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The potential therapeutic use of renin-angiotensin system inhibitors in the treatment of inflammatory diseases

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Abstract

Inflammation is a normal part of the immune response to injury or infection but its dysregulation promotes the development of inflammatory diseases, which cause considerable human suffering. Non-steroidal anti-inflammatory agents (NSAIDs) are the most commonly prescribed agents for the treatment of inflammatory diseases but they are accompanied by a broad range of side effects, including gastrointestinal and cardiovascular events. The renin-angiotensin system (RAS) is traditionally known for its role in blood pressure regulation. However, there is increasing evidence that RAS signalling is also involved in the inflammatory response associated with several disease states. Angiotensin II increases blood pressure by binding to angiotensin type 1 (AT₁) receptor, and direct renin inhibitors (DRIs), angiotensin-converting enzyme (ACE) inhibitors and AT₁ receptor blockers (ARBs) are clinically used as anti-hypertensive agents. Recent data suggest that these drugs also have anti-inflammatory effects. Therefore, this review summarizes these recent findings for the efficacy of two of the most widely used antihypertensive drug classes, ACE inhibitors and ARBs, to reduce or treat inflammatory diseases such as atherosclerosis, arthritis, steatohepatitis, colitis, pancreatitis and nephritis.

Keywords: Renin-angiotensin system; angiotensin-converting enzyme inhibitors; angiotensin receptor blockers; inflammatory diseases.

1. Introduction

Inflammation is a normal part of the immune response to injury or infection characterized by redness, heat, swelling and pain (Wallach et al., 2014). When this regulation fails, inflammation then promotes the development of inflammatory diseases, which cause considerable morbidity. Chronic inflammatory conditions cause substantial physical and mental disabilities, and the treatment of these diseases remains a therapeutic challenge for efficacy and safety reasons (Michetti et al., 2005; Nurmohamed and Dijkmans, 2005). It has been reported that non-steroidal anti-inflammatory agents (NSAIDs) are the most commonly prescribed agents for the treatment of inflammatory diseases (Papich and Messenger, 2015). However, NSAIDs are associated with a broad range of side effects, that include gastrointestinal (GI) and cardiovascular events, increased blood pressure, renal toxicity, and deterioration of congestive heart failure (Sostres et al., 2013). Thus, novel treatment modalities, with fewer side effects, and greater patient satisfaction are required for improvement of therapy.

The renin-angiotensin system (RAS) is best known for its role in blood pressure regulation through changes in peripheral vascular resistance and fluid and electrolyte balance (Peach, 1977). According to this traditional view, kidney juxtaglomerular cells secrete renin, which converts angiotensinogen (the main precursor peptide of RAS) to angiotensin I (Ang I). This is then cleaved by angiotensin converting enzyme (ACE) originating from the lung and kidney to generate Ang II (the main effector peptide of RAS) (Castrop et al., 2010). Ang II exerts its physiological effects by binding to two pharmacologically distinct G-protein coupled receptors, Ang II type 1 (AT₁) and type 2 (AT₂) receptors (Timmermans et al., 1992). Since Ang II increases blood pressure via binding to AT₁ receptor, direct renin inhibitors (DRIs), ACE inhibitors and AT₁ receptor blockers (ARBs) are clinically used as anti-hypertensive agents (Heran et al., 2008a; Heran et al., 2008b; Webb et al., 2010).

Interestingly, there is now increasing evidence that RAS signalling also induces inflammatory responses in several disease states (Mann, 2002; Marchesi et al., 2008;

Montecucco et al., 2009). Ang II stimulation of AT1 receptor, activates nuclear factor (NF)- κ B, which leads to the production of pro-inflammatory cytokines, chemokines and adhesion molecules by resident cells, thereby amplifying the inflammatory responses (Alvarez et al., 2004; Han et al., 2010; Piqueras et al., 2000). Furthermore, the activation of RAS, particularly the two key enzymes renin and ACE, have been implicated in the pathogenesis of several inflammatory diseases (Cobankara et al., 2005; Sata and Fukuda, 2010; Shi et al., 2016). Preclinical and clinical experiments have revealed that pharmacological blockade of the RAS with ACE inhibitors and ARBs is able to diminish the expression of inflammatory mediators and is effective in the treatment of pro-inflammatory diseases such as atherosclerosis, rheumatoid arthritis, steato-hepatitis, colitis, pancreatitis and nephritis (Chen et al., 2008; Flammer et al., 2008; Kuno et al., 2003; Lonn et al., 2001; Nagib et al., 2013; Yokohama et al., 2004). The aim of the present review is to summarize the evidence regarding the efficacy of RAS pharmacological inhibitors in the treatment of inflammatory diseases.

2. Renin-angiotensin system blockers

Blockade of the RAS may be accomplished using DRIs, ACE inhibitors or ARBs. ACE inhibitors and ARBs are commonly used as antihypertensive agents but are also useful in the treatment of other disease states such as chronic kidney disease, chronic heart failure, and myocardial infarction, in which the RAS plays a significant role (Remuzzi et al., 2005; Sleight, 2002; Zucker et al., 2014). These drugs exert their pharmacological effects by preventing the downstream activity of Ang II via either decreased production (ACE inhibitors) or receptor inhibition (ARBs). In 2007, the first-in-class direct renin inhibitor, aliskiren, was approved as an antihypertensive drug with a new strategy in blocking the RAS (Maibaum et al., 2007). DRIs decrease the plasma renin activity by binding to its active sites and inhibit the conversion of angiotensinogen to Ang I. Currently, data regarding the efficacy of DRIs in reducing blood pressure are limited and this class of RAS blockers will not be discussed further in this review.

2.1. Angiotensin-converting-enzyme (ACE) inhibitors

ACE inhibitors can be classified into three main chemical classes according to the zinc ion ligand of ACE: i) sulfhydryl-containing ACE inhibitors, structurally related to Captopril (e.g., Alacepril, Fentiapril, Pivalpril, and Zofenopril); ii) dicarboxyl-containing ACE inhibitors, structurally related to Enalapril (e.g., Benazepril, Cilazapril, Indolapril, Indalapril, Lisinopril, Moexipril, Pentopril, Perindopril, Quinapril, Ramipril, and Spirapril); and iii) phosphorus-containing ACE inhibitors structurally related to Fosinopril (Jackson, 2006; Salvetti, 1990). The first ACE inhibitor, Captopril (Capoten), was approved by the Food and Drug Administration (FDA) in 1981. Currently, 9 other ACE inhibitors including Benazepril (Lotensin), Enalapril/Enalaprilat (Vasotec oral and injectable), Fosinopril (Monopril), Lisinopril (Zestril and Prinivil), Moexipril (Univasc), Perindopril (Aceon), Quinapril (Accupril), Ramipril (Altace), and Trandolapril (Mavik) are also approved for therapeutic use in United States (FDA).

