Renin-angiotensin system inhibitors linked to anemia: a systematic review and meta-analysis

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Summary

Background: The objective of this meta-analysis was to evaluate the risk of anemia in patients who received renin-angiotensin system (RAS) inhibitors.

Methods: A literature search was performed using MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews from inception through November, 2014. Studies that reported relative risks, odd ratios or hazard ratios comparing the anemia risk in patients who received angiotensin-converting-enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) vs. those who did not were included. We performed the prespecified sensitivity analysis including only studies with confounder adjusted analysis. Pooled risk ratios (RRs) and 95% confidence interval (CI) were calculated using a random-effect, generic inverse variance method.

Results: Seven studies (2 cohort and 5 cross-sectional studies) with 29,061 patients were included in the analysis to assess the risk of anemia and the RAS inhibitors use. The pooled RR of anemia in patients receiving ACEIs was 1.56 (95% CI, 1.40–1.73, I² = 17%). When meta-analysis was limited only to studies with confounder adjusted analysis, the pooled RR of anemia in patients using ACEIs was 1.57 (95% CI, 1.43–1.73, I² = 0%). The pooled RR of anemia in patients receiving ARBs was 1.60 (95% CI, 1.27–2.00, I² = 39%). The meta-analysis of studies with confounder adjusted analysis demonstrated the pooled RR of anemia in patients using ARBs of 1.59 (95% CI, 1.38–1.83, I² = 0%).

Conclusions: Our meta-analysis demonstrates an association between anemia and the use of RAS inhibitors. Hematological parameters should be monitored in patients treated with RAS inhibitors.

Introduction

Anemia is common among patients with medical comorbidities such as congestive heart failure (CHF), chronic kidney disease (CKD), chronic inflammatory states, autoimmune disorders and is associated with poor outcomes. Moreover, patients with postoperative anemia also encounter higher in-hospital morbidity and mortality. Every 1 g/dl decrease in hemoglobin (Hb), after coronary artery bypass graft surgery, is associated with a 13% increase in cardiovascular events and a 22% increase in all-cause mortality. Because the long-term use of Renin-angiotensin system (RAS) inhibitors including angiotensin converting enzyme
inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) has been shown to provide cardioprotective and renoprotective effects especially in proteinuric patients with diabetic or non-diabetic CKD, they are now commonly prescribed. However, there have been raising concerns if these agents can cause anemia.

The findings of studies evaluating the association between RAS inhibitors and anemia; however, are conflicting. Several studies have demonstrated that the use of ACEIs or ARBs is associated with anemia. Conversely, a number of studies have shown no significant associations between anemia and the use of ACEIs or ARBs. Conversely, a few studies have shown less anemia with the use of RAS inhibitors especially in CHF patients treated with ACEIs.

Thus, we conducted a meta-analysis to assess the risk of anemia in patients who used RAS inhibitors.

Materials and methods

Search strategy

Two investigators (W.C. and C.T.) independently searched published studies indexed in MEDLINE, EMBASE and the Cochrane database from inception through November, 2014 using the search strategy described in Supplemntary Item S1 in online Supplementary Data. A manual search for additional relevant studies using references from retrieved articles was also performed.

Inclusion criteria

The inclusion criteria were as follows: (i) RCTs or observational studies (case-control, cross-sectional or cohort studies) published as original studies or conference abstracts to evaluate the risk of anemia in patients receiving RAS inhibitors with ACEIs or ARBs, (ii) odds ratios, relative risks, hazard ratios or standardized incidence ratio with 95% confidence intervals (CIs) were provided and (iii) a reference group composed of participants who did not use preoperative RAS inhibitors. No limits were applied for language.

Study eligibility was independently determined by the two investigators noted earlier. Differing decisions were resolved by mutual consensus. The quality of each study was independently evaluated by each investigator using Jadad quality assessment scale for RCTs and Newcastle-Ottawa quality assessment scale for observational studies.

