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 their 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 July 2023. 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 literatures, it has been demonstrated that angiotensin II is essential for stimulation of erythropoiesis and inhibition of it by drugs such as ARBs can lower haematocrit levels, leading to anaemia. Accordingly, dose reduction or stopping administration of ARBs could be a choice for correction of anaemia. However, such 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 a number of 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 do 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), with an aim 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 a number of 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 own 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 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 surrounded tubule-interstitial fibrous regions. On the other hand, AT2-R is located in large preglomerular vessels of the human cortex and by interlobular endothelial arterial cells of healthy adult.[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 positive impact on hyperglycaemia, 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 via 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 hematopoiesis 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 hematopoiesis. 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 a number of 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.[56,57]

It is anticipated that Ang II will increase intraglomerular pressure and filtration fraction while concurrently reducing oxygen delivery to the tubulointerstitium through the postglomerular 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 tubulointerstitium experiences parenchymal hypoxia, which causes the release of EPO due to a combination of decreased oxygen supply and increased oxygen demand.[58] 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.[59] Furthermore, the growth factor Ang II can directly promote the development of erythrocytes in erythroid progenitors in the bone marrow.[58] 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 a number of 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.[41,60] The renin-angiotensin system may not significantly affect erythropoiesis in normal or nearly normal circumstances, such as those with simple hypertension and T2DM,[61] 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 polycythemia, post-transplant erythrocytosis, or polycythemia linked to chronic obstructive pulmonary disease can help normalize haematocrit levels.[6,62,63] An estimated 16% rise in anaemia prevalence was observed over the period of time from 1979 to 2002, when RAS inhibition became a mainstay of management, according to a community study looking at anaemia and heart failure.[64] 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.[65]

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.[66,67] There is an increase in pro-inflammatory cytokines, as seen in heart failure and CKD, and decreased hematopoiesis 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 applying to colony-forming units-erythroid.[68] 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.[69,70] 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.[71] Additionally, it is negatively correlated with haematocrit values in some clinical studies, although not in all.[72,73] 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).[74–77] 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.[78]

Through a number of 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,[79] although the comparable reduction in haematocrit 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 have an adverse effect on 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.[63,80] 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.[8,81] 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.[82] 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.[83,84] 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. Similar to this, intravenous iron administration to patients with heart failure improved their clinical state but did not lower death rate.[85]

Although the rate of change in 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.[86,87] 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 renal failure, even in cardiac focused studies that have excluded patients with severe CKD.[88] 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.[89] 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 a 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.[90] 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.[91]

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.

Conflict of interest

The authors declare that they have no conflicting interest.