2.2. Angiotensin receptor blockers (ARB)

At least seven ARBs are currently available in the US for clinical use. Losartan became the first approved ARB in 1995, followed by six others, Valsartan (Diovan), Candesartan (Atacand), Irbesartan (Avapro), Telmisartan (Micardis), Olmesartan (Benicar) and Eprosartan (Teveten) (Hernández-Hernández et al., 2002). Regarding their chemical structure, five ARBs (Valsartan, Candesartan, Irbesartan, Olmesartan, and Losartan) belong to the biphenyl-tetrazole class. Telmisartan and Candesartan have a common benzimidazole group and the other ARB (Eprosartan) has a nonbiphenyl, nontetrazole chemical structure (Taylor et al., 2011). All ARBs except Irbesartan share a free carboxylic acid group.

3. RAS pharmacological inhibitors in the treatment of inflammatory diseases

In the following section, we summarize the existing research that explores the therapeutic efficacy of RAS pharmacological inhibitors in the treatment of inflammatory diseases including atherosclerosis, arthritis, steatohepatitis, colitis, pancreatitis and nephritis.

The anti-inflammatory effects of both ACE inhibitors and ARBs that have been reported in clinical trials are summarized in Table 1.

3.1. Atherosclerosis

Atherosclerosis is an inflammatory response of the arterial wall to the plaque, which is associated with high morbidity and mortality (Pagidipati and Gaziano, 2013). Recent evidence suggests that RAS plays a crucial role in the pathogenesis of atherosclerosis (Montecucco et al., 2009; Sata and Fukuda, 2010). Moreover, it has been found that Ang II has the potential to promote atherosclerotic lesions in a murine model of atherosclerosis (ApoE deficient mice) (Daugherty et al., 2000). Thus, pharmacological inhibition of RAS appears to interfere with development and progression of atherosclerosis.

3.1.1. ACE inhibitors in the treatment of atherosclerosis

The anti-inflammatory and antiatherogenic effects of ACE inhibitors, alone or in combination with other drugs, have been investigated in previous preclinical (Chen et al., 2003; Da Cunha et al., 2005; Hayek et al., 1999; Hayek et al., 2002; Hernández-Presa et al., 1998; Husain et al., 2010; Knowles et al., 2000; Li et al., 2015a; Ochiai et al., 2002; Schlimmer et al., 2011; Shimozawa et al., 2004; Yang et al., 2013) and clinical studies (Ceconi et al., 2009; Han et al., 2012; Lonn et al., 2001; McMurray et al., 2006; Mitrovic et al., 2005; Zanchetti et al., 2004). Shimozawa et al., showed that treatment of human aortic endothelial cells (HAECs) with alacepril inhibited the expression of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) and reduced the adhesion of monocyte following treatment with 7-ketocholesterol or tumor necrosis factor (TNF)- α -stimulated HAECs (Shimozawa et al., 2004). Quinaprilat treatment was shown to reduce the activation of NF- κ B, the surface expression of VCAM-1, the production of monocyte chemoattractant protein-1 (MCP-1) and interleukin (IL)-6, and the number of mononuclear leukocytes adhering to endothelial cells induced by TNF- α and oxidized low-density lipoprotein (Ox-LDL). These antiatherogenic effects of quinaprilat were suggested to be due to increased production of endothelial nitric

oxide resulting from activated endothelial nitric oxide synthase (eNOS) (Ochiai et al., 2002). In apolipoprotein (Apo) E-deficient mice, enalapril treatment (25 mg/kg/day) prevented the Ang II-induced over-expression of adhesion molecules (E-selectin, ICAM-1 and VCAM-1) and chemokines MCP-1 in the aorta, while up-regulated the expression of potential anti-inflammatory transcription factors peroxisome proliferator-activated receptors (PPARs)- α and - γ , suggesting the role of Ang II-independent mechanisms in the anti-inflammatory and antiatherogenic effects of ACE inhibitors (Da Cunha et al., 2005). Treatment of ApoE-deficient atherosclerotic mice with enalapril ameliorated the inflammatory and oxidative injury by restoring glutathione (GSH) levels and CuZn-SOD and eNOS protein expression and by decreasing MCP-1, TNF- α , cyclooxygenase (COX)-2, NADPH oxidase subunit p22^{phox}, manganese superoxide dismutase (Mn-SOD) and inducible NOS protein expressions, as well as malondialdehyde (MDA) levels. However, the combination of paricalcitol and enalapril was more efficacious in aortic inflammatory and oxidative injury (Husain et al., 2010). Furthermore, treatment with enalapril interrupted the cycle of atheroma formation and kidney damage in mice that were atherosclerotic and hypertensive due to lack of ApoE and eNOS. The observed linear relationship between lesion size and blood pressure suggests an important role of controlling hypertension in preventing atherosclerotic disease (Knowles et al., 2000). Hayek et al. also reported that the anti-atherogenic effects of fosinopril in ApoE-deficient atherosclerotic mice were mainly due to blood pressure reduction as well as direct inhibition of Ang II actions in the arterial wall such as the inhibition of LDL oxidation (Hayek et al., 1999). However, Schlimmer and colleagues reported that the beneficial effects of telmisartan and ramipril on endothelial function of aortic and cavernosal tissues in ApoE-deficient mice appear to be largely blood pressure-independent and are associated with a reduction of oxidative stress as well as expression of eNOS (Schlimmer et al., 2011). The administration of ramipril to ApoE-deficient mice with already advanced atherosclerosis was shown to block the progression of the atherosclerotic lesion build-up through inhibition of oxidized LDL uptake by macrophages (Hayek et al., 2002). In a study investigating the effects of imidapril on inflammatory vascular injury, it was demonstrated that not only direct inhibition of Ang II

