REVIEW ARTICLE

THE INTERPLAY OF THE ANGIOTENSIN RECEPTOR BLOCKERS AND HAEMATOLOGICAL ABNORMALITIES: INSIGHTS AND IMPLICATIONS

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Antihypertensive medications known as angiotensin receptor blockers (ARBs) have become increasingly popular for treating conditions beyond hypertension. The reason for this widespread use is mainly due to its reno-protective and cardioprotective properties in patients with congestive heart failure and diabetes mellitus. There have been conflicting studies on the relationship between ARBs and haematological abnormalities. Using the supplied search terms, we carried out a thorough search for relevant papers written in English and published before January 2024. All of the studies that met the selection criteria were searched for on PubMed, Cochrane Library, and Google Scholar. Based on the examined data from the searched literature, it has been demonstrated that angiotensin II is essential for the stimulation of erythropoiesis and inhibition of it by drugs such as ARBs can lower haematocrit levels, leading to anaemia. Accordingly, dose reduction or stopping the administration of ARBs could be a choice to correct anaemia. However, such a decision is based on the clinical situation and the requirements for other management options.

Keywords: Angiotensin receptor blockers; Haematological abnormalities; Anaemia

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INTRODUCTION

Renin-angiotensin-aldosterone system (RAS) activation is a key factor in several prevalent clinical disorders, such as hypertension, heart failure, and kidney disease. RAS blockers were initially created to treat hypertension, but in addition to being successful at lowering blood pressure, they are also commonly used because of their potential for protecting the kidneys and the heart, independent of their blood pressure-dropping effects.[1,2] Numerous investigations have discovered a connection between RAS and haematological disorders, such as alterations in the number of red blood cells that cause secondary erythrocytosis. However, it has been demonstrated that angiotensin receptor blockers (ARBs) lower haemoglobin levels in people who are at risk for erythrocytosis. Experimental investigations have shown that RAS blockage lowers haemoglobin and haematocrit levels, presumably because angiotensin II is involved in the release of erythropoietin or because of its direct stimulation of erythroid progenitors.[3–6] Clinical investigations, however, have yielded conflicting findings regarding whether RAS blockers lower haemoglobin levels. Some studies implied that angiotensin-converting enzyme inhibitors (ACEis) have a greater impact on lowering Hb levels than ARBs[7], while other studies suggest the contrary[8]. Thus, the objective of this review is to explore any possible associations between the use of ARBs and haematological abnormalities, including variations in haemoglobin levels and red blood cell synthesis (erythropoiesis), to establish the potential role for ARBs in the onset or treatment of haematological abnormalities by examining the existing researches.

Renin-Angiotensin system

The renin-angiotensin system, or RAS, is a polypeptide hormone system that has been extensively studied and is connected to several physiological and pathological processes. The single precursor of all angiotensin peptides, angiotensinogen (AGT), is created and secreted by the liver. Renin-proteinase, which cleaves AGT to create angiotensin I (Ang-I), is released by the kidneys in response to variations in blood pressure or plasma sodium levels. Ang-I is transformed into Ang-II by the angiotensin-converting enzyme (ACE), a vital part of the RAS with a variety of functions.[9] Angiotensin II stimulates the angiotensin type 1 receptor (AT1-R) and angiotensin type 2 receptor (AT2-R), two different types of G protein-coupled receptors.[10] Additionally, aminopeptidases A and N can further alter Ang-II to create angiotensin III (Ang-III) and angiotensin IV (Ang-IV), respectively. While Ang-IV has its receptor, AT4-R, Ang-III binds to both AT1-R and AT2-R.[9]

