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

**Marwa Hamed [1], Salma Al-Dakhakhny [1], Hassaan Rathore [1] and Mohamed Izham [1]**

[1] College of Pharmacy, QU Health, Qatar University, Doha, Qatar

## 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 murine models on the reno-protective effect of ARBs in hypertensive population to provide a high quality pre-clinical baseline for future investigations.

## 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 or mice, 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 looked into four main outcomes reported as means and SEM, including creatinine clearance, proteinuria, albuminuria and/or BUN
- **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.

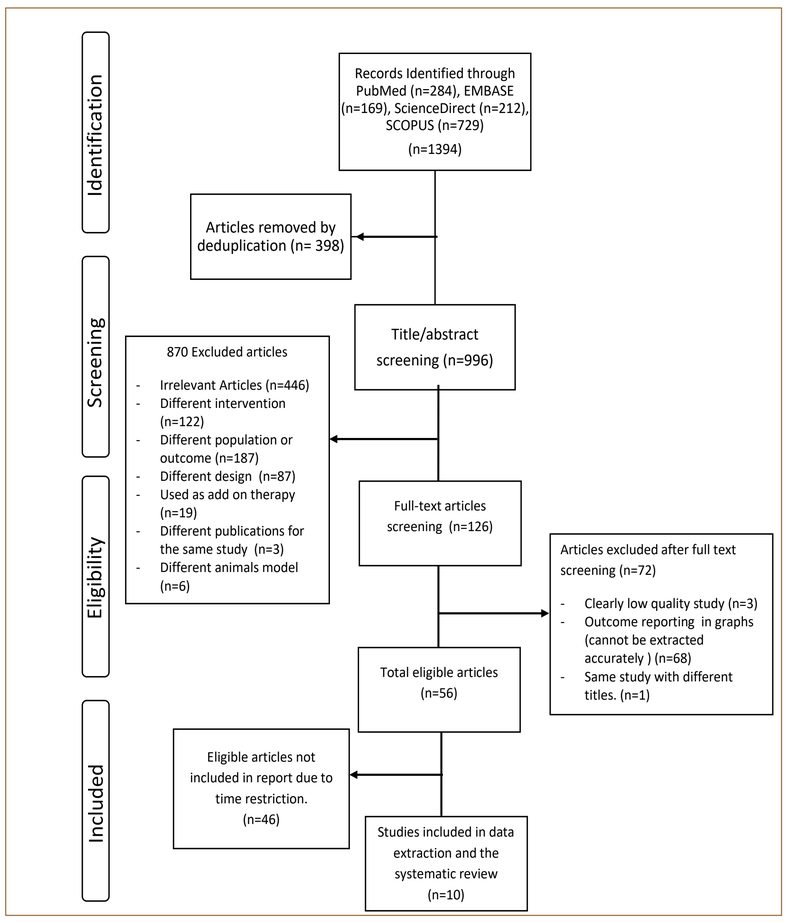



**Figure 1. The flow chart for screening and inclusion**

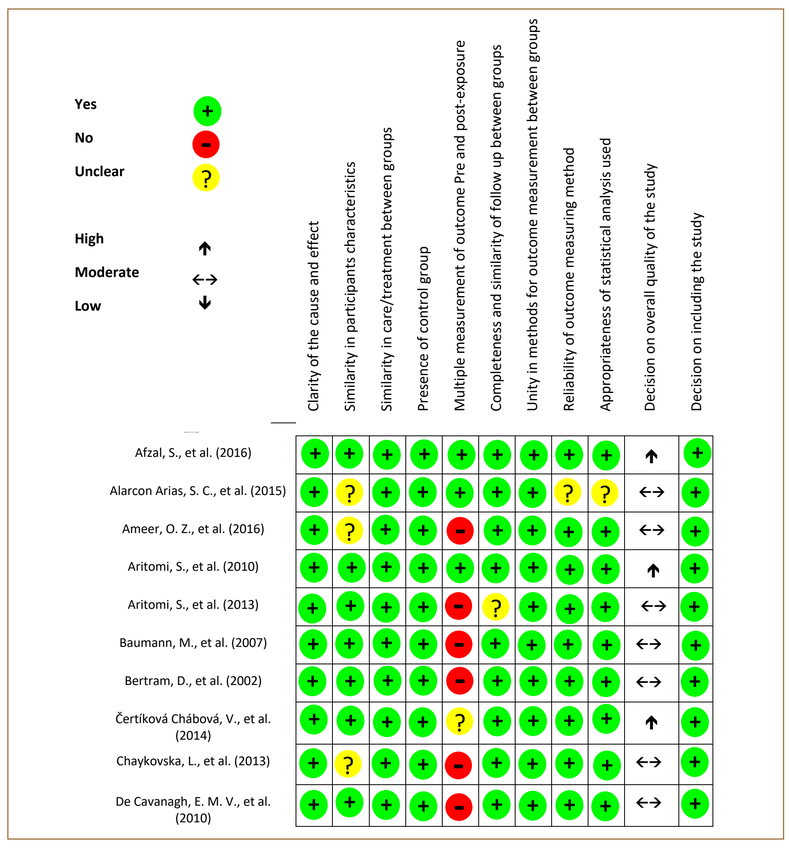
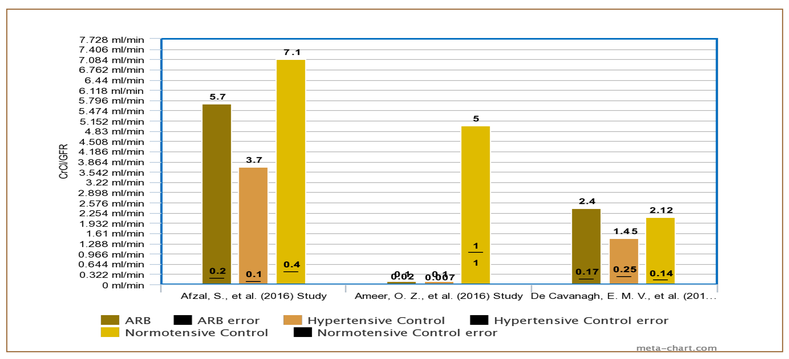
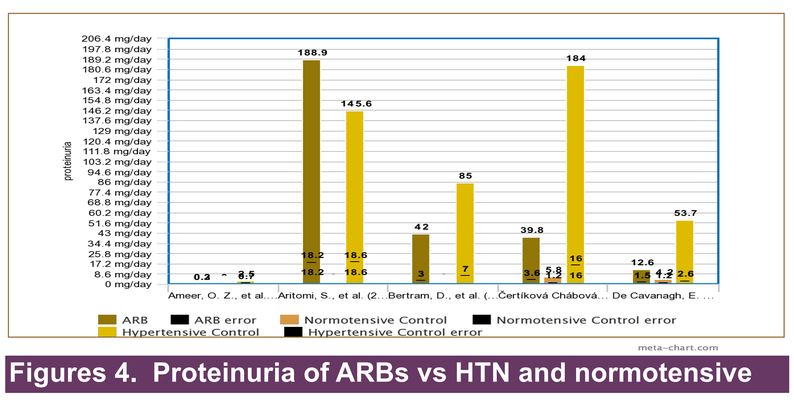