production but also activation of the bradykinin-NO system is involved in the beneficial effects of ACE inhibitors on vascular remodeling (Chen et al., 2003). In a rabbit model of atherosclerosis, fosinopril treatment significantly decreased the atherosclerotic plaque and inhibited the increased expression of Toll-like receptor (TLR)-4 and NF- κ B. Yang et al. suggested that ACE inhibitor has the potential to be considered as a new anti-atherosclerotic drug (Yang et al., 2013). Hernández-Presa and colleagues showed that treatment of atherosclerotic rabbits with quinapril results in the attenuation of several parameters associated with inflammation including IL-8 and MCP-1 within the atherosclerotic lesions, which are controlled by NF- κ B (Hernández-Presa et al., 1998). In another study, treatment of atherosclerotic rats with captopril (10, 20 mg/kg/day) inhibited the maturation of dendritic cells (DCs) and maintained their tolerogenic property, which is associated with DC anti-atherosclerosis activity. Moreover, captopril treatment promoted IL-10 and transforming growth factor (TGF)- β production while decreased that of IL-6 and IL-12 in splenic DCs (Li et al., 2015a). Fukuda et al. found that the inhibition of RAS by either ACE inhibitor or ARB attenuates peri-adventitial inflammation and reduces atherosclerotic lesion formation. However, ACE inhibitors and ARBs may act differently with potential synergistic effects (Fukuda et al., 2009). Furthermore, it has been reported that the co-administration of ACE inhibitor (quinapril) and statin (atorvastatin) would exert a synergistic effect on vascular inflammation, which individual treatment is not able to modify (Oubina et al., 2003). Grothusen et al. showed that combination treatment with an ACE inhibitor (ramipril or telmisartan) and statin (atorvastatin) might have additive effects on cardiovascular inflammatory markers such as IL-6 even in the absence of lipid-reduction (Grothusen et al., 2005). The anti-inflammatory effects of ACE inhibitors observed in preclinical studies are reported in Table 2.

In a clinical trial, 732 patients aged 55 years and over, who had vascular disease or diabetes were randomly assigned to receive ramipril 2.5 mg/day or 10 mg/day and vitamin E 400 IU/day or their matching placebos. Based on the findings reported by Lonn et al., long-term treatment with ramipril, but not vitamin E, had a beneficial effect on atherosclerosis

progression (Lonn et al., 2001). In an uncontrolled, open-label multicenter study, ACE inhibitor therapy with 10 mg ramipril daily significantly reduced serum levels of hs-CRP in patients with atherosclerosis, which was suggested to be aside from the blood pressure lowering effect (Mitrovic et al., 2005). However, in a study comparing the efficacy of fosinopril (20 mg/day) and the diuretic hydrochlorothiazide (25 mg/day) in carotid atherosclerosis progression, Zanchetti et al. reported that the greater anti-atherogenic action of fosinopril versus hydrochlorothiazide was related to greater BP reduction (Zanchetti et al., 2004). In the PERTINENT study, the biomarkers of atherosclerosis and thrombosis were measured at baseline and 1 year in a population with stable coronary artery disease, receiving either perindopril (8 mg/day) or placebo. The authors observed significant effects of perindopril on the pro-inflammatory cytokine, TNF- α , and biomarkers of the atherothrombotic complications (D-dimer), but not on biomarkers of inflammation associated with atherosclerosis such as CRP and fibrinogen (Ceconi et al., 2009). McMurray et al. compared the effects of captopril, valsartan, and their combination on atherosclerotic events in 14,703 patients with acute MI. They showed ARBs are as effective as ACE inhibitors in reducing atherosclerotic events and their combination may have a small additional anti-infarction effect (McMurray et al., 2006). In another study, a total of 40 patients with intermediate CAD were randomly assigned to receive either rosuvastatin alone (20 mg/day) or combined rosuvastatin (20 mg/day) and ramipril (10 mg/day). The authors reported that by adding ramipril to rosuvastatin atheroma volume was significantly reduced, which could be partly explained by anti-inflammatory effects (Han et al., 2012). These findings clearly suggest that the combined therapy with ACE inhibitor and statin may be a promising strategy to prevent atherosclerotic disease progression by synergistic anti-inflammatory effects.

3.1.2. ARBs in the treatment of atherosclerosis

The anti-atherogenic and anti-inflammatory effects of ARBs have been investigated in previous pre-clinical (Blessing et al., 2008; Dasu et al., 2009; Fukuda et al., 2010; Ge et al., 2004; Hadi et al., 2013; Hayashi et al., 2012; Johnstone et al., 2004; Li et al., 2010; Shimada

et al., 2011; Strawn et al., 2000; Torres et al., 2014; Xu et al., 2007; Xu et al., 2013; Zhao et al., 2014) and clinical studies (Dandona et al., 2003; Gong et al., 2015; Graninger et al., 2004; Hirohata et al., 2012; Hirohata et al., 2010; Janic et al., 2014; Koh et al., 2004; Navalkar et al., 2001; Rahman et al., 2002; Ramadan et al., 2016; Stumpe et al., 2007; Yamamoto et al., 2011; Yano et al., 2012). Treatment of ApoE-deficient spontaneously hyperlipidemic mice with high-dose candesartan caused a clear regression of atherosclerotic lesions by decreasing lipid-retaining proteoglycan biglycan and suppressing ACAT1 expression (Hayashi et al., 2012). In another *in vivo* study, candesartan exerted anti-inflammatory effects via inhibiting the expression of TLR2 and TLR4 (Dasu et al., 2009) which have been shown to promote atherosclerosis in animal models (Shinohara et al., 2007). Torres et al., investigated the effects of candesartan treatment in hypercholesterolemic rabbits and found reduced expression of ICAM-1 and consequent macrophage accumulation in the sclera and choroid (Torres et al., 2014). Hadi et al. have reported that candesartan reduces cytokine (TNF- α , IL-6, IL-1 β) and chemokine levels (MCP-1) as well as plasma lipid profile including total cholesterol, triglycerides, and LDL-C, whilst also increasing plasma HDL-C levels in treated rabbits. Additionally, candesartan significantly attenuated atherosclerosis lesions via interference with NF- κ B and oxidative pathways (Hadi et al., 2013). Moreover, candesartan attenuated the degree of atherosclerosis and reduced both plaque disruption and macrophage accumulation while increasing collagen deposition in the aortas of treated rabbits (Johnstone et al., 2004). Yao et al. reported that irbesartan attenuated atherosclerosis in high cholesterol-diet ApoE knockout mice partly via inhibition of oxidative stress and inflammatory signal transduction pathways. Likewise, Zhao et al. suggested remissions of inflammation and apoptosis as potential mechanisms mediating the therapeutic effects of irbesartan on atherosclerosis (Zhao et al., 2014). Xu et al. reported that the effect of losartan on atherosclerosis is related to inhibiting inflammatory process but not lipid metabolism (Xu et al., 2013). In another study, losartan exerted an antiatherogenic effect on nonhuman primates possibly through protection of LDL from oxidation as well as suppression of vascular monocyte activation and recruitment factors (Strawn et al., 2000). Moreover, losartan inhibited atherosclerotic progression in

