STATE OF THE ART REVIEW

A systematic review on randomized control trials on rennin angiotensin aldosterone system inhibitors role in managing hypertension among hemodialysis patients

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ABSTRACT
Randomized control trials (RCTs) are considered as most rigorous way of determining the cause–effect relationship of a treatment and outcome. Activation of rennin angiotensin aldosterone system (RAAS) is an important contributor to hypertension in hemodialysis patients. The prevalence of hypertension in hemodialysis patients varies from 60% to 80% and hypertension management alone with conventional hemodialysis is insufficient. Hence, the current review was aimed to investigate the effect of RAAS inhibitors in managing hypertension among hemodialysis patients in a randomized control trial. Using PUBMED and EMBASE databases, randomized control trial with primary or secondary outcomes related to the effect of RAAS inhibitors on blood pressure among hemodialysis patients were included for analysis. The current review also assessed the quality of reporting of RCT. A total of eight RCT met inclusion criteria for current review. According to modified Jadad scale, one (12.5%) study scored four points for quality reporting, whereas two (25%) studies scored one point that was the least score. The mean score for all included studies was 2.25. Six (75%) of the eight RCT included, involved ARB in hypertension management among hemodialysis patients, whereas two (25%) studies involved angiotensin-converting enzyme (ACE) inhibitors. Of the six RCT involving ARB, two (33.3%) RCT also included ACE inhibitors comparison group. Altogether six (75%) studies report a reduction in blood pressure with the use of RAAS inhibitors compared to control group; however, of the six studies, two (33.3%) reported that the reduction in blood pressure was not significant. Whereas, two (25%) studies reported no reduction in blood pressure compared to the control group. The findings from current review do not indicate a clear pattern for a role of RAAS inhibitors for hypertension control among hemodialysis patients.

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Introduction
As a part of evidence-based clinical practice, randomized control trials are considered as most rigorous way of determining the cause effect relationship of a treatment and outcome.1 Although randomized control trial are long been recognized as an important tool for effective treatment options, their use is limited by ethical and practical concerns.2 Exposing patients to an inferior intervention when a superior available is often unethical3; however, on the other hand, failure to perform a trial may result in harmful treatment being used. Hence, maintaining a balance of ethical and practical constraints is important. The impact of randomized control trial (RCT) is higher compared to other study designs as it reduces biasness. Study design, randomization technique bias in outcome assessment and data analysis are important indicators for the quality of reporting for research to report whether a result of a trial justify change in clinical practice.4 Assessment of validity and quality of research studies have been identified as one of the important key component of systematic reviews. For this purpose, it has been suggested that validity and quality of primary trials should be assessed under blind conditions so as to avoid or reduce biasness.5,6

Hemodialysis is the most common method used for fluid replacement therapy to treat permanent kidney failure. Among hemodialysis patients, hypertension is common and poorly controlled. An important cause of hypertension is volume overload but even after thrice weekly, aggressive fluid management therapy, a population of patient still remains hypertensive. In such patients, nonvolume mechanisms, such as activation of rennin angiotensin system or sympathoadrenal activity, are important contributors to hypertension.7–9

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Hypertension management alone with conventional hemodialysis is insufficient. Nonpharmacological interventions as low sodium intake and achieving targeted dry weight play a minor role in maintaining blood pressure; however, pharmacological interventions form the backbone for treating hypertension among these patients. Inhibitors of rennin angiotensin aldosterone system (RAAS) are considered to be one of the first lines of agents to treat hypertension among hemodialysis patients because of their safety, tolerability and therapeutic efficacy. The national kidney foundation kidney disease outcomes quality initiative (KDOQI) guideline also recommend RAAS inhibitors to be used among dialysis patients with diabetes and heart failure. Studies suggest that angiotensin-converting enzyme (ACE) inhibitors help preserve residual renal function and improve outcomes in hemodialysis patients. Efrati et al. in their retrospective analysis conclude that ACE inhibitors are associated with improved survival. Most of ACE inhibitors are dialyzable; however, the removal of ACE inhibitors during dialysis is not problematic since it avoids interdialytic hypotension. In case of interdialytic hypertension, dialyzable ACE inhibitors can be replaced by nondialyzable ACE inhibitors or ARB. The effect of ARB on lowering blood pressure has produced mixed results, and this is likely because of different blood pressure measuring procedures; however, ARB are well tolerated and are relatively effective in controlling blood pressure. Combination of ARB and ACE inhibitor improves blood pressure control and cardiovascular outcomes. The β and α blockers are also used in hypertensive patients with cardiovascular diseases, whereas calcium channel blocker and other vasodilators are also effective in managing blood pressure. The main purpose of this review is to explore RCT undergone to assess the effects of RAAS inhibitors in managing hypertension among hemodialysis patients and assess the quality of reporting of RCT.