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REFERENCES

1. Brugts JJ, Boersma E, Chonchol M, Deckers JW, Bertrand M, Remme WJ, *et al*. The cardioprotective effects of the angiotensin-converting enzyme inhibitor perindopril in patients with stable coronary artery disease are not modified by mild to moderate renal insufficiency: insights from the EUROPA trial. J Am Coll Cardiol 2007;50(22):2148–55.
2. Mahmood IH, Abed MN, Merkhan MM. Effects of blocking of angiotensin system on the prevalenceof metabolic syndrome in type 2 diabetic patients. Pak J Med Sci 2012;29(1):140–3.
3. Marusic-Vrsalovic M, Dominis M, Jaksic B, Kusec R. Angiotensin I-converting enzyme is expressed by erythropoietic cells of normal and myeloproliferative bone marrow. Br J Haematol 2003;123(3):539–41.
4. Marathias K, Agroyannis B, Mavromoustakos T, Matsoukas J, Vlahakos D. Hematocrit-lowering effect following inactivation of renin-angiotensin system with angiotensin converting enzyme inhibitors and angiotensin receptor blockers. Curr Top Med Chem 2004;4(4):483–6.
5. Cheungpasitporn W, Thongprayoon C, Chiasakul T, Korpaisarn S, Erickson SB. Renin-angiotensin system inhibitors linked to anemia: a systematic review and meta-analysis. QJM 2015;108(11):879–84.
6. Plata R, Cornejo A, Arratia C, Anabaya A, Perna A, Dimitrov BD, *et al*. Angiotensin-converting-enzyme inhibition therapy in altitude polycythaemia: A prospective randomised trial. Lancet 2002;359(9307):663–6.
7. Winkelmayer WC, Kewalramani R, Rutstein M, Gabardi S, Vonvisger T, Chandraker A. Pharmacoepidemiology of anemia in kidney transplant recipients. J Am Soc Nephrol 2004;15(5):1347–52.
8. Inoue A, Babazono T, Iwamoto Y. Effects of the Renin-Angiotensin system blockade on haemoglobin levels in type 2 diabetic patients with chronic kidney disease. Am J Hypertens 2008;21(3):317–22.
9. Fountain JH, Lappin SL. Physiology, Renin Angiotensin System. StatPearls. 2022.
10. Tetzner A, Gebolys K, Meinert C, Klein S, Uhlich A, Trebicka J, *et al*. G-Protein-Coupled Receptor MrgD Is a Receptor for Angiotensin-(1-7) Involving Adenylyl Cyclase, cAMP, and Phosphokinase A. Hypertension 2016;68(1):185–94.
11. Patel VB, Zhong JC, Grant MB, Oudit GY. Role of the ACE2/angiotensin 1-7 axis of the renin-angiotensin system in heart failure. Circ Res 2016;118(8):1313–26.
12. Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, Stagliano N, *et al*. UltraRapid Communication A Novel Angiotensin-Converting Enzyme – Related to Angiotensin 1-9. Circ Res 2000;87:e1–9.
13. Zhuo JL, Li XC. New insights and perspectives on intrarenal renin-angiotensin system: Focus on intracrine/intracellular angiotensin II. Peptides 2011;32(7):1551–65.
14. Villapol S, Saavedra JM. Neuroprotective Effects of Angiotensin Receptor Blockers. Am J Hypertens 2015;28(3):289–99.