treated rabbits by decreasing macrophage proliferation and accumulation in the arterial wall as well as reducing the activation of NF- κ B (Xu et al., 2007). Down-regulation of lectin-like oxidized LDL receptor-1 (LOX-1) has also been suggested as a potential mechanism for attenuating effect of losartan on vein grafts atherosclerosis (Ge et al., 2004). Olmesartan also showed anti-atherosclerotic effects by reducing superoxide production and oxidative stress in a mouse model of atherosclerosis (Shimada et al., 2011). Moreover, high-cholesterol diet-induced atherosclerotic lesions in rabbit pulmonary arteries has been shown to be ameliorated by treatment with valsartan, possibly through a NO and endothelin-1-dependent mechanism (Li et al., 2010). Fukuda et al. suggested that telmisartan has protective effects on the development of atherosclerosis beyond AT₁ receptor blockade in ApoE-deficient mice (Fukuda et al., 2010). Furthermore, Blessing and colleagues showed that chronic treatment with telmisartan is more effective than ramipril in reducing the progression of advanced atherosclerosis in older ApoE-deficient mice (Blessing et al., 2008). Several studies have also found that combination treatment with ARB and statins such as fluvastatin, simvastatin and pravastatin produce a greater antiatherogenic effect than monotherapy possibly via the combination of the different antiatherosclerotic mechanisms of each drug (Chatzizisis et al., 2009; Kato et al., 2005; Lee et al., 2012; Li et al., 2004; van der Hoorn et al., 2007; Yang et al., 2011). The anti-inflammatory effects of ARBs observed in preclinical studies are reported in Table 3.

In a randomized controlled trial by Graninger et al., twenty-one hypercholesterolemic patients received either losartan (50 mg/day) or enalapril (20 mg/day) or placebo for 12 weeks. Enalapril and losartan induced a small but stable decrease of circulating ICAM-1 and VCAM-1, which may indicate an anti-atherogenic effect of angiotensin II blockade in hypercholesterolemia (Graninger et al., 2004). In another study, 33 normotensive patients with stable CAD were treated with irbesartan for a 24-week period and were compared against a control population with no known coronary atherosclerosis. Treatment with irbesartan (75-150 mg/day) significantly reduced levels of atherosclerotic and inflammatory markers including

soluble VCAM-1, soluble TNF- α , and superoxide (Navalkar et al., 2001). In order to investigate the effects of ARBs on tissue factor (TF) activity, tissue plasminogen activator (tPA), plasminogen activator inhibitor type-1 (PAI-1) antigen levels, plasma renin activity and aldosterone levels, losartan (100 mg/day), irbesartan (300 mg/day), and candesartan (16 mg/day) were administered to 122 hypertensive patients for 2 months. Koh et al. found that TF activity, PAI-1 antigen levels, and aldosterone levels were significantly reduced following ARB therapy in hypertensive patients (Koh et al., 2004). Three months treatment with olmesartan (20 mg/day) promoted the mobilization of endothelial progenitor cells and increased the serum levels of eNOS and NO in patients with carotid atherosclerosis (Gong et al., 2015). Considering the role of endothelial progenitor cells in repairing damaged blood vessels (Werner et al., 2003), the effect of olmesartan on mobilization and function of these cells can be considered as a potential antiatherogenic mechanism for ARBs. In a prospective, randomized, multicenter trial evaluating the impact of olmesartan on progression of coronary atherosclerosis, 247 stable angina pectoris patients with native CAD were randomly assigned to receive 10-40 mg of olmesartan or control. Treatment with olmesartan significantly reduced total atheroma volume (TAV) and percent change in percent atheroma volume (PAV), which suggest a positive role in a potentially lower rate of coronary atheroma progression through the administration of olmesartan (Hirohata et al., 2010). In another study on the same population, examination of the 4-year clinical outcomes revealed that administration of olmesartan in stable angina pectoris patients is associated with reduced incidence of long-term cardio- and cerebrovascular events, probably due to atheroma volume changes (Hirohata et al., 2012). In a double-blind trial, 165 hypertensive patients with carotid wall thickening and a defined atherosclerotic plaque were randomized to receive either olmesartan (20–40 mg/day) or atenolol (50–100 mg/day). Olmesartan decreased carotid intima-media thickness (IMT) and reduced the volume of larger atherosclerotic plaques, independent of its blood pressure-lowering effect (Stumpe et al., 2007). Moreover, in subjects with carotid wall thickening, 2 years treatment with valsartan (160-320 mg/day) was associated with regression in carotid atherosclerosis, which was unaffected by changes in blood pressure (Ramadan et

al., 2016). In a study by Rahman and colleagues, 38 subjects with previously undiagnosed essential hypertension randomly received 600 mg/day of eprosartan or 50 mg/day of hydrochlorothiazide. In this 4-week trial, eprosartan, compared with hydrochlorothiazide, effectively reduced systemic blood pressure, neutrophil superoxide anion generating capacity, soluble MCP-1, VCAM-1, while increased LDL oxidation lag time, suggesting that eprosartan exerts beneficial effects in the vasculature by inhibiting mechanisms of inflammation and oxidation (Rahman et al., 2002). Yamamoto et al. compared the effects of losartan and amlodipine, a calcium channel blocker, on atherosclerosis of the carotid artery in Japanese patients with mild-to-moderate hypertension, left ventricular hypertrophy and diastolic dysfunction. Under similar reduction of blood pressure, losartan was more effective than amlodipine in protecting the progression of atherosclerosis (Yamamoto et al., 2011). In another study on 116 patients with acute myocardial infarction (AMI), additional ARB (5 mg of valsartan twice daily) therapy had minimal impact on the progression of coronary atherosclerosis as compared with an ACE inhibitor (3 mg of captopril 3 times daily) alone (Yano et al., 2012). It has been shown that short-term treatment with valsartan (160 mg/day) inhibited reactive oxygen species (ROS) generation, suppressed NF- κ B while induced I κ B and suppressed plasma CRP concentration. However, simvastatin (80 mg/day) and quinapril (40 mg/day) did not produce similar effects over the period of 1 week (Dandona et al., 2003). Furthermore, a low-dose combination of fluvastatin (10 mg/day) and valsartan (20 mg/day) decreased inflammatory parameters (hs-CRP and VCAM-1) and increased antioxidant defenses (total antioxidant status and glutathione peroxidase) more effectively than low-dose valsartan alone (Janic et al., 2014). These findings suggest that both inhibition of Ang II production and AT₁ receptor blockade produce anti-atherogenic and anti-inflammatory effects by several mechanisms, particularly inhibiting NF- κ B signaling or up-regulating anti-inflammatory transcription factors PPAR- α and γ .

3.2. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic systemic inflammatory arthritis of autoimmune origin characterized by inflammation, persistent synovitis, and eventual joint destruction. RA affects up to 1% of the general adult population worldwide (Silman and Pearson, 2002). Locally-generated active renin and ACE has been reported to contribute to joint destruction in RA (Cobankara et al., 2005).