Methods

Search strategy

A systematic review of published randomized control trial evaluating the role of RAAS inhibitors in managing hypertension among hemodialysis patients was conducted (2004 onwards). For this purpose, GOOGLE SCHOLAR, PUBMED, EBSCO HOST and EMBASE search engine were used for relevant studies. RAAS inhibitors, ACE inhibitors, ARB inhibitors, aldosterone inhibitors, randomized control trial, blood pressure, systolic blood pressure, diastolic blood pressure, hypertension, pre-dialysis and postdialysis search terms were used for data search in conjunction with end-stage renal disease (ESRD), mortality, survival, prognosis, predictive. Both medical subject headings and text terms were used. The search was limited to hemodialysis patients and English language only.

Inclusion/exclusion criteria

All RCT that evaluated relationship between RAAS inhibitors and blood pressure control among hemodialysis patients (>18 years) and were published from 2004 on words were included in current review. RCTs with primary or secondary outcomes related to the effect of RAAS inhibitors on blood pressure among hemodialysis patients were included for analysis. All meta-analyses, systematic reviews, editorials, commentaries and case reports were excluded. Furthermore, studies with patients on other forms of renal replacement therapy, age less than 18 years and with no relevant outcome were excluded.

Data extraction, quality of reporting

Two reviewers independently reviewed titles and abstracts for all potential research papers that were related to current systematic review objectives. Papers that met inclusion criteria were retrieved. Any differences were resolved through discussion or were resolved by a third reviewer. The main reason for randomization in a clinical trial is to avoid any biasness that may result in any systematic differences between patients in the treatment group. Random allocation is intended in a clinical trial to provide equal opportunity of receiving intervention and to ensure intervention cannot be predicted. Appropriate randomization methods that reduce biasness include computer-generated random number, drawing of lots and envelop; however, assigning patients to treatment group by registration number, day of visit or similar method introduces selection biasness. Such method may not give equal opportunities to patients in receiving interventional treatment. To assess the quality of reporting of RCT in this study, a Jadad scale was used. The Jadad scale is a three-item scale covering the randomization, blinding and dropout method (Table 1). For each item, a study was awarded one point if it described randomization, double blind or dropout, respectively. If randomization or blinding method was judged appropriate, an additional one point was awarded. Conversely, if the randomization or blinding method was judged inappropriate, one point was deducted from that item. Since randomization procedure is fundamental to quality of reporting, a
point was deduced if randomization procedure was not described.

The original Jadad scale considers only double blinding. Keeping in view of our objectives, Jadad scale was modified to single blinding as well. The blinding was considered appropriate if manuscript specified whom the blinding involved. The articles were also assessed with regards to patient withdrawal or exclusion after enrollment for any reason. These included decision by patient or investigator, loss to follow-up, change in treatment or any reason that may introduce biasness. Articles were also assessed if they had mentioned or were clear from data shown that all patients were included in final outcome analysis or provided details of patient dropout.

The final quality score for each article may range from 0 (lowest quality) to 5 (highest quality).\textsuperscript{17}

**Results**

A total of eight RCT met inclusion criteria for current review (Table 2). These RCTs involved hypertension management using ARB inhibitors, ACE inhibitors and aldosterone inhibitors among hemodialysis patients. According to modified jaded scale, one (12.5\%) study scored four points for quality reporting whereas two (25\%) studies scored one point that was the least score. The mean score for all included studies was 2.25. Studies scored the most in withdrawal and dropout domain, whereas the least was scored in blinding domain where studies failed to clearly describe blinding protocols. Seven studies (87.5\%) used parallel design, whereas only Huber et al. used a cross over design to for their RCT. Altogether three (37.5\%) RCT used blinding to avoid biasness in their study. Six (75\%) studies used two treatment arms (standard & interventional arm) whereas two (25\%) studies used three arms (2 interventional & 1 standard arm) in their analysis.

Six of the eight RCT included, involved ARB in hypertension management among hemodialysis patients, whereas two (25\%) studies involved ACE inhibitors (Table 2). Of the six RCT involving ARB, two (33.3\%) RCT also included ACE inhibitors group. RCT by Huber et al. was the only study that directly assessed hypertension management using ARB in hemodialysis patient, whereas all other RCT primary outcome was to assess cardiovascular morbidity and mortality; in doing so, hypertension control was also assessed.