15. Alnori H, Alassaf FA, Alfahad M, Qazzaz ME, Jasim M, Abed MN. Vitamin D and Immunoglobulin E Status in Allergic Rhinitis Patients Compared to Healthy People. J Med Life 2020;13(4):463–8.
16. Yosypiv IV. Renin-angiotensin system in mammalian kidney development. Pediatr Nephrol 2021;36(3):479–89.
17. Bagby SP, Lebard LS, Luo Z, Ogden BE, Corless C, Mcpherson ED, *et al*. ANG II AT 1 and AT 2 receptors in developing kidney of normal microswine. Am J Physiol Ren Physiol 2002;283(4):755–64.
18. Norwood VF, Craig MR, Harris JM, Gomez RA. Differential expression of angiotensin II receptors during early renal morphogenesis. Am J Physiol 1997;272(2 Pt 2):R662–8.
19. Schrankl J, Fuchs M, Broeker K, Daniel C, Kurtz A, Wagner C. Localization of angiotensin II type 1 receptor gene expression in rodent and human kidneys. Am J Physiol Renal Physiol 2021;320(4):F644–53.
20. Li XC, Zhuo JL. Recent Updates on the Proximal Tubule Renin-Angiotensin System in Angiotensin II-Dependent Hypertension. Curr Hypertens Rep 2016;18(8):63.
21. Pei N, Mao Y, Wan P, Chen X, Li A, Chen H, *et al*. Angiotensin II type 2 receptor promotes apoptosis and inhibits angiogenesis in bladder cancer. J Exp Clin Cancer Res 2017;36(1):77.
22. de la Sierra A. Angiotensin receptor blockers in hypertension and cardiovascular diseases. Cardiovasc Hematol Agents Med Chem 2006;4(1):67–73.
23. Steckelings UM, Artuc M, Wollschläger T, Wiehstutz S, Henz BM. Angiotensin-converting enzyme inhibitors as inducers of adverse cutaneous reactions. Acta Derm Venereol 2001;81(5):321–5.
24. Raimondo DDi, Tuttolomondo A, Buttà C, Miceli S, Licata G, Pinto A. Effects of ACE-Inhibitors and Angiotensin Receptor Blockers on Inflammation. Curr Pharm Des 2012;18(28):4385–413.
25. Benson SC, Pershadsingh HA, Ho CI, Chittiboyina A, Desai P, Pravenec M, *et al*. Identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPARγ–modulating activity. Hypertension 2004;43(5):993–1002.
26. Feig DI, Soletsky B, Johnson RJ. Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. JAMA 2008;300(8):924–32.
27. Silveira KD, Coelho FM, Vieira AT, Barroso LC, Queiroz CM, Costa VV, *et al*. Mechanisms of the anti-inflammatory actions of the angiotensin type1 receptor antagonist losartan in experimental models of arthritis. Peptides 2013;46:53–63.
28. Mrug M, Stopka T, Julian BA, Prchal JF, Prchal JT. Angiotensin II stimulates proliferation of normal early erythroid progenitors. J Clin Invest 1997;100(9):2310.
29. Kato H, Ishida J, Imagawa S, Saito T, Suzuki N, Matsuoka T, *et al*. Enhanced erythropoiesis mediated by activation of the renin-angiotensin system via angiotensin II type 1a receptor. FASEB J 2005;19(14):2023–5.
30. Doan TN, Gletsu N, Cole J, Bernstein KE. Genetic manipulation of the renin-angiotensin system. Curr Opin Nephrol Hypertens 2001;10(4):483–91.
31. Naito M, Kawashima A, Akiba T, Takanashi M, Nihei H. Effects of an angiotensin II receptor antagonist and angiotensin-