3.2.1. ACE inhibitors in the treatment of arthritis

Several previous studies have evaluated the beneficial anti-arthritic effects of ACE inhibitors in animal and human models of arthritis (Agha and Mansour, 2000; Dalbeth et al., 2004; Flammer et al., 2008; Liu and Wang, 2014; Shi et al., 2012; Tang et al., 2015; Wahba et al., 2015). Wahba et al., treated rats with chemically induced RA with ramipril (0.9 mg/kg/day) that restored all the measured immunological (serum immunoglobulin G and antinuclear antibody), inflammatory (serum myeloperoxidase (MPO) and CRP) and oxidative stress (MDA and GSH) biomarkers back to normal levels. Specific rheumatoid biomarkers including serum rheumatoid factor and cartilage oligomeric matrix protein, but not matrix metalloproteinase (MMP)-3, restored back to normal levels, as well (Wahba et al., 2015). Similarly, a study investigating the therapeutic effect of captopril treatment in animal model of arthritis found that captopril possesses anti-inflammatory and anti-rheumatoid effects through reducing TNF- α level in serum of RA rats (Liu and Wang, 2014). Dalbeth et al. showed that quinapril (10 mg/kg/day) treatment of mice with collagen-induced arthritis inhibited disease activity and reduced articular expression of TNF- α . However, treatment with candesartan (5 mg/kg/day) also inhibited disease activity in collagen-induced arthritis, suggesting that both drugs act predominantly through suppression of Ang II (Dalbeth et al., 2004). In experimentally induced-arthritic rats, captopril exerted antiarthritic effects via inhibition of local and systemic leukotriene B₄ and subsequent reduction of IL-6 levels. In addition, captopril treatment reduced elevated levels of lipid peroxide, SOD, and GSH (Agha and Mansour, 2000). The oral administration of ramipril (10 mg/kg/day) for 28 days significantly reduced 4-hydroxynonenal (HNE) and AT1 receptor levels and restored mitochondrial NADP-isocitrate dehydrogenase

(mNADP-ICDH) activity and redox status in left ventricular tissues of adjuvant-induced arthritis rats. Ramipril also reduced arthritis scoring and inflammatory markers, suggesting ACE inhibition as a novel strategy to prevent heart diseases in RA (Shi et al., 2012). Tang and colleagues also reported that captopril is able to attenuate osteoarthritis (OA)-induced osteoarticular injury in rats, at least partially, through suppression local RAS (Tang et al., 2015). Furthermore, in a randomized, double-blind, crossover study, eleven patients with RA received ramipril (2.5-10 mg/day) for 8 weeks followed by placebo, or vice versa, in addition to standard anti-inflammatory therapy. ACE inhibition with 10 mg/day ramipril markedly improved endothelial function in patients with RA (Flammer et al., 2008). These findings clearly suggest that ACE inhibitor therapy has a potential therapeutic effect in inflammatory arthritis and may provide a novel strategy to prevent cardiovascular events in RA patients.

3.2.2. ARBs in the treatment of arthritis

The effects of olmesartan was investigated in zymosan-induced intra-articular inflammation in Wistar rats found protective effects for olmesartan in doses of 15 and 30 mg/kg as evidenced by improved histopathological parameters of synovium, reduced total leukocyte counts, reduced MPO and MDA levels, and increased non-protein sulfhydryl (NPSH) levels. Olmesartan also reduced immunostaining for COX-2, TNF- α and IL-17 and increased immune-staining for SOD and GPx (Guerra et al., 2016). In a collagen-induced arthritis model, ARBs (olmesartan, candesartan, and telmisartan) were administered to mice to investigate their preventive or therapeutic effects on the development of arthritis. All ARBs suppressed antigen-specific immune responses for Th1 and Th2, and showed therapeutic potential in RA. However, olmesartan suppressed the development of severe arthritis and joint destruction, even when it was administered only after disease onset (Sagawa et al., 2005). In another experimental model of arthritis in rats, losartan (20mg/kg/day) monotherapy not only significantly reduced all parameters of inflammation and arthritis but also, when combined with methotrexate (1mg/kg/week), provided more effective anti-inflammatory and hepato-protective effects (Refaat et al., 2013). Price et al. reported that both prophylactic and

therapeutic administration of losartan (15 mg/kg) substantially reduced knee joint swelling in rats with adjuvant monoarthritis through targeting the angiotensin pathway (Price et al., 2007). In two experimental models of arthritis in rats and mice, treatment with losartan decreased neutrophil recruitment, hypernociception and the production of TNF- α , IL-1 β and chemokine ligand 1, which was accompanied by functional improvement of the joint (Silveira et al., 2013). Wang and colleagues suggested the up-regulation of AT2 receptor might be a potential mechanism by which losartan exerts its therapeutic effects in adjuvant-induced arthritis rats (Wang et al., 2013). Losartan also exerted anti-inflammatory and antiosteoclastic effects in *Aggregatibacter actinomycetemcomitans* infection-induced and arthritis-associated alveolar bone loss in mice (Queiroz-Junior et al., 2015). Furthermore, Sakuta et al. suggested that ARB therapy reduces vascular damage in adjuvant-induced arthritis in rats by suppressing the activity of RAS which is involved in the increased vascular oxidative stress and endothelial dysfunction (Sakuta et al., 2010). Similarly, Perry et al. recommended ARBs as the first choice antihypertensive agent in patients with RA, since they possess both anti-inflammatory and cardiovascular protective effects (Perry et al., 2008).

3.3. Steatohepatitis

Nonalcoholic steatohepatitis (NASH) is the aggressive form of nonalcoholic fatty liver disease (NAFLD) characterized by liver injury and inflammation which often progresses to liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC) (Matteoni et al., 1999). Approximately 3% of individuals in general population may have NASH; although it is more than 25% in patients with obesity (Pan and Fallon, 2014). It has been suggested that Ang II plays a role in the development and progression of NAFLD throughout the disease spectrum (Morris et al., 2013).