Altogether, six (75\%) studies report a reduction in blood pressure, of which two (25\%) studies report that the reduction in blood pressure was not significant from the control (Table 3). Takahashi et al. and Atsuhiro et al. report that there was no change in blood pressure among hemodialysis patients during their study period. Hiromichi et al. in their study report a reduction in blood pressure, however, do not mention any statistical analysis to report a significant conclusion. Nevertheless, a blood pressure drop of 154±20 baseline to 140±12 during 3-year duration is an important finding.

**Table 1.** Jadad scale (modified for current systematic review).

| Item                          | Points |
|-------------------------------|--------|
| Randomization                 |        |
| Study described as randomized | +1     |
| Randomized method described and appropriate | +1     |
| Randomized method described and inappropriate | −1     |
| Randomization method not described | −1     |
| Blinding                      |        |
| Study described as double or single blind | +1     |
| Blinding method described and appropriate | +1     |
| Blinding method described and inappropriate | −1     |
| Blinding method not described | 0      |
| Study not described as blinded | 0      |
| Withdrawal and dropouts       |        |
| Withdrawals and dropouts described | +1     |
| Withdrawals and dropouts not described | 0      |

**Table 2.** The modified jaded score for quality of reporting for published RCTs.

| Item                          | Points |
|-------------------------------|--------|
| Randomization                 |        |
| Study described as randomized | +1     |
| Randomized method described and appropriate | +1     |
| Randomized method described and inappropriate | −1     |
| Randomization method not described | −1     |
| Blinding                      |        |
| Study described as double or single blind | +1     |
| Blinding method described and appropriate | +1     |
| Blinding method described and inappropriate | −1     |
| Blinding method not described | 0      |
| Study not described as blinded | 0      |
| Withdrawal and dropouts       |        |
| Withdrawals and dropouts described | +1     |
| Withdrawals and dropouts not described | 0      |
| Total                         | 2      | 2  | 2  | 3  | 4  | 1  | 1  | 3  |
Table 3. Summaries of RCT demonstrating an impact of RAAS inhibitors on blood pressure among hemodialysis patients.

| References          | Population                                      | Study type                                      | Trial period | Objective                                                                 | Finding                                                                                       | Intervention          |
|---------------------|--------------------------------------------------|-------------------------------------------------|--------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-----------------------|
| Hiromichi et al. 2008<sup>25</sup> | 366 hemodialysis patients                        | Open label randomized control trial            | Parallel design, 3 years        | To evaluate fatal and nonfatal CVD among patients receiving ARB          | Systolic blood pressure reduced from 154 ± 20 baseline to 140 ± 12                           | ARB & non-ARB         |
| Huber et al. 2013<sup>21</sup>       | 29 hemodialysis patients                          | Randomized, placebo-controlled, double-blind | Cross-over trial, 3 years       | Effect of telmisartan on managing hypertension among hemodialysis patients | Patients exhibited a significant reduction of systolic pre-HD BP from 141.9 ± 21.8 before to 131.3 ± 17.3 mmHg | Telmisartan or placebo |
| Iseki et al. 2012<sup>24</sup>       | 469 patients with chronic HD                     | Prospective, randomized, open-label, blinded-endpoint trial, | Parallel design, 3.5 years     | The RCT was designed to assess composite of death, nonfatal stroke, nonfatal myocardial infarction and coronary revascularization | The mean BP was 0.9/0.0 mmHg lower in the olmesartan group than in the control group (not significant) | ARB & Control          |
| Zannad et al. 2006<sup>23</sup>      | 397 patients randomized to placebo (n = 201) and to fosinopril (n = 196) | Randomized, placebo-controlled, double-blind | Parallel design                 | To evaluate the effect of fosinopril on CVEs in patients with ESRD.      | Blood pressures were significantly decreased in the fosinopril compared to the placebo group. | Fosinopril & placebo  |
| Atsuhiro et al. 2005<sup>10</sup> | 22 patients randomly assigned to one of three groups. | Multicenter, randomized, prospective study    | Parallel design                 | To determine the low-dose effects of the angiotensin II receptor blocker losartan and the angiotensin-converting enzyme inhibitor trandolapril on pulse wave velocity (PWV) | There were no changes in blood pressure, hematocrit, erythropoietin dose, or serum C-reactive protein levels during the 12-month study period | Losartan or tandolapril or placebo |
| Matsumoto et al. 2006<sup>15</sup>  | 30 patients with end-stage renal diseases undergoing maintenance hemodialysis | Randomized, placebo-controlled, 6 month       | Parallel design                 | To examine the effects of an angiotensin converting enzyme (ACE) inhibitor, imidapril on left ventricular mass in patients with end-stage renal diseases on maintenance hemodialysis. | Imidapril did not significantly lower either systolic or diastolic blood pressure, and the averaged blood pressure values were comparable between the two groups throughout the 6-month study period. | Imidapril and placebo |
| Takahashi et al. 2006<sup>26</sup>  | A total of 80 chronic hemodialysis patients       | Prospective, randomized, open blinded-endpoint trial | Parallel design                 | To investigate whether candesartan reduces the incidence of cardiovascular events in these patients. | Blood pressure was not different between the two groups and no changes were noted in the either group during follow-up (p = 0.21/p = 0.18). | Candesartan & control group |
| Suzuki et al. 2004<sup>22</sup>     | Thirty-three type 2 diabetic patients on hemodialysis | Randomized controlled trial                    | Parallel design                 | To assess the effects of an ACE inhibitor, an AT1 antagonist and their combination on the regression of LVH in diabetic patients on dialysis therapy. | An initial steady in blood pressure decline was observed for up to 6 months followed by maintenance and then a fall toward the end of the study. | ACE inhibitor, AT1 antagonist & combination group |
Takahashi et al. reporting no change in blood pressure conducted their RCT among 80 hemodialysis patients for a period of 2 years. Alongside Atsuhiro et al. who also reported no change in blood pressure conducted their study in 22 patients over a period of 12 months. In comparison to six studies that reported decline in blood pressure conducted their RCT among patients sample ranging from 29 by Huber et al. to 469 patients by Iseki et al.