The ability of Ang-II to be broken down into angiotensin 1-7 (Ang 1-7) by Ang-converting enzyme 2 is demonstrated. Ang 1-7 molecule interacts with the G protein-coupled receptor Mas (MasR) to counterbalance the cardiovascular impacts of Ang-II.[11,12] Additionally, cathepsin G, CAGE, or chymase can create Ang-II from Ang-I 8 via a different mechanism. Through the AT-1R, Ang-II produces vasoconstriction, raises plasma aldosterone, retains sodium and water, and intensifies thirst and salt cravings. This preserves fluid and salt equilibrium and raises blood pressure as a result. Hypertension in particular is associated with cardiovascular illnesses when the system is de-regulated or hyper-activated.[9] In addition to the classical RAS, numerous organs, including the brain, kidneys, heart, and blood vessels, can locally produce RAS components that can function alone or in conjunction with circulating RAS molecules. Angiotensins made locally are anticipated to influence tissue homeostasis and dysfunction.[13]

Angiotensin Receptors

Angiotensin receptors are essential for many body activities in conjugation with different agents, including the growth of the kidney.[14–16] Both AT1-R and AT2-R are present and remain throughout embryonic life during embryogenesis. At embryonic day 20, AT1-R reaches its peak expression level and is maintained until maturity, but AT2-R is not seen until day 28 of the postnatal period.[17,18] Their expression is noticeably decreased in adult kidneys. While AT2-R also focuses on actively differentiating cortical cells, both receptor types are co-localized in differentiated nephrons and blood vessels.[18] Human kidneys contain the majority of the AT1-R, which has an 8–10-fold higher mRNA expression than AT2-R. AT1-R is normally found in human glomeruli, interlobular arteries, and their surrounding tubule-interstitial fibrous regions. On the other hand, AT2-R is located in large preglomerular vessels of the human cortex and in interlobular endothelial arterial cells of healthy adults.[19] Additionally, Ang-II drives proximal tubule cell proliferation via the AT1-R receptor[20], and it triggers neo-angiogenesis, apoptosis, and tubular cell proliferation through AT2-R[21].

Angiotensin receptor blockers

Angiotensin receptor blockers selectively target and block the AT-1 receptor, resulting in effective inhibition of the harmful effects of angiotensin II. Losartan was the first ARB introduced to the market for hypertension treatment, with subsequent marketing of other ARBs such as valsartan, irbesartan, candesartan, telmisartan, eprosartan, and olmesartan worldwide.[22] The blood pressure-lowering effects of ARBs result from their displacement of angiotensin II from the angiotensin I receptor, thereby they inhibit angiotensin II-induced vasoconstriction, aldosterone release, catecholamine release, arginine vasopressin release, water intake, and hypertrophic response.[23] At therapeutically effective doses, telmisartan exhibits peroxisome proliferator-activated receptor gamma activity, which may have a positive impact on hyperglycemia, independent of renin RAS blockade. Treatment with telmisartan was linked to reduced visceral fat, reduced vascular inflammation, and increased serum adiponectin[24], with decreased growth of cardiovascular (CV) cells[25]. In contrast to valsartan and candesartan, telmisartan and losartan both show platelet anti-aggregatory activity. Moreover, losartan lowers uric acid, a byproduct of purine metabolism linked to the development of hypertension in children as well as increased CV risk and renal disease progression.[26]. As a group, ARBs have strong anti-inflammatory properties through localized inhibition of cytokine synthesis, reduction of leukocyte accumulation, and direct regulation of interactions between leukocytes and endothelium.[27]

Angiotensin receptor blockers and haematopoiesis of red blood cells

Following studies that revealed the manipulation of ACE activity could impede erythropoiesis, it was evident that the involvement of the RAS in erythropoiesis is complicated, encompassing nearly every stage between the hematopoietic stem cell and the fully differentiated erythrocyte. Upon closer examination, it was demonstrated that the activation of the AT1 receptor promoted the development of early erythroid progenitors, which necessitated the presence of erythropoietin (EPO).[28] Furthermore, genetically induced AT1a receptor over-activity in mice resulted in an elevation in haematocrit.[29] On the other hand, when compared to wild-type animals, AT1-receptor-knockout mice exhibit a reduction in haematocrit values.[30] The activating function of AT1 receptors in erythropoiesis carries clinical significance, similar to ACEis, treatment with ARBs was found to impede erythropoiesis in both healthy individuals and patients undergoing haemodialysis.[31]