3.3.1. ACE inhibitors in the treatment of steatohepatitis

There are limited numbers of studies evaluating the efficacy of ACE inhibitors in the treatment of steatohepatitis and liver fibrosis (Amirshahrokhi et al., 2010; Fayez et al., 2011;

Karimian et al., 2008; Reza et al., 2016). In a study conducted on 50 albino Wistar rats, treatment of steatohepatitis by oral gavage of either perindopril (3 mg/kg/day) or irbesartan (50 mg/kg/day) led to significant amelioration in the biochemical parameters and insulin resistance with significant improvement in histopathological grading (Fayez et al., 2011). In a hepatic fibrosis rat model, captopril treatment (10 mg/kg/day, orally) increased the hepatic content of the anti-inflammatory cytokine IL-10 and decreased the proinflammatory cytokine TNF- α , suggesting a cytokine-mediated protective role for captopril on hepatic fibrosis (Amirshahrokhi et al., 2010). Likewise, both captopril and enalapril decreased lipid peroxidation, increased GSH and improved hepatic fibrosis in the livers of rats with bile duct ligation. However, enalapril was shown to be significantly more effective than captopril (Karimian et al., 2008). Moreover, ramipril therapy normalized the elevated hepatic enzymes activities, improved catalase activity, and reduced hepatic fibrosis in carbon tetrachloride (CCl₄)-administered rats, which was suggested to be due to inhibition of Ang-II mediated oxidative stress and inflammation (Reza et al., 2016).

3.3.2. ARBs in the treatment of steatohepatitis

The therapeutic efficacy of ARBs in animal and human models of hepatic steatosis and inflammation has been studied in several previous preclinical (Fujita et al., 2007; Kato et al., 2012; Kudo et al., 2009; Kurita et al., 2008; Kuwashiro et al., 2011; Nakagami et al., 2010; Yoshiji et al., 2009) and clinical studies (Alam et al., 2016; Fogari et al., 2012; Hidaka et al., 2011; Yokohama et al., 2004). Kurita et al., investigated the effects of oral administration of olmesartan for 8 weeks suppressed hepatic steatosis and the hepatic expression of lipogenic genes in rats with methionine- and choline-deficient diet-induced steatohepatitis. Additionally, olmesartan inhibited hepatic oxidative stress and expression of NADPH oxidase as well as hepatic fibrosis, stellate cell activation, and expression of fibrogenic genes such as TGF- β and PAI-1 (Kurita et al., 2008). In another animal model, treatment with losartan significantly attenuated a choline-deficient L-amino acid-defined diet-induced steatohepatitis in rats. In addition, the pro-fibrotic cytokine TGF- β was suppressed following administration of losartan

(Yoshiji et al., 2009). Eight-week administration of telmisartan (10 mg/kg/day) attenuated steatohepatitis progression in mice fed a methionine- and choline-deficient high-fat diet through suppressing the macrophage infiltration into the liver and reducing adipocyte size (Kudo et al., 2009). Likewise, Kuwashiro et al. found that telmisartan administration increased expression of liver PPAR- γ , carnitine palmitoyltransferase 1 and acyl-CoA oxidase 1, decreased the number of 8-hydroxydeoxyguanosine-positive hepatocytes and reduced the infiltration of macrophages into the liver (Kuwashiro et al., 2011). In a study by Nakagami et al., telmisartan was effective in improving NASH induced by an L-methionine- and choline-deficient diet possibly through increased hepatocyte growth factor (HGF) production via partial agonist of PPAR- γ (Nakagami et al., 2010). Moreover, Fujita and colleagues reported that telmisartan, but not valsartan, markedly attenuated hepatic steatosis, inflammation, and fibrosis in a rat model of NASH (Fujita et al., 2007). Kato et al. suggested that irbesartan administration improved hepatic steatosis by reducing the expression of sterol regulatory element-binding protein 1c (SREBP1c) and attenuated the progression of hepatic fibrosis by inhibiting the activation of hepatic stellate cells (HSCs) and Kupffer cells as well as reducing oxidative stress and pro-inflammatory cytokines (Kato et al., 2012).

Yokohama conducted a study on seven patients with both NASH and hypertension and found that treatment with losartan (50 mg/day for 48 weeks) significantly decreased plasma TGF- β 1 and serum ferritin concentration concurrently with an improvement in serum aminotransferase levels as well as hepatic necroinflammation and fibrosis (Yokohama et al., 2004). In another study conducted on 150 normocholesterolemic, hypertensive patients with nonalcoholic hepatic steatosis, 6-month treatment with losartan (100 mg/day) significantly decreased the steatosis degree, subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) diameter compared with amlodipine therapy. Furthermore, the addition of simvastatin improved the therapeutic efficacy of losartan (Fogari et al., 2012). In a 1 year randomized control trial, Alam et al. observed that treatment of NASH patients with telmisartan together with lifestyle modification improved NAFLD activity score (NAS) and fibrosis score

without any significant adverse events (Alam et al., 2016). In a study conducted by Hidaka et al., forty-eight patients with cirrhosis were randomly assigned to receive either olmesartan or no therapy for 1 year. Based on the findings, olmesartan significantly reduced TGF- β 1, which is the key cytokine for liver fibrosis (Hidaka et al., 2011). Taken together, the present findings give evidence that ARBs may be therapeutically efficacious for NASH particularly via suppressing the expression of pro-fibrotic cytokine TGF- β .

3.4. Colitis

Inflammatory bowel disease (IBD) is a group of disorders linked to inflammation of GI tract and colitis is a type of IBD affecting the inner lining of the colon. Increased colonic mucosal Ang I and II concentrations have been observed in Crohn's colitis, suggesting their potential role in the inflammation associated with colitis (Jaszewski et al., 1990).

3.4.1. ACE inhibitors in the treatment of colitis

The therapeutic efficacy of pharmaceutical ACE inhibitors has been investigated in several animal models of colitis (Jahovic et al., 2005; Koga et al., 2008; Lee et al., 2014; Spencer et al., 2007; Sueyoshi et al., 2013; Wengrower et al., 2004). In a study investigating the effects of ACE inhibitor therapy on trinitrobenzene sulphonic acid (TNBS)-induced colonic inflammation in rats, the injection of captopril (0.1 and 1 mg/kg/day) 5 min after induction of colitis suppressed TNF- α production and superoxide generation, but had no effect on colonic GSH content. On the other hand, although TNF- α production and lipid peroxidation were reduced by injection of lisinopril (0.1 and 1 mg/kg/day), the morphology of the lesions remained unchanged, suggesting that captopril is superior to lisinopril in improving colonic inflammation (Jahovic et al., 2005). Lee et al. observed that treatment of human intestinal epithelial cell and peritoneal macrophages with enalapril significantly inhibited lipopolysaccharide (LPS)-induced I κ B α phosphorylation, NF- κ B binding activity, and pro-inflammatory cytokine production. In addition, the administration of enalapril to mice subjected to dextran sulfate sodium (DSS)-

induced colitis significantly reduced the severity of disease and attenuated the up-regulation of I κ B α phosphorylation (Lee et al., 2014). Spencer et al., have reported that enalaprilat treatment reduced the severity of DSS-induced colitis in mice and reduced epithelial cell apoptosis, possibly through suppressing TNF- α mRNA and reducing the ratio of pro-apoptotic Bax to anti-apoptotic Bcl-2 (Spencer et al., 2007). Likewise, enalaprilat was shown to be effective in reducing disease severity in an IL-10 knockout colitis model, which was minimally augmented by prednisolone (Sueyoshi et al., 2013). Furthermore, prophylactic administration of captopril reduced the score of macroscopic and histologic lesions and prevented colonic fibrosis in TNBS-induced colitis, possibly due to blockade of TGF β -1 overexpression or direct down-regulation of TGF β -1 transcript (Wengrower et al., 2004). Similarly, Koga et al. found that transanal administration of enalaprilat/polyethylene glycol (PEG) is an effective strategy to decrease the severity of fibrosis in a DSS-induced colitis model, most likely by down-regulating the TGF- β signaling pathway (Koga et al., 2008). The findings suggest that ACE inhibitor therapy could be a new therapeutic strategy for patients with colitis.