Data extraction

A standardized data collection form was used to extract the following information: last name of the first author, study design, year of study, country of origin, year of publication, sample size, characteristics of included participants, type of RAS inhibitors, definition of anemia, confounder adjustment and adjusted effect estimates with 95% CI. The two investigators mentioned earlier independently performed this data extraction.

Statistical analysis

Per our study protocol, we conducted a meta-analysis in all included studies and also a prespecified analysis of anemia including only studies with confounder adjusted analysis. Review Manager 5.2 software from the Cochrane Collaboration was used for data analysis. Point estimates and standard errors were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird. Given the high likelihood of inter-study variances, we used a random-effect model rather than a fixed-effect model. Statistical heterogeneity was assessed using the Cochran’s Q test. This statistic is complemented with the I² statistic, which quantifies the proportion of the total variation across studies that is due to heterogeneity rather than chance. A value of I² of 0–25% represents insignificant heterogeneity, 26–50% low heterogeneity, 51–75% moderate heterogeneity, and >75% high heterogeneity. The presence of publication bias was assessed by funnel plots of the logarithm of odds ratios vs. their standard errors.

Results

Our search strategy yielded 14354 potentially relevant articles. A total of 13206 articles were excluded based on title and abstract for clearly not fulfilling inclusion criteria on the basis of the type of study, article subject, population or outcome of interest; 1148 articles underwent full-length article review and 1141 articles were excluded (902 articles did not report the outcomes of interest and 239 articles were not observational studies or RCTs). Two cohorts and five cross-sectional studies with 29061 patients were identified and included in the data analysis. Of seven studies, four studies used confounder adjusted analysis. Seven studies were included in the data analysis for the association between anemia and the use of ACEIs. Supplementary Item S2 outlines our search methodology and selection process. Table 1 describes the detailed characteristics and quality assessment of the included studies.

Study participants

Out of seven included studies, one study were conducted in all adults (age >25 years) with a first purchase of an ACEI or an ARB. Three studies included kidney transplant recipients. Two studies enrolled the patients with cardiovascular diseases from patients undergoing cardiovascular surgery. A study was conducted only in non-dialysis patients with stage four to five CKD. Table 1 describes the detailed patient characteristics.

Type of RAS inhibitors and the risk of anemia

Almost all studies did not specify the name of ACEIs or ARBs (Table 1). There was only an included study that defined the use of ACEIs with enalapril initiating at 2.5 or 5 mg twice daily and gradually increased to 10 twice daily in cardiovascular patients. The duration of RAS inhibitors use ranged from 3 months to 1 year.

The risk of anemia in the use of ACE inhibitors

The pooled RR of anemia in patients receiving ACEIs was 1.56 (95% CI, 1.40–1.73, I² = 17%). Figure 1 shows the forest plot of the included studies. When meta-analysis was limited only to studies with confounder adjusted analysis, the pooled RR of anemia in patients using ACEIs was 1.57 (95% CI, 1.43–1.73, I² = 0%) as shown in Supplementary Figure S1.