Suzuki et al. report an initial decline in blood pressure followed by a maintenance period during first six months of the study followed by a gradual decrease in blood pressure the next 6 months. Similar findings are also reported by Hiromichi et al. in their 3-year prospective RCT, which reports a rapid decline in blood pressure during the first year followed by a slow and gradual decrease the following 2 years.

Discussion

Hypertension is common in hemodialysis patients with studies reporting prevalence of 60–80%.18 The burden of cardiovascular morbidity among hemodialysis patients is often associated with constant elevated blood pressure, and for this reason, most of the hypertension management RCTs are focused on cardiovascular events. RAAS inhibitors are associated with reduction in cardiovascular morbidity and reduce blood pressure in hypertensive individual; however, limited literature is available on role of RAAS inhibitors on hypertension management among hemodialysis patients. For this purpose, current review was aimed to evaluate the role of RAAS inhibitors in hypertension management in hemodialysis patients in a RCT.

According to National clinical practice guidelines of United States, a predialysis BP of less than 140/90 mmHg and postdialysis BP of less than 130/80 mmHg are recommended.20 However, achieving these standards in clinical practice is a rare scenario. Similar blood pressure ranges have been proposed by different guidelines and hence provide a possible explanation for the use of different targeted blood pressure ranges in their studies. Huber et al. in their RCT reports an initial significant decrease in blood pressure with the use of telmisartan; however, no average significant influence was observed at the completion of trial.21 These negative findings are attributed to individual blood pressure variation, where blood pressure changes were reported to be 40 mmHg of the total mean of the group. Another important limitation attributed to Huber et al. findings was the small number of patients from single-center hemodialysis unit, which does not portray an overall scenario. Similarly, Suzuki et al. also reports an initial drop in blood pressure with the use of ARB followed by an maintenance period22 can also be attributed to same reasons; however, no such explanation was provided for their finding.

Zannad et al. in their trial with a larger sample size and with longer duration report a significant reduction in systolic and diastolic blood pressure from baseline with the use of ACE inhibitor.23 They also suggest that fosinopril may also be associated with lowering cardiovascular events. Since major reason for cardiovascular events in hemodialysis patients are attributed to uncontrolled hypertension; hence, trials following cardiovascular changes with antihypertensive are often of longer duration. In doing so, blood pressure is constantly monitored and its effect is related to cardiovascular morbidity and mortality; however, blood pressure management does not remain their primary objective, which is why discussed scarcely in their findings. Zanad et al. report that a low mortality rates were reported in patients on ACE inhibitors, these findings suggest that survival of patients may be attributed to ACE inhibitors therapy in hemodialysis patients.13 Similar findings were also reported by McCullough et al. that reported an overall 37% reduction in cardiovascular events with use of ACE inhibitor compared to those who did not use ACE inhibitor over a period of 3 years.24

A retrospective analysis by Efrati et al. suggest an improved survival rates in hemodialysis patients up to almost 37% in patients receiving ACE inhibitors.13 These observational findings require RCT for their confirmation; however, limited trials are conducted to support such findings. Suzuki et al. in their RCT report an initial drop in blood pressure during first year of trial followed by a maintenance period during the next two years.25 The study concludes that an ARB may be an effective in reducing cardiovascular events; however, considering the importance of blood pressure on cardiovascular events, ARB beneficial effects are not medicated by blood pressure. This gives rise to a new debate and a platform for future RCTs that is the positive influence of ARB on survival of patients mediated by the control of blood pressure or by cardioprotective properties of the drug.