3.4.2. ARBs in the treatment of colitis

Similar to ACE inhibitors, ARBs have also been shown to be effective in animal models of colitis (Arab et al., 2014; Guerra et al., 2015; Li et al., 2015b; Liu et al., 2016; Nagib et al., 2013; Okawada et al., 2011). The administration of olmesartan to mice, prior to the induction of colitis, dose-dependently ameliorated the UC, which was comparable or even better than that of observed in the sulfasalazine-treated group. Additionally, TNF- α , MPO, PGE₂, and MDA were significantly decreased, while GSH was significantly increased following olmesartan therapy. All these beneficial effects were attributed to anti-inflammatory and antioxidant properties of olmesartan (Nagib et al., 2013). Likewise, telmisartan treatment (5 mg/kg) of rats subjected to acetic acid-induced UC significantly reduced levels of TNF- α , MPO, and MDA and increased production of IL-10. In addition, macroscopic damage, number of ulcers and histopathological processes were reduced following treatment with telmisartan. All of these beneficial effects could be explained by decreased TNF- α and increased production

of IL-10, together with down-regulation of receptor activator of NF- κ B (RANK) and receptor activator of NF- κ B ligand (RANKL) (Guerra et al., 2015). Li et al. showed that treatment with telmisartan not only ameliorated the severity of colitis in IL-10 knockout mice but also attenuated mesenteric adipose tissue alteration, at least in part, through suppressing the neurotensin/microRNA-155 pathway (Li et al., 2015b). In another study, AT₁ receptor blocker losartan attenuated TNBS-induced colitis in mice and inhibited the apoptosis of intestinal epithelial cell possibly through increasing the Bcl-2/ Bax ratio and down-regulating the proapoptotic caspase-3 activity (Liu et al., 2016). Pretreatment of rats subjected to TNBS-induced colitis with telmisartan attenuated the severity of disease and suppressed the inflammatory response via attenuation of TNF- α , PGE₂ and MPO activity and restoration of IL-10. Telmisartan also inhibited oxidative stress as evidenced by suppression of lipid peroxides and NO as well as boosting GSH, total antioxidant capacity (TAC) and the activities of SOD and GPx. Additionally, telmisartan suppressed mRNA and protein expression of NF- κ B, p65 and mRNA of COX-2 and inducible NOS proinflammatory genes with concomitant upregulation of PPAR- γ . Telmisartan also inhibited apoptosis via downregulating the mRNA, protein expression and activity of caspase-3, suppressing the elevation of cytochrome c and Bax mRNA as well as upregulation of Bcl-2 (Arab et al., 2014). In another study, ARBs significantly improved clinical and histologic scores and epithelial cell apoptosis in DSS-induced colitis in mice. Moreover, TNF- α , IL-1 β , and IL6 mRNA were significantly decreased with ARB therapy (Okawada et al., 2011). Taken together, these findings support the beneficial effects of ARBs in colitis through modulation of inflammation, oxidative stress and apoptosis.

3.5. Pancreatitis

Chronic pancreatitis is a relatively common and potentially fatal inflammatory disease, which leads to the progressive and irreversible destruction of exocrine and endocrine glandular pancreatic parenchyma (Spanier et al., 2008). It has been found that mRNA levels of the major RAS components (angiotensinogen, AT₁ and AT₂ receptors) are expressed in pancreatic acinar cells, and they are upregulated during pancreatitis (Tsang et al., 2004).

3.5.1. ACE inhibitors in the treatment of pancreatitis

A limited number of studies have investigated the efficacy of ACE inhibitors in treating chronic pancreatitis or alleviating pancreatic inflammation (Chen et al., 2006; Kuno et al., 2003; Yu et al., 2016). Kuno et al., studied the effects of lisinopril (20, 50, or 200 mg/L in drinking water) in rats for 10 weeks significantly alleviated chronic pancreatitis and fibrosis through suppressing the expression of TGF- β 1 mRNA and subsequent prevention of pancreatic stellate cell activation (Kuno et al., 2003). Chen et al. observed that intra-peritoneal injection of captopril (4 mg/kg) to rats attenuated vascular permeability by reducing MMP-9 expression, thereby ameliorating severity of severe acute pancreatitis (Chen et al., 2006). In another study, pretreatment of rats with 5 mg/kg captopril 1 hour prior to acute pancreatitis induction protected the lung against acute pancreatitis associated lung injury possibly through inhibition of Ang II production and the suppression of the Rho/ROCK pathway (Yu et al., 2016).

3.5.2. ARBs in the treatment of pancreatitis

Similar to ACE inhibitors, there are few studies investigating the efficacy of ARBs for chronic pancreatitis (El-Rahman et al., 2011; Yamada et al., 2003; Yamada et al., 2005). The administration of candesartan into drinking water (10.5, 42, or 125 mg/L) of 10-week-old male rats for 10 weeks was shown to alleviate chronic pancreatitis and fibrosis by suppressing the overexpression of TGF- β 1 (Yamada et al., 2003). Moreover, Yamada and colleagues showed that combination therapy with candesartan plus lisinopril, but not by either agent alone, synergistically alleviated pancreatic inflammation and fibrosis in rats, which was suggested to be due to suppression of TNF- α , platelet-derived growth factor-receptor β , and TGF- β 1 mRNA (Yamada et al., 2005). In another study, losartan was more efficient than pentoxifylline in the treatment of L-arginine induced-acute pancreatitis in adult albino rats as indicated by histological and biochemical results (El-Rahman et al., 2011).

3.6. Nephritis

Nephritis is an inflammation of one or both kidneys which is categorized into lupus nephritis (an autoimmune disease factor leading to the inflammation), glomerulonephritis (inflammation of the glomeruli), interstitial nephritis (swelling of the area between the renal tubules), and pyelonephritis (swelling due to the spread of a urinary infection to the kidney) (Hodgin et al., 2009).