converting enzyme inhibitors on burst forming units-erythroid in chronic hemodialysis patients. Am J Nephrol 2003;23(5):287–93.
32. Jelkmann W. Regulation of erythropoietin production. J Physiol 2011;589(Pt 6):1251.
33. Nakamoto H, Kanno Y, Okada H, Suzuki H. Erythropoietin resistance in patients on continuous ambulatory peritoneal dialysis. Adv Perit Dial 2004;20:111–6.
34. Hu X, Li J, Fu M, Zhao X, Wang W. The JAK/STAT signaling pathway: from bench to clinic. Signal Transduct Target Ther 2021;6(1):1–33.
35. Yasuoka Y, Izumi Y, Fukuyama T, Inoue H, Oshima T, Yamazaki T, *et al*. Effects of Angiotensin II on Erythropoietin Production in the Kidney and Liver. Molecules 2021;26(17):5399.
36. Iriyama T, Wang W, Parchim NF, Song A, Blackwell SC, Sibai BM, *et al*. Hypoxia-independent upregulation of placental hypoxia inducible factor-1α gene expression contributes to the pathogenesis of preeclampsia. Hypertension 2015;65(6):1307–15.
37. An JN, Hwang JH, Lee JP, Chin HJ, Kim S, Kim DK, *et al*. The Decrement of Haemoglobin Concentration with Angiotensin II Receptor Blocker Treatment Is Correlated with the Reduction of Albuminuria in Non-Diabetic Hypertensive Patients: Post-Hoc Analysis of ESPECIAL Trial. PLoS One 2015;10(6):e0128632.
38. Singer CE, Vasile CM, Popescu M, Popescu AIS, Marginean IC, Iacob GA, *et al*. Role of Iron Deficiency in Heart Failure-Clinical and Treatment Approach: An Overview. Diagnostics (Basel) 2023;13(2):304.
39. Westenbrink BD, Visser FW, Voors AA, Smilde TDJ, Lipsic E, Navis G, *et al*. Anaemia in chronic heart failure is not only related to impaired renal perfusion and blunted erythropoietin production, but to fluid retention as well. Eur Heart J 2007;28(2):166–71.
40. Jensen JD, Eiskjær H, Bagger JP, Pedersen EB. Elevated level of erythropoietin in congestive heart failure relationship to renal perfusion and plasma renin. J Intern Med 1993;233(2):125–30.
41. Kato H, Ishida J, Matsusaka T, Ishimaru T, Tanimoto K, Sugiyama F, *et al*. Erythropoiesis and Blood Pressure Are Regulated via AT1 Receptor by Distinctive Pathways. PLoS One 2015;10(6):e0129484.
42. Gossmann J, Burkhardt R, Harder S, Lenz T, Sedlmeyer A, Klinkhardt U, *et al*. Angiotensin II infusion increases plasma erythropoietin levels via an angiotensin II type 1 receptor-dependent pathway. Kidney Int 2001;60(1):83–6.
43. Ishizaka N, Saito K, Noiri E, Sata M, Ikeda H, Ohno A, *et al*. Administration of ANG II induces iron deposition and upregulation of TGF-beta1 mRNA in the rat liver. Am J Physiol Regul Integr Comp Physiol 2005;288(4):R1063–70.
44. Tajima S, Tsuchiya K, Horinouchi Y, Ishizawa K, Ikeda Y, Kihira Y, *et al*. Effect of angiotensin II on iron-transporting protein expression and subsequent intracellular labile iron concentration in human glomerular endothelial cells. Hypertens Res 2010;33(7):713–21.
45. Tajima S, Ikeda Y, Enomoto H, Imao M, Horinouchi Y, Izawa-Ishizawa Y, *et al*. Angiotensin II alters the expression of duodenal iron transporters, hepatic hepcidin, and body iron distribution in mice. Eur J Nutr 2015;54(5):709–19.
46. Rodgers KE, Xiong S, Steer R, diZerega GS. Effect of angiotensin II on hematopoietic progenitor cell proliferation. Stem Cells 2000;18(4):287–94.
47. Shen XZ, Bernstein KE. The peptide network regulated by angiotensin converting enzyme (ACE) in hematopoiesis. Cell Cycle 2011;10(9):1363.
48. Cao DY, Saito S, Veiras LC, Okwan-Duodu D, Bernstein EA, Giani JF, *et al*. Role of angiotensin-converting enzyme in myeloid cell immune responses. Cell Mol Biol Lett 2020;25(1):1–12.