Sensitivity analysis

We performed a sensitivity analysis excluding the studies with cross-sectional design, which could not establish a temporal
<table>
<thead>
<tr>
<th>Country</th>
<th>Study sample</th>
<th>Exposure definition</th>
<th>Exposure measurement</th>
<th>Outcome definition</th>
<th>Adjusted OR or RR</th>
<th>Confounder adjusted</th>
<th>Quality assessment (Newcastle-Ottawa scale)</th>
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<tr>
<td>16 European</td>
<td>Kidney transplant recipients</td>
<td>Use of ACEI/ARB</td>
<td>Survey</td>
<td>Hb level of ≤13 g/dl for male and ≤12 g/dl for female</td>
<td>1.55 (1.34–1.80)</td>
<td>Serum creatinine, age of donor, mycophenolate mofetil or azathioprine use, polycystic kidney disease, recent infection</td>
<td>Selection:2 Comparison:2 Outcome:3</td>
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<tr>
<td>countries</td>
<td></td>
<td></td>
<td>Medical record review</td>
<td>HCT &lt;33% after transplant</td>
<td>1.56 (1.26–1.93)</td>
<td>gender, kidney function, the use of tacrolimus</td>
<td>Selection:3 Comparison:2 Outcome:3</td>
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<td></td>
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<td>Use of ACEI/ARB</td>
<td>Medical record review</td>
<td>New anemia (HCT ≤39% in men and ≤36% in women) at 1 year after randomization</td>
<td>1.06 (0.70–1.61)</td>
<td>Trial type, age, gender, race, creatinine, diabetes, EF, NYHA functional class, weight</td>
<td>Selection:3 Comparison:2 Outcome:3</td>
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<td>Use of ACEI/ARB</td>
<td>Medical record review</td>
<td>Mean Hb &lt;11 g/dl after 3 months after transplant</td>
<td>1.62 (1.15–2.29)</td>
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<td>Use of ACEI/ARB</td>
<td>Medical record review</td>
<td>Preoperative anemia (Hb &lt;13 g/dl for men and &lt;12 g/dl for women)</td>
<td>4.46 (1.47–13.49)</td>
<td>None</td>
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<td></td>
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<td>Computerized database of a large health maintenance organization</td>
<td>EPO resistance index &gt; 2.6 IU wk/kg/g Hb per 100 ml</td>
<td>4.46 (1.47–13.49)</td>
<td>Sex, age</td>
<td>Selection:3 Comparison:2 Outcome:3</td>
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<td>USA</td>
<td>Patients with a functioning renal transplant</td>
<td>Enalapril initiated at 2.5 or 5 mg twice daily and gradually increased to 10 twice daily</td>
<td>Treatment assignment after randomization</td>
<td>Hb &lt;13 g/dl in men and 12 g/dl in women</td>
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<td>USA</td>
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<td>Selection:2 Comparison:0 Outcome:0</td>
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<td>Kidney transplant patients</td>
<td>Use of ACEI/ARB</td>
<td>Medical record review</td>
<td>New anemia (HCT ≤39% in men and ≤36% in women) at 1 year after randomization</td>
<td>1.06 (0.70–1.61)</td>
<td>Trial type, age, gender, race, creatinine, diabetes, EF, NYHA functional class, weight</td>
<td>Selection:3 Comparison:2 Outcome:3</td>
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<td>Medical record review</td>
<td>Preoperative anemia (Hb &lt;13 g/dl for men and &lt;12 g/dl for women)</td>
<td>4.46 (1.47–13.49)</td>
<td>None</td>
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<td>Non-dialysis patients with stage 4-5 CKD on ESA</td>
<td>Use of ACEI/ARB</td>
<td>Medical record review</td>
<td>Hb &lt;13 g/dl in men and 12 g/dl in women</td>
<td>4.46 (1.47–13.49)</td>
<td>Sex, age</td>
<td>Selection:3 Comparison:2 Outcome:3</td>
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<td>EPO resistance index &gt; 2.6 IU wk/kg/g Hb per 100 ml</td>
<td>4.46 (1.47–13.49)</td>
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*Weekly weight-adjusted dose of ESA divided by the Hb level. Abbreviation: ACEI, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers; CKD, chronic kidney disease; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; Hct, hematocrit; IU, international unit; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.*
relationship between anemia and the use of ACEIs. The result remained significant (RR, 1.58 [95% CI, 1.38–1.80], $I^2 = 0\%$).

The risk of anemia in the use of ARBs

The pooled RR of anemia in patients receiving ARBs was 1.60 (95% CI, 1.27–2.00, $I^2 = 39\%$). Figure 2 shows the forest plot of the included studies. When meta-analysis was limited only to studies with confounder adjusted analysis, the pooled RR of anemia in patients using ARBs was 1.59 (95% CI, 1.38–1.83, $I^2 = 0\%$) as shown in Supplementary Figure S2. A sensitivity analysis excluding the studies with cross-sectional design could not be performed for the risk of anemia in the use of ARBs due to limited data (only one of 6 studies was cohort study).

