Reno-Protective Effects of Angiotensin Receptor Blockers in Hypertensive Rodent Models: A systematic review

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Background

- Essential hypertension is a major risk factor for chronic kidney disease.
- There is no conclusive evidence that lowering blood pressure alone significantly improves renal function.
- Based on animal studies on hypertensive models, angiotensin-II receptor blockers (ARBs) are proposed to have a protective renal effect that is independent of blood pressure lowering.
- Clinical evidence of the reno-protective effect of ARBs in hypertensive patients is lacking.
- Some preclinical evidence exists. However, no structured assessment for the preclinical evidence has been done to serve as preclinical baseline hypothesis.

Study Objective

- The objective of this study was to structurally assess the evidence from preclinical rats models on the reno-protective effect of ARBs in hypertensive population to provide a high quality pre-clinical baseline for future investigations.

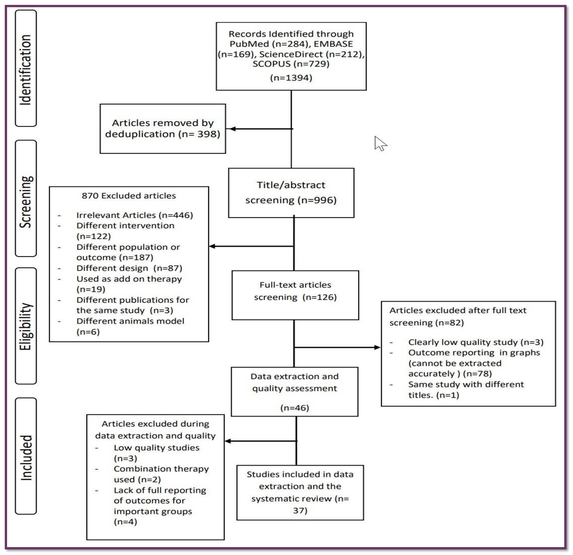

Figure 1. The flow chart for screening and inclusion

Table 1. Appreciations Used in Poster

Nx	Nephrectomised Rats	SHR-HS	Spontaneously Hypertensive Rats with High Salt Diet
ANG-II IH	Angiotensin II Induced Hypertension	RSCNC	Reduction is significant Compared to Normotensive Control
LH	Lewis Hypertensive Rats	RSCHC	Reduction in Significant Compared to Hypertensive Control
SIH	Salt Induced Hypertension	RSCOA	Reduction is Significant Compared to Other Antihypertensives
SHR	Spontaneously Hypertensive Rats		

Methods

- **Search Strategy:**
  - Systematic review following PRISMA checklist for quasi-experimental murine studies.
  - Four databases were searched including; PubMed, EMBASE, Scopus and ScienceDirect.
  - Keywords words include; hypertension AND (rats or mice) AND (renal or kidney) AND ARBs (with synonyms and names of single agents) and NOT patients
  - Search was limited to English articles published between 2000 and 2020.
- **Study Selection:**
  - Included articles were studies conducted on hypertensive rats, reporting means and standard error of mean (SEM), with moderate or high quality and reporting any of the predetermined outcomes.
  - Excluded articles were studies with low quality, studies with designs other than quasi-experimental designs or studies not following any point in the inclusion criteria
  - Deduplication was done in duplicate, screening was done as single screening then a sample of 100 articles were double screened to insure consistency
- **Quality Assessment**
  - The quality was assessed using Joanna Briggs Institute criteria for quasi-experimental studies.
  - Two reviewers (SA and MH) independently assessed the quality of the included studies, and the decision was made with an agreement between both reviewers.
- **Outcomes of interest**
  - The study investigated four main outcomes reported as means and SEM, including proteinuria and albuminuria as the primary outcomes and creatinine clearance, and/ BUN as the secondary outcomes.
- **Data Extraction**
  - Data extraction was performed by the two reviewers independently.
  - Extraction was mainly for hypertensive animal model, baseline characteristics, intervention and comparators, reduction in blood pressure (if reported) and exclusion of diabetic models.

Results

Figure 2. JBI quality assessment example

Table 2. Number of low, moderate and high-quality studies

High	Moderate	Low
11	26	3

Table 3. Overall number of studies showing significant positive results to total studies reporting the outcome

	Albuminuria	Proteinuria	CrCl	BUN
RSCNC	3 of 5 studies	6 of 7 studies	6 of 12	4 of 5
RSCHC	11 of 11 studies	12 of 14 studies	11 of 15	1 of 3

Irbesartan data summary (n=2)

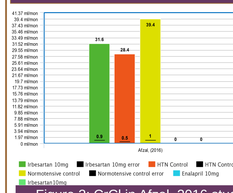

Figure 3: CrCl in Afzal, 2016 study

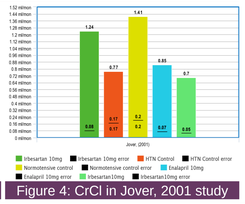

Figure 4: CrCl in Jover, 2001 study

Valsartan data summary (n=6)