The precise pathways through which AngII regulates erythropoiesis are still not well understood, however it seems that it has primary impact in the early stages of erythropoiesis.[28,31] Investigators suggest that AngII indirectly affects erythropoiesis by influencing EPO levels or sensitivity.[32,33] The JAK/STAT (signal transducer and activator of transcription) pathway, which is stimulated by AngII and is essential to the erythrocyte-stimulating activity of EPO, is another potential second messenger mechanism that AngII used to alter erythropoiesis.[34,35] Haemoglobin concentrations are influenced by plasma volume, haematocrit/packed cell volume. While the RAS and antidiuretic hormone are acknowledged to play significant role in controlling plasma volume, EPO is

believed to be the primary regulator of red blood cell synthesis. The RAS's function in modulating erythropoiesis is less clear, though. Although the mechanism through which the RAS increases red blood cell mass is not fully known, the most recent research indicates that angiotensin II is essential for controlling erythropoiesis. Angiotensin II may be able to accomplish this by acting as an EPO secretagogue. This happens as a result of a mechanism in which angiotensin II constricts the efferent arteriole, reducing blood flow in the peritubular capillaries, and ultimately causing ischemia in the renal parenchyma. Additionally, angiotensin II can directly affect hypoxia-inducible factor 1, which controls the production of EPO, to enhance the secretion of EPO.[36] In patients with renovascular hypertension, cardiac failure, and non-diabetic hypertension, studies have shown that serum EPO concentrations and renin levels are directly correlated.[37–40] Serum EPO levels were reduced after RAS inactivation by ACEis or ARBs in healthy volunteers, chronic kidney disease (CKD) patients, and patients with heart failure.

However, compared to wild-type controls, serum EPO levels and kidney EPO messenger RNA expression were significantly higher in double-transgenic mice expressing the human renin and angiotensinogen genes. This suggests that angiotensin II may have a role in controlling the production of EPO.[41] The AT1 receptor appears to mediate the stimulatory effect of the RAS on EPO secretion, as losartan has been shown to fully block the EPO over-secretion induced by angiotensin II infusion in healthy volunteers.[42] However, angiotensin II may also act as a direct growth factor for erythroid progenitors by activating specific AT1 receptors on their surface, as demonstrated by *in vitro* experiments conducted by Mrug *et al*.[28] Given that angiotensin II can stimulate the production of red blood cells, therefore, it is not unexpected that this substance might also affect iron metabolism and the function of iron transporters. Rats given angiotensin II led to greater ferritin levels and a buildup of iron in different tissues, including the kidney, heart, and liver, according to Ishizaka *et al*. Losartan, a selective AT1 receptor blocker, could be used to prevent this effect.[43] In human glomerular endothelial cells, angiotensin II enhanced the protein expression of the transferrin receptor, divalent metal transporter 1, and ferroprotein 1, according to research by Tajima *et al*.[44] Additionally, studies on mice revealed that angiotensin II decreased hepcidin levels while increasing the expression of duodenal iron transporters. The effects of pre-treating with ARBs could be enhanced.[45] Therefore, the prevalent use of ARBs, in conjunction with the common occurrence of low-grade inflammation among heart failure patients, may serve as the primary pathophysiological factor responsible for the emergence of iron deficiency in this group.

Angiotensin receptor blockers and haematopoiesis of white blood cells and platelets

Studies have demonstrated that *in vitro*, AngII is capable of inducing the proliferation of mouse bone marrow and human cord blood hematopoietic stem cells (HSCs). This impact is partially mediated by the direct activation of HSCs in the presence of colony-stimulating factor (CSF) and through the stimulation of bone marrow stromal cells. Losartan blocks this effect, indicating that it is mediated by AT1-R. The presence of AT1 receptors in both HSCs and stromal cells is consistent with this dual pathway. Additionally, AngII/AT1 receptor signalling can promote the differentiation and proliferation of bone marrow monocyte lineage cells mediated by monocyte colony-stimulating factor (M-CSF).[46]