However, Takahashi et al. in their RCT reported that there was no significant difference in blood pressure in the control and the treatment group (ARB) at the end of trial.26 Although the main aim of study was to investigate the effect of candesartan in reducing the incidence of cardiovascular events in dialysis patients, blood pressure control was constantly studied during the trial. The findings suggest that candesartan (ARB) plays an important role in maintaining the levels of BNP, where the elevated level of BNP indicates an increased risk of cardiovascular events in chronic hemodialysis...
Moreover, the blockade of RAS system by ARB helps to reserve cardiac hypertrophy in hemodialysis patients. On the contrary, ARBs unlike ACE inhibitors do not have protective effects against myocardial infarction and are either neutral or increase rates of myocardial infarction despite the beneficial effect of reducing blood pressure. All these cardiovascular effects exerted by ARBs, leads to improve survival of chronic hemodialysis patients that seem to be independent of their antihypertensive effects.

Often an area of debate is the type of hypertension that portrays actual uncontrolled blood pressure in hemodialysis patients. Predialysis, interdialytic and postdialysis hypertension are associated with hemodialysis patients; however, no set conclusion is yet made that actually represents uncontrolled blood pressure among hemodialysis patients. Moreover, systolic or diastolic hypertension as a risk factor for cardiovascular events is an ongoing debate that further complexes the matter. Agarwal (2005) reported that when systolic and diastolic blood pressures are considered separately, an inverse relationship is seen between total mortality and blood pressure. However, when systolic and diastolic blood pressures are considered together, a direct relationship between total mortality and systolic blood pressure is seen while an inverse relationship observed between diastolic blood pressure and total mortality. Similarly, Agarwal in another study concluded that ambulatory BP measurements have better prognostic significance as compared to pre- and postdialysis BP measurements. These findings were supported by other studies that suggested better prognostic significance of ambulatory and home BP as compared to dialysis BP measurements. Variation in different study findings can be attributed to complex and ongoing debate that truly represents research in hypertension management in hemodialysis patients.

**Limitation**

As with all reviews, the main limitation for current review is the bias selection. Although efforts were made to ensure inclusion of all relevant studies and to elaborate results of studies however chances of shortcomings cannot be neglected. Moreover, impact of unidentified cofounders on hypertension control cannot be ruled out in our selected studies. In addition, formal assessment of comorbidities was not done in all studies. Assessment of baseline comorbidities is crucial as it has been reported that relationship between low BP and mortality is stronger in diabetics as compared to nondiabetics.

The effect of RAAS on hypertension control in hemodialysis patients was not the primary objective in our selected studies, rather majority of studies primary objective was to assess CVS mortality with the use of RAAS inhibitors and in doing so, hypertension control was assessed. Hence, attributing to an important flaw for selected studies.

**Recommendation**

Identification of appropriate hypertension criteria with well-defined BP goals in a RCT can help understand the role of RAAS inhibitors in hemodialysis patients in detail. In addition, detailed methodology, adjustment of known cofounders by statistical analysis, elaborative techniques for long follow-up, standardization of BP measurements, appropriate randomization technique, important covariates (diabetes, smoking) of BP and pulse pressure by including both systolic and diastolic BP for pre, post and interdialytic BP could aid in better understanding the use of RAAS inhibitors in hypertension management among dialysis patients.

**Conclusion**

Lack of agreement on pre-, post- or interdialytic blood pressure as a true marker of hypertension among hemodialysis patients leads to inconsistent findings. The role of RAAS in blood pressure control cannot be neglected; however, the RAAS system may influence its effect on CVS independent of blood pressure control, thereby making the scenario more complicated. RAAS inhibitors have shown variable results in hypertension control, in most instants they have reduced blood pressure from baseline; however, reduction in blood pressure has not always been statistical significance. A RCT with a clear hypertensive criteria and well-defined protocols could provide concrete findings on the effect of RAAS inhibitors in hypertension control among hemodialysis patients.

**Disclosure statement**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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