The risk of anemia in renal transplant recipients and patients with cardiovascular diseases

The pooled RR of anemia in renal transplant patients receiving ACEI was 1.45 (95% CI, 1.12–1.87, $I^2 = 41\%$). Supplementary Figure S3 shows the forest plot of the included studies. The pooled RR of anemia in renal transplant patients using ARBs was 1.44 (95% CI, 1.08–1.93, $I^2 = 45\%$) as shown in Supplementary Figure S4. The pooled RR of anemia in patients with cardiovascular diseases receiving ACEI was 1.58 (95% CI, 1.32–1.89, $I^2 = 0\%$). The analyses of other subgroups were not performed due to limited data of included studies.

Evaluation for publication bias

Funnel plots to evaluate publication bias for the risk of anemia in the use of ACEIs and ARBs are summarized in Supplementary Figures S5 and S6, respectively. The graph for assessing publication bias of postoperative AKI risk is slight asymmetric and suggests the presence of publication in favor of positive studies.

Discussion

Our meta-analysis showed a significant association between anemia and the use of RAS inhibitors, with an overall 1.56-fold increased anemia risk in the use of ACEIs and a 1.60-fold increased anemia risk in the use of ARBs. The heterogeneity of the prespecified analyses including only studies with confounder adjusted analysis was insignificant in both analyses of ACEIs and ARBs.

There are several plausible explanations for the increased anemia risk in patients who used RAS inhibitors. First, activation of an angiotensin II type 1 receptor with angiotensin II can enhance erythropoietin (EPO)-stimulated erythroid proliferation.31 Thus, RAS inhibitors are effective to inhibit erythropoiesis.9 A significant decrease in mean plasma EPO concentration was observed in healthy volunteers treated with ACE inhibitors, enalapril and captopril, and returned to baseline after discontinuation the medications.32 The suppression of EPO by ACEIs was also demonstrated in patients with CKD.33 Second, ACEIs therapy was also found to reduce circulating insulin-like growth factor 1, a factor promoting erythropoiesis produced by the liver under growth hormone control.34 Our meta-analysis demonstrates a significant association between anemia and both ACEIs and ARBs therapy.

The association between anemia and the use of RAS inhibitors was found since 3 months after the therapy. Kamper et al.33 showed a suppression of EPO production could potentially be occurring at 90 days after RAS inhibitors therapy.
This association is also found in subgroup analyses of patients with renal transplantation and cardiovascular diseases. Post-cardiac surgery, quinapril and enalapril maleate were reported to slower postoperative recovery of Hb levels.\(^6\)\(^,\)\(^15\) In addition, our the finding of our meta-analysis confirmed the effects of RAS inhibitor the previous systematic review of RAS inhibitors use in renal transplant patients.\(^3\)\(^5\) The use of ACEIs or ARBs may result in a reduction in hematocrit.\(^3\)\(^5\) Therefore, the RAS inhibitor therapy has been proposed as a therapeutic modality for a post-transplant erythrocytosis.\(^3\)\(^6\)

Although almost all included studies were of moderate to high quality, there are some limitations. First, although the meta-analysis of observational studies with confounder adjusted analysis helps remove potential bias, a causal relationship needs to be cautiously interpreted because most included studies conducted with cross-sectional design. Second, there are low statistical heterogeneities in the complete analysis of the anemia risk in patients who received ARBs. The potential sources of these heterogeneities include the differences in the diagnosis methodology of anemia, exposure definition (type and dosage of ARBs) and the differences in confounder adjusted methods. However, heterogeneities were insignificant when meta-analyses were limited only to studies with confounder adjusted analysis.

In summary, our meta-analysis demonstrates a significant association between anemia and the use of RAS inhibitors, either ACEIs or ARBs. Hematological parameters should be monitored in patients treated with RAS inhibitors.

**Supplementary material**

**Supplementary material** is available at QJMED online.

**Conflict of interest:** None declared.

**References**