By acting on the bone marrow and blood vessels, AngII can play a role in regulating the production of white blood cells. However, under normal physiological conditions, AT1 receptor signalling appears to be of limited importance for haematopoiesis. It has been demonstrated through research on ACE-Knockout mice that the lack of ACE, which is required for the generation of AngII, results in a block in terminal granulopoiesis and a decrease in segmented neutrophils. Even while monocytes and macrophages are present in both ACE-Knockout and AT1 receptor-Knockout mice at normal levels, they show functional immaturity.[47,48] This suggests that the lack of reduction in WBC levels with ARB treatment may be because AngII/AT1 receptor signalling does not play a major role in WBC production under normal physiological conditions. However, it has been shown that under hematopoietic stress conditions, such as chemotherapy or irradiation, AngII/AT1 receptor signalling has noticeable effects. In these situations, infusion of AngII can improve the re-population of BM with HSCs, thereby accelerating the restoration of WBC counts.[47,49]

Concerning platelets, under normal conditions, Ang II counterbalances the antithrombotic properties of the endothelium by inducing platelet activation and promoting platelet aggregation through the AT1-receptors expressed on the surface of platelets. Blocking the action of Ang II using ARBs can potentially have direct anti-platelet effects. These drugs inhibit platelet aggregation, which is thought to be partly due to the inhibition of thromboxane A2 release and improvement of calcium dynamics. This action is evident in several studies.[50,51]

Clinical implication

RAS activation in diabetes could be caused by several different methods. First off, sodium-glucose cotransporters link glucose reabsorption in the

proximal tubule to sodium reabsorption, which decreases sodium delivery to the macula densa and boosts renin release.[52,53] Secondly, experimental evidence suggests that insulin may cause RAS activation in subjects with insulin resistance and hyperinsulinemia, which is common in individuals with metabolic syndrome or diabetes.[54,55] Acute hyperinsulinemia has been shown to elevate renin and circulating Ang II levels even in healthy subjects. Finally, there may be a connection between diabetes, RAS activation, and systemic hypertension via GPR91, a metabolic receptor in the kidney that can cause the activation of the renin-dependent RAS system and subsequent elevation of systemic blood pressure.[56]

It is anticipated that Ang II will increase intraglomerular pressure and filtration fraction while concurrently reducing oxygen delivery to the tubulointerstitial through the post-glomerular peritubular capillary bed since it works as a selective vasoconstrictor for efferent arterioles. Furthermore, Ang II can promote proximal sodium reabsorption, increasing the need for oxygen in tubular cells. As a result, following RAS activation, the tubulointerstitial experiences parenchymal hypoxia, which causes the release of EPO due to a combination of decreased oxygen supply and increased oxygen demand.[57] Additionally, Ang II can directly influence HIFs and promote EPO secretion. Ang II promotes HIF-1 expression in human placental explant cells, both at the mRNA and protein levels.[58] Furthermore, the growth factor Ang II can directly promote the development of erythrocytes in erythroid progenitors in the bone marrow.[57] Hepcidin and iron transporter expression are both changed concurrently, promoting iron uptake and utilization.[45]

For hypertensive, cardiac, and renal patients with T2DM, pharmacologically disrupting the RAS with ACEis or ARBs can have positive effects, according to several seminal research. Medications or treatments that inactivate RAS may likely cause a haematocrit-lowering impact and/or anaemia if RAS up-regulates erythropoiesis as stated above.[42] Significant anaemia is present in ACE or angiotensinogen gene knockout mice, which is treated with Ang II infusion for two weeks.[41,59] The renin-angiotensin system may not significantly affect erythropoiesis in normal or nearly normal circumstances, such as those with simple hypertension and T2DM.[60] RAS may have no discernible effect on erythropoiesis. However, the action of RAS is more obvious in conditions where the bone marrow needs every stimulus to increase erythropoiesis, such as in individuals with severe renal insufficiency, congestive heart failure, or immunosuppression. Giving ACEi or ARB to patients with altitude polycythaemia, post-transplant erythrocytosis, or polycythaemia linked to chronic obstructive pulmonary disease can help normalize haematocrit levels.[6,61,62] An estimated 16% rise in anaemia prevalence was observed over the period from 1979 to 2002, when RAS inhibition became a mainstay of management, according to a community study looking at anaemia and heart failure.[63] RAS inhibition reduced haemoglobin levels in CKD patients by about 0.6–0.9 g/dL, even though no changes in haemoglobin levels were seen in CKD patients on other traditional anti-hypertensive medications.[64]