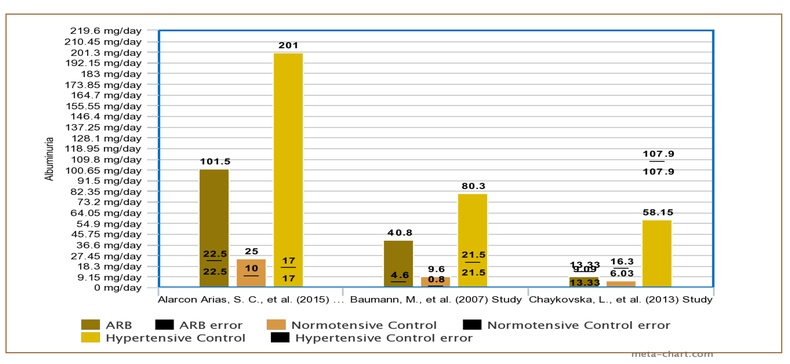

**Figure 2. JBI quality assessment for included studies**



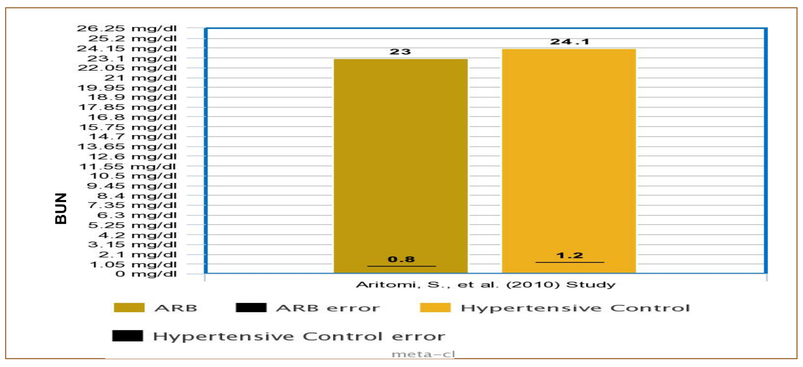

**Figures 3. CrCl of ARBs vs HTN and normotensive control**




**Figures 4. Proteinuria of ARBs vs HTN and normotensive**




**Figures 5. Albuminuria of ARBs vs HTN and normotensive**




**Figures 6. BUN of ARBs vs HTN and normotensive control**

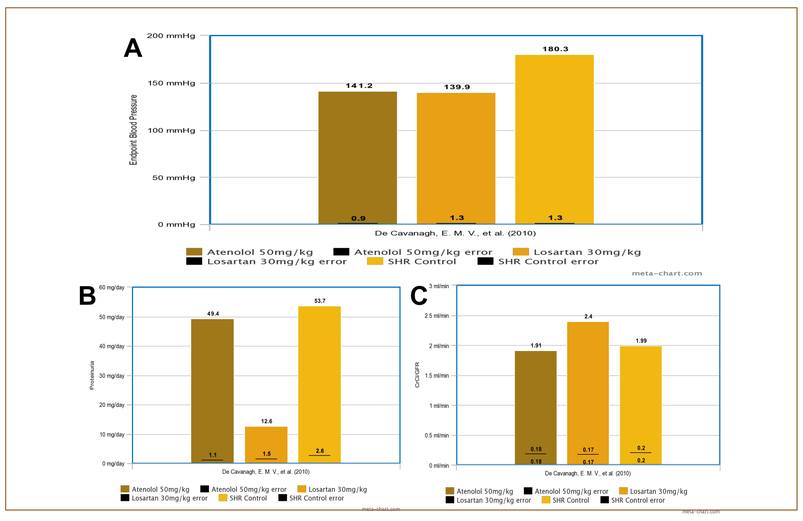



**Figure 7. The endpoint BP (A), proteinuria (B), and CrCl (C) for atenolol 50mg vs losartan 30mg vs hypertensive(SHR) control.**

## Results

- **Literature Search**
  - 996 article remained after deduplication.
  - 126 remaining after title-abstract screening.
  - 56 were eligible after full test screening.
  - Quality assessment done for 13 articles.
  - Data were extracted from ten articles identified to have moderate or high-quality and were included in the preliminary analysis.
- **Included Studies**
  - Ten studies conducted on a total of 537 rats.
  - Four ARBs were reported in the ten studies, including; irbesartan (n=1), losartan (n=5), valsartan (n=3) and telmisartan (n=1).
  - GRF/CrCl was reported in three studies. Two studies showed significant increase and one study showed no difference. Figure 3. represents average GFR from these studies.
  - Proteinuria was reported in five studies. Four out of five studies showed significant reduction in albuminuria. Figure 4 represent average urinary protein excretion in one day for ARBs vs controls.
  - Albuminuria was reported in three studies and all studies had significant reduction. figure 5. represents data from these studies.
  - BUN was reported in one study with no significant difference. Figure 6. presents the data

## Limitations

- The review did not include all eligible studies due to time limitations.
- Variations in models of HTN, administered doses or agents contributed to variations in results.
- Inclusion was restricted to English articles only which might have contributed to missing eligible articles

## Conclusions

- Initial data are encouraging. ARBs have shown reno-protective effect in different hypertensive models in eight of ten studies.
- Primary results from one study (figure 7.) support that the reno-protective effect is independent of blood pressure lowering effect.
- Reno-protective effect was seen with all agents at appropriate dosing and results would be further empowered after the completion of this review.