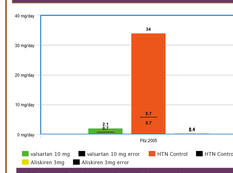

Figure 5: Albuminuria in Valsartan studies

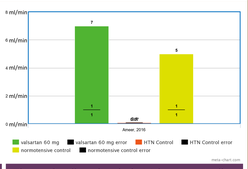

Figure 6: Albuminuria in Valsartan studies

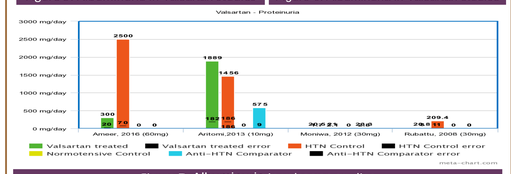

Figure 7: Albuminuria in valsartan studies

Losartan studies data summary (n=17)

Table 4. Qualitative summary of Proteinuria data from losartan studies

High Dose (>30mg)	Intermediate Dose Losartan (20mg)			Low dose losartan (10mg)													
Long Follow up (n=1)	Short follow up (n=2)			Long Follow up (n=1)			Short follow up (n=2)						Long Follow up (n=1)				
SHR-HS (n=1)	NX			SIH (180mg/L)			SHR			SHR			LH			NX	
De Cavanagh, 2010	Dumont, (2001)			Sorooshian, 2000			Tang, 2011			Jessup, (2006)			Bertra, (2002)			Čertíková, (2014)	
RSCNC	RSCHC	RSCOA	RSCNC	RSCHC	RSCOA	RSCNC	RSCHC	RSCOA	RSCNC	RSCHC	RSCOA	RSCNC	RSCHC	RSCOA	RSCNC	RSCHC	RSCOA	RSCNC	RSCHC	RSCOA
Yes	Yes	Yes (Atenolol)	Yes	Yes	NA	No	NA	No (enalapril 150mg/L)	No	Yes	NA	NA	No	No (lisinopril 10mg/kg	NA	Yes	No (Perindopril 0.4&3mg/kg)	No	Yes	NA

Table 5. Qualitative summary of Albuminuria data from losartan studies

High Dose Losartan (>30mg) (n=5)	Intermediate Dose Losartan (20mg)									Low dose losartan (10mg)		
Short follow up	Short follow up (n=1)	Long Follow up (n=3)								Long Follow up (n=1)		
NX (n=1)	SIH (n=1)	SHR (n=2)							Nx (n=1)	NX (n=1)		
Fanelli, (2011)	Kong, (2011)	Lin, 2012			Baumann, (2007)			Gonçalv, (2004)		Alarcon, 2015		
RSCNC	RSCHC	RSCOA	RSCNC	RSCHC	RSCOA	RSCNC	RSCHC	RSCOA	RSCNC	RSCHC	RSCOA	RSCNC	RSCHC	RSCOA	RSCNC	RSCHC	RSCOA	RSCNC	RSCHC	RSCOA
NA	Yes	NA	NA	Yes	NA	No	Yes	Yes (Amlodipine 10mg/kg)	No	Yes	NA	No	Yes	NA	Yes	Yes	NA

Table 6. Qualitative summary of CrCl data from losartan studies

High Dose Losartan (>30mg) (n=5)			Intermediate Dose Losartan (20mg)						Low dose losartan (10mg)		
Short follow up (n=3)			Long Follow up (n=1)			Short follow up (n=2)			Long Follow up (n=1)		Short follow up (n=1)
NX		ANG-II Induced	SHR-HS			NX (n=2)			SHR		SHR
Hyewon 2012	Hyewon 2007	Wang, 2000	De Cavanagh, 2010			García,(2017)		Dumont,(2001)	Lin, 2012		Jessup,(2006)		
RSCNC	RSCHC	RSCOA	RSCNC	RSCHC	RSCOA	RSCNC	RSCHC	RSCOA	RSCNC	RSCHC	RSCOA	RSCNC	RSCHC	RSCOA	RSCNC	RSCHC	RSCOA	RSCNC	RSCHC	RSCOA
No	Yes	NA	No	No	NA	Yes	Yes	NA	Yes	Yes	Yes (Amlodipine 10mg)	Yes	Yes	NA	No	Yes	NA	Yes	Yes	Yes (Atenolol 50mg/kg)	NA	No	No

Table 7: Qualitative summary of CrCl data from losartan studies

Intermediate Dose Losartan (20mg)								
Short follow up (n=1)			Long Follow up (n=2)					
NX			SHR					
García, (2017)			Tang, 2011			Lin, 2012		
RSCNC	RSCHC	RSCOA	RSCNC	RSCHC	RSCOA	RSCNC	RSCHC	RSCOA
No	Yes	NA	No	Yes	No (fosinopril 10mg/kg)	No	Yes	NA

Conclusion

- Qualitative data from this systematic review support that ARBs have a Reno-protective effect.
- Of 25 reported primary outcomes in comparison to hypertensive untreated controls, 23 outcomes showed positive results supporting that ARBs induce reduction in proteinuria and/or albuminuria compared to hypertensive untreated controls. Similar results were noticed in secondary outcomes.
- Studies comparing ARBs to non-ACE-inhibitors antihypertensives as atenolol and amlodipine, support that the reno-protective effect of ARBs is independent of the blood pressure lowering effect in most cases where blood pressure reduction was similar at the end point.