The majority of patients who have both anaemia and heart failure do not have a discernible underlying cause for their anaemia. Consequently, this condition is referred to as chronic disease anaemia. Anaemia can develop in individuals with heart failure for a variety of reasons. Some of these causes include haemodilution, iron depletion (either absolute or relative), decreased EPO production, pro-inflammatory cytokine activation, aspirin- or anticoagulant-induced blood loss, and uremic toxin-induced bone marrow suppression. Most patients with heart failure do not have iron, B12, or folate deficiency as the main underlying cause of anaemia.[65,66]

There is an increase in pro-inflammatory cytokines, as seen in heart failure and CKD, and decreased haematopoiesis in anaemia may be caused by a large drop in the number of progenitor cells. This might be because pro-inflammatory chemicals in the bone marrow are having a direct effect. In bone marrow culture, the proliferation of burst-forming units-erythroid is suppressed by TNF-alpha and interleukin-6, this is also applied to colony-forming units-erythroid.[67] High amounts of pro-inflammatory substances and inflammation can cause reticulo-endothelial blockade and decrease the uptake of iron by raising serum hepcidin levels. These factors collectively contribute to the development of anaemia.[68,69] It has been speculated for a while that people with CKD may have specific inhibitory uremic toxins present that could affect erythropoiesis. Indoxyl sulphate is one of these toxins and is recognized as a prototype uremic toxin that has received a lot of attention. It can hinder the development of erythroid colonies, interfere with tubular cells' oxygen metabolism, and weaken oxygen-sensing systems, all of which contribute to insufficient *in vitro* EPO production.[70] Additionally, it is negatively correlated with haematocrit values in some clinical studies, although not in all.[71,72] Nevertheless, it is important to note that in patients with heart failure and CKD, the widespread use of RAS inhibition may also contribute to the emergence or progression of anaemia. Therefore, the administration of ARBs could be a potential iatrogenic cause of anaemia in these patients.

Anaemia has a significant and independent prognostic impact, raising the likelihood of hospitalizations and mortality by 20–50% in patients with heart failure with reduced ejection fraction (HFrEF) or Heart failure with preserved ejection fraction (HFpEF).[73–76] The development of hemodynamic and non-hemodynamic compensatory mechanisms that have a detrimental effect on myocardial function and viability is a consequence of decreased tissue oxygenation caused by anaemia.[77]

Through several different pathways, the inactivation of RAS caused by the use of ARBs may contribute to the onset of anaemia. RAS inhibitors can firstly worsen renal function, which can result in uremic toxin buildup, bone marrow suppression, salt and water retention, and haemodilution. Additionally, RAS inhibitors may prevent hemopoiesis by preventing EPO release and preventing angiotensin II from acting directly on erythroid progenitor cells. The natural stem cell suppressor tetrapeptide Ac-SDKP (goralatide), which is degraded more slowly by ACEis in particular, may rise in concentration[78], although the comparable reduction in hematocrit values observed with ARBs suggests that the impact of this oligopeptide on the haematocrit-lowering effect may not be significant. Finally, RAS inhibitors could potentially hurt iron absorption and utilization.[45] Therefore, the inhibition of RAS via the use of ARBs is related to a reduction in haematocrit and/or anaemia in various clinical circumstances. RAS inhibition has been utilized to regulate haematocrit levels in secondary erythrocytosis patients, such as those with post-transplant erythrocytosis, altitude erythrocytosis, and erythrocytosis linked to chronic obstructive pulmonary disease.[62,79] A meta-analysis encompassing seven studies and 29,061 patients demonstrated that the use of RAS inhibitors resulted in a greater than 50% increase in the risk of anaemia in patients.[5] It is worth noting that other smaller studies revealed a slight or no reduction in haematocrit following RAS inhibition.[8,80] It is unclear why the results are inconsistent, but it is possible that patient population variances, variations in the kind and severity of the underlying illness, variations in the type, dosage, and duration of RAS inhibition, as well as variations in study design and statistical analysis, are contributing factors.