49. Kim S, Zingler M, Harrison JK, Scott EW, Cogle CR, Luo D, *et al*. Angiotensin II Regulation of Proliferation, Differentiation and Engraftment of Hematopoietic Stem Cells. Hypertension 2016;67(3):574.
50. Lo Â Pez-Farre A, Sa Â Nchez De Miguel L, Ân MM, Jime Ânez A, Lopez-Bloya A, Go Â Mez J, *et al*. Angiotensin II AT1 receptor antagonists and platelet activation. Nephrol Dial Transplant 2001;16(Suppl 1):45–9.
51. Montezano AC, Nguyen Dinh Cat A, Rios FJ, Touyz RM. Angiotensin II and vascular injury. Curr Hypertens Rep 2014;16(6):431.
52. Ahmed GM, Abed MN, Alassaf FA. An overview of the effects of sodium-glucose co-transporter-2 inhibitors on haematological parameters in diabetic patients. Iraqi J Pharm 2023;20(1):65–71.
53. Alicic RZ, Neumiller JJ, Johnson EJ, Dieter B, Tuttle KR. Sodium–Glucose Cotransporter 2 Inhibition and Diabetic Kidney Disease. Diabetes 2019;68(2):248–57.
54. Shinozaki K, Ayajiki K, Nishio Y, Sugaya T, Kashiwagi A, Okamura T. Evidence for a causal role of the renin-angiotensin system in vascular dysfunction associated with insulin resistance. Hypertension 2004;43(2):255–62.
55. Underwood PC, Adler GK. The Renin Angiotensin Aldosterone System and Insulin Resistance in Humans. Curr Hypertens Rep 2013;15(1):59.
56. Alassaf FA, Jasim MHM, Alfahad M, Qazzaz ME, Abed MN, Thanoon IA. Effects of bee propolis on FBG, HbA1c and insulin resistance in healthy volunteers. Turk J Pharm Sci 2021;18(4):405–9.
57. Peti-Peterdi J, Kang JJ, Toma I. Activation of the renal renin–angiotensin system in diabetes—new concepts. Nephrol Dial Transplant 2008;23(10):3047.
58. Vlahakos DV, Marathias KP, Madias NE. The role of the renin-angiotensin system in the regulation of erythropoiesis. Am J Kidney Dis 2010;56(3):558–65.
59. Iriyama T, Wang W, Parchim NF, Song A, Blackwell SC, Sibai BM, *et al*. Hypoxia-independent upregulation of placental hypoxia inducible factor-1α gene expression contributes to the pathogenesis of preeclampsia. Hypertenssion 2015;65(6):1307–15.
60. Cole J, Ertoy D, Lin H, Sutliff RL, Ezan E, Guyene TT, *et al*. Lack of angiotensin II-facilitated erythropoiesis causes anemia in angiotensin-converting enzyme-deficient mice. J Clin Invest 2000;106(11):1391–8.
61. Raptis AE, Bacharaki D, Mazioti M, Marathias KP, Markakis KP, Raptis SA, *et al*. Anemia due to coadministration of renin-angiotensin-system inhibitors and PPARγ agonists in uncomplicated diabetic patients. Exp Clin Endocrinol Diabetes 2012;120(7):416–9.
62. Alzoubi B, Kharel A, Machhi R, Aziz F, Swanson KJ, Parajuli S. Post-transplant erythrocytosis after kidney transplantation: A review. World J Transplant 2021;11(6):220–30.
63. Vlahakos DV, Marathias KP, Kosmas EN. Losartan reduces hematocrit in patients with chronic obstructive pulmonary disease and secondary erythrocytosis. Ann Intern Med 2001;134(5):426–7.
64. Dunlay SM, Weston SA, Redfield MM, Killian JM, Roger VL. Anemia and heart failure: a community study. Am J Med 2008;121(8):726–32.
65. Kamper AL, Nielsen OJ. Effect of enalapril on haemoglobin and serum erythropoietin in patients with chronic nephropathy. Scand J Clin Lab Invest 1990;50(6):611–8.
66. Witte KKA, Desilva R, Chattopadhyay S, Ghosh J, Cleland JGF, Clark AL. Are hematinic deficiencies the cause of anemia in chronic heart failure? Am Heart J 2004;147(5):924–30.
67. Nanas JN, Matsouka C, Karageorgopoulos D, Leonti A, Tsolakis E, Drakos SG, *et al*. Etiology of anemia in patients with advanced heart failure. J Am Coll Cardiol 2006;48(12):2485–9.
68. Macdougall IC, Cooper AC. Hyporesponsiveness to erythropoietic therapy due to chronic inflammation. Eur J Clin