3.6.1. ACE inhibitors in the treatment of nephritis

Several *in vivo* studies have been performed to investigate the beneficial effects of ACE inhibitor treatment on nephritis or renal inflammation (Husain et al., 2015; Shinosaki et al., 2002; Zhang et al., 2005; Zoja et al., 2003). Shinosaki reported that lisinopril exerted a potent antiproteinuric effect on Thy-1.1 induced chronic nephritis in rats, which was attributable to protection against glomerular epithelial cells (GEC) damage. The preventive effect of lisinopril on extracellular matrix deposition was also attributed to suppression of TGF- β and PAI-1 expression (Shinosaki et al., 2002). In another study, fosinopril attenuated renal damage in rats with modified immune complex glomerulonephritis through downregulation of signal transducer and activator of transcription 3 (STAT-3) activation and ED-1 influx (Zhang et al., 2005). Moreover, combining lisinopril and L-arginine was reported to be effective in reversing proteinuria and protecting against renal function impairment in passive Heymann nephritis rats (Zoja et al., 2003). Likewise, in a study by Husain et al., combined treatment of ApoE-knockout mice with paricalcitol and enalapril significantly ameliorated the renal inflammation and oxidative stress (Husain et al., 2015).

3.6.2. ARBs in the treatment of nephritis

The efficacy of ARBs in the treatment of nephritis or renal inflammation have been examined in several previous preclinical (Chen et al., 2008; Leh et al., 2004; Villa et al., 2011) and clinical studies (Qiu et al., 2014; Tsuruoka et al., 2013; Tylicki et al., 2005; Woo et al., 2008). Chen et al. found that candesartan suppressed redox-sensitive NF- κ B-mediated renal inflammation by a direct antioxidant effect independent of AT1 receptor blockade in cultured

renal tubular epithelial cells (Chen et al., 2008). In another study, both candesartan (4 mg/kg/day) and pirfenidone (500 mg/kg/day) were found to have beneficial effects on proteinuria and morphological changes in rats with chronic anti-glomerular basement membrane glomerulonephritis. However, combined treatment resulted in superior preservation of morphology (Leh et al., 2004). Villa and colleagues showed that treatment with high-dose, but not low-dose, telmisartan ameliorated glomerular and tubulointerstitial damage in a rat anti-Thy1.1 model of glomerulonephritis (Villa et al., 2011).

A 6-year randomized trial in IgA nephritis showed that high dose losartan (200 mg/day) was more efficacious in reducing proteinuria as well as preserving renal function when compared with normal dose losartan (100 mg/day) and enalapril (20 mg/day) (Woo et al., 2008). In a randomized controlled trial conducted by Qiu et al., irbesartan significantly reduced proteinuria in 479 patients with primary chronic glomerulonephritis. However, its combination with *Rehmannia glutinosa* acteosides yielded a greater reduction in proteinuria (Qiu et al., 2014). Moreover, in an open, randomized, 12-month study, 10 mg of enalapril and 25 mg of losartan equally reduced proteinuria in 34 patients with primary glomerulonephritis (Tylicki et al., 2005). In a study investigating the anti-inflammatory effects of irbesartan in 29 nondiabetic hypertensive patients with chronic glomerulonephritis, treatment with irbesartan for 26 weeks significantly decreased proteinuria and improved the concentrations of adiponectin and hsCRP (Tsuruoka et al., 2013). Thus, ARBs may be beneficial for reducing proteinuria and inflammatory markers in patients with nephritis or renal inflammation.

4. Conclusion

In this paper, we have reviewed the anti-inflammatory effects of two of the most widely used antihypertensive drug classes. The potential mechanisms responsible for these anti-inflammatory effects are presented in Figure 1. Given the above, it seems that both ACE inhibitors and ARBs are effective pharmacological treatments for a wide variety of

inflammatory diseases such as atherosclerosis, arthritis, steatohepatitis, colitis, pancreatitis and nephritis. Moreover, their combination with some other drugs such as statins can further improve the anti-inflammatory properties of these drugs. However, long-term trials are required before a final recommendation can be made for their use as a primary or adjunctive therapy for patients with inflammatory diseases.

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Table 1. Anti-inflammatory activities of ACE inhibitors and ARBs in clinical trials

Author	Inflammatory condition	Sample size	Drug (Dosage)	Findings
Lonn et al. (2001)	Atherosclerosis	732 patients	Ramipril (2.5 mg/day or 10 mg/day) and/or vitamin E (400 IU/day)	Long-term treatment with ramipril, but not vitamin E, had a beneficial effect on atherosclerosis progression.
Mitrovic et al. (2005)	Atherosclerosis	24 patients	Ramipril (10 mg/day)	Treatment with ramipril significantly reduced serum levels of hs-CRP in patients with atherosclerosis.
Zanchetti et al. (2004)	Atherosclerosis	508 patients	Fosinopril (20 mg/day) or hydrochlorothiazide (25 mg/day)	Progression of carotid atherosclerosis occurred with hydrochlorothiazide but not with fosinopril.
Ceconi et al. (2009)	Atherosclerosis	1157 patients	Perindopril (8 mg/day)	ACE inhibition had significant effects on biomarkers of the atherothrombotic complications (D-dimer) and the proinflammatory cytokine TNF- α , but not on biomarkers of inflammation associated with atherosclerosis (CRP and fibrinogen).
McMurray et al. (2006)	Atherosclerosis	14,703 patients	Captopril (150 mg/day) and/or valsartan (160-320 mg/day)	Valsartan was as effective as captopril in reducing atherosclerotic events and their combination had a small additional anti-infarction effect.
Han et al. (2012)	Atherosclerosis	40 patients	Rosuvastatin (20 mg/day) and/or ramipril (10 mg/day)	Adding ramipril to rosuvastatin significantly reduced atheroma volume, which could be partly explained by anti-inflammatory effects.
Graninger et al. (2004)	Atherosclerosis	21 patients	Losartan (50 mg/day) or enalapril (20 mg/day)	Enalapril and losartan induced a small but stable decrease of circulating ICAM-1 and VCAM-1.
Navalkar et al. (2001)	Atherosclerosis	33 patients	Irbesartan (75-150 mg/day)	Treatment with irbesartan significantly reduced levels of atherosclerotic and inflammatory markers including soluble VCAM-1, soluble TNF- α , and superoxide.
Koh et al. (2004)	Atherosclerosis	122 patients	Losartan (100 mg/day), irbesartan (300 mg/day), and candesartan (16 mg/day)	TF activity, PAI-1 antigen levels, and aldosterone levels were significantly reduced following ARB therapy in hypertensive patients