Haematocrit readings often fall after RAS blockage, albeit this depends on the medication's dosage. The nadir haematocrit value is typically attained within the first month of treatment and remains steady throughout long-term follow-up. Haematocrit readings may progressively revert to pre-treatment levels for three months after stopping ARB treatment. The patient's clinical situation's severity and the availability of other treatments should be taken into account when deciding whether to change the dosage or withdraw these medications.[81] It has not been determined whether correcting iron deficiency through intravenous iron administration or correcting anaemia using drugs that stimulate erythropoiesis is beneficial for patients with cardiorenal syndrome (CRS) and anaemia.[82,83] Individuals with CKD or heart failure were previously treated with medications that induce erythropoiesis to normalize their haemoglobin levels, but the results did not enhance their cardiovascular prognosis. Similarly, to this, intravenous iron administration to patients with heart failure improved their clinical state but did not lower the death rate.[84]

Although the rate of change in the estimated glomerular filtration rate was marginally greater in the through-collective therapy group after the first six months of the SPRINT study, which involved patients over 50 years old with increased cardiovascular disorders but no diabetes, there was a higher incidence of acute renal failure (2 times more frequent) and the development of CKD (3–4 times more frequent) of the through-collective therapy group. These undesirable renal outcomes in the through-collective therapy group may be attributable to the overuse of diuretics and ACEis or ARBs, which may have an intraglomerular hemodynamic effect.[85,86] However, following the administration of ARBs to patients with cardiac failure, the drop in GFR is typically reversible upon medication discontinuation.

Although the majority of ARBs are predominantly processed in the liver and are not necessarily nephrotoxic medications, care must be taken when administering them to individuals with CRS. The ideal dose of RAS inhibition in these patients has not been studied in a randomized, placebo-controlled experiment. There is a considerable percentage of patients who need a reduction in post-randomization dose, mostly because they are older, have hypotension, hyperkalaemia, or have renal failure, even in cardiac-focused studies that have excluded patients with severe CKD.[87] To effectively block the RAS in patients with CRS, it is best to start them on a low dose of ARBs and progressively increase it, following the 2016 ESC guidelines for heart failure patients. Potassium levels and renal function should be closely monitored. If hyperkalaemia cannot be controlled or baseline creatinine levels rise by more than 20–30%, the ARBs should be temporarily stopped with dose reduction later.[88] Even though ARBs are not inherently nephrotoxic, individuals with CRS should use them with caution because there is no solid trial for the optimum dose of RAS inhibition in CRS patients. Many patients required dose minimization after randomization in cardiac-focused trials that already

exclude individuals with severe CKD, mostly because of advanced age, hypotension, hyperkalaemia, and kidney impairment.[89] Physicians might decide to discontinue ARBs therapy in patients who are approaching end-stage renal disease as a policy for improvement of kidney function levels and transplantation avoidance.[90]

In conclusion, it has been repeatedly demonstrated that anaemia, which is common in patients with CRS, raises hospitalization and mortality rates. RAS inhibition is a crucial component of both cardiovascular and renal disease therapies. However, RAS inhibition can lower haematocrit levels, lead to anaemia, and compromise renal function in patients with CRS since angiotensin II is essential for controlling GFR and stimulating erythropoiesis. The choice to reduce the dose or stop administrating such medications should be based on the clinical condition and the presence of other management options. Preventing cardiovascular complications in patients with CRS is essential, and RAS inhibition can be helpful.

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