Invest 2005;35(Suppl 3):32–5.
69. Iversen PO, Woldbaek PR, Tønnessen T, Christensen G. Decreased hematopoiesis in bone marrow of mice with congestive heart failure. Am J Physiol Regul Integr Comp Physiol 2002;282(1):R166–72.
70. Jankowska EA, Malyszko J, Ardehali H, Koc-Zorawska E, Banasiak W, Von Haehling S, *et al*. Iron status in patients with chronic heart failure. Eur Heart J 2013;34(11):827–34.
71. Chiang CK, Tanaka T, Inagi R, Fujita T, Nangaku M. Indoxyl sulfate, a representative uremic toxin, suppresses erythropoietin production in a HIF-dependent manner. Lab Invest 2011;91(11):1564–71.
72. Huang JY, Hsu CW, Yang CW, Hung CC, Huang WH. Role of anuria in the relationship between indoxyl sulfate and anemia in peritoneal dialysis patients. Ther Clin Risk Manag 2016;12:1797–803.
73. Bataille S, Pelletier M, Sallée M, Berland Y, McKay N, Duval A, *et al*. Indole 3-acetic acid, indoxyl sulfate and paracresyl-sulfate do not influence anemia parameters in hemodialysis patients. BMC Nephrol 2017;18(1):251.
74. Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: insights from a cohort of 12 065 patients with new-onset heart failure. Circulation 2003;107(2):223–5.
75. Anand IS, Kuskowski MA, Rector TS, Florea VG, Glazer RD, Hester A, *et al*. Anemia and change in haemoglobin over time related to mortality and morbidity in patients with chronic heart failure: results from Val-HeFT. Circulation 2005;112(8):1121–7.
76. Go AS, Yang J, Ackerson LM, Lepper K, Robbins S, Massie BM, *et al*. Haemoglobin level, chronic kidney disease, and the risks of death and hospitalization in adults with chronic heart failure: the Anemia in Chronic Heart Failure: Outcomes and Resource Utilization (ANCHOR) Study. Circulation 2006;113(23):2713–23.
77. Mozaffarian D, Nye R, Levy WC. Anemia predicts mortality in severe heart failure: The prospective randomized amlodipine survival evaluation (PRAISE). J Am Coll Cardiol 2003;41(11):1933–9.
78. Sîrbu O, Floria M, Dascalita P, Stoica A, Adascalitei P, Sorodoc V, *et al*. Anemia in heart failure - from guidelines to controversies and challenges. Anatol J Cardiol 2018;20(1):52–9.
79. Azizi M, Junot C, Ezan E, Ménard J. Angiotensin I-converting enzyme and metabolism of the haematological peptide N-acetyl-seryl-aspartyl-lysyl-proline. Clin Exp Pharmacol Physiol 2001;28(12):1066–9.
80. Vlahakos DV, Marathias KP, Agroyannis B, Madias NE. Posttransplant erythrocytosis. Kidney Int 2003;63(4):1187–94.
81. Salzberg DJ, Karadsheh FF, Haririan A, Reddivari V, Weir MR. Specific management of anemia and hypertension in renal transplant recipients: influence of renin-angiotensin system blockade. Am J Nephrol 2014;39(1):1–7.
82. Vlahakos D V., Tsioufis C, Manolis A, Filippatos G, Marathias KP, Papademetriou V, *et al*. Inhibition of the renin-angiotensin system in the cardiorenal syndrome with anaemia: a double-edged sword. J Hypertens 2019;37(11):2145–53.
83. Drüeke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, *et al*. Normalization of Haemoglobin Level in Patients with Chronic Kidney Disease and Anemia. N Engl J Med 2006;20(16):2071–84.
84. Swedberg K, Young JB, Anand IS, Cheng S, Desai AS, Diaz R, *et al*. Treatment of anemia with darbepoetin alfa in systolic heart failure. N Engl J Med 2013;368(13):1210–9.
85. Jankowska EA, Tkaczyszyn M, Suchocki T, Drozd M, von Haehling S, Doehner W, *et al*. Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials. Eur J Heart Fail. 2016 Jul;18(7):786–95.
86. Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, *et al*. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med 2015;373(22):2103–16.
87. Cheung AK, Rahman M, Reboussin DM, Craven TE, Greene T, Kimmel PL, *et al*. Effects of Intensive BP Control in CKD. J Am Soc Nephrol 2017;28(9):2812–23.
88. Vardeny O, Claggett B, Packer M, Zile MR, Rouleau J, Swedberg K, *et al*. Efficacy of sacubitril/valsartan vs. enalapril at lower than target doses in heart failure with reduced ejection fraction: the PARADIGM-HF trial. Eur J Heart Fail 2016;18(10):1228–34.
89. Yamada S, Inaba M. Potassium Metabolism and Management in Patients with CKD. Nutrients. 2021;13(6).
90. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? Arch Intern Med 2000;160(5):685–93.
91. Burnier M. Renin-Angiotensin System Blockade in Advanced Kidney Disease: Stop or Continue? Kidney Med 2020;2(3):231–4.

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