of heart failure (Figure.5).

Conclusions : UACR showed a favorable outcome with Sparsentan and addition of ERA, and non-inferiority to RASi was seen with them on eGFR slope. However, adverse effects, especially heart failure events, and drug-to-drug interaction should be taken seriously.

Figure1.png

Table.1 Different NMA models for UACR at 3 month

NMA model	Heterogeneity	SMD (95%CI) of interaction between SGLT2i and ERA
Traditional NMA	Q = 224.01, df = 2	—
Additional CNMA	$\Delta Q = 101.52, \Delta df = 1$	—
Interactive CNMA	$\Delta Q = 0, \Delta df = 0$	1.08 (0.87; 1.29)

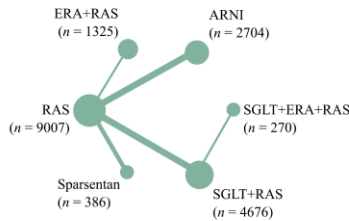


Figure 1: Network plot for UACR at 3 month

Interventions	UACR (SMD, 95%CI)
SGLT+ERA+RAS	-2.11 (-2.20, -2.01)
ERA+RAS	-1.44 (-1.52, -1.35)
SGLT+RAS	-0.67 (-0.71, -0.63)
Sparsentan	-0.75 (-0.95, -0.55)
ARNI	-0.17 (-0.37, 0.02)
RAS	Reference

High to moderate certainty evidence
Among the most effect
Among the intermediate effective
Not convincingly different from standard treatment
Among the intermediate harmful
Among the most harmful
Low to very low certainty evidence
Possibly among the most effective
Possibly among the intermediate effective
Possibly not convincingly different from standard treatment
Possibly among the intermediate harmful
Possibly among the most harmful

Figure 2: UACR impact of medications

Figure1.png

SGLT+RAS	0.07 (0.00, 0.15)	0.09 (-0.04, 0.21)	0.07 (-0.09, 0.24)	0.20 (0.16, 0.23)
0.82 (0.56, 1.09)	ERA+RAS	0.01 (-0.12, 0.15)	0.00 (-0.18, 0.17)	0.13 (0.06, 0.19)
1.08 (0.34, 1.81)	1.31 (0.34, 2.28)	Sparsentan	-0.02 (-0.22, 0.19)	0.11 (-0.00, 0.23)
1.14 (0.37, 1.91)	1.38 (0.37, 2.40)	1.06 (-0.01, 2.12)	ARNI	0.13 (-0.03, 0.29)
0.67 (0.57, 0.77)	0.82 (0.58, 1.05)	0.62 (0.21, 1.04)	0.59 (0.21, 0.98)	RAS

Figure 3: Network estimates for EGFR slope (SMD, 90%CI, upper right) and ESRD (OR, 90%CI, lower left)

SGLT+RAS	0.42 (0.25, 0.69)	0.74 (0.55, 1.00)	0.58 (0.46, 0.73)
0.94 (0.66, 1.35)	ERA+RAS	1.27 (0.78, 2.07)	1.39 (0.89, 2.18)
-	-	ARNI	0.78 (0.65, 0.95)
0.83 (0.72, 0.97)	0.88 (0.64, 1.22)	-	RAS

Figure 4: Network estimates for hospitalization of heart failure (OR, 95%CI, upper right) and major adverse cardiovascular events (OR, 95%CI, lower left)

- High certainty evidence
- Moderate certainty evidence
- Low certainty evidence
- Very low certainty evidence

SGLT+ERA+RAS	0.94 (0.81, 1.08)	1.16 (0.91, 1.49)	0.77 (0.48, 1.24)	1.48 (0.91, 2.40)	1.21 (0.77, 1.90)
ERA+RAS	1.24 (0.93, 1.66)	0.90 (0.53, 1.53)	1.14 (0.90, 1.45)	0.94 (0.81, 1.08)	
SGLT+RAS		0.96 (0.58, 1.60)	1.33 (0.94, 1.87)	1.09 (0.82, 1.45)	
		Sparsentan	1.42 (1.04, 1.93)	1.16 (0.91, 1.49)	
			ARNI	0.82 (0.68, 0.99)	
				RAS	

Figure 5: Network estimates for adverse events leading to discontinuation (OR, 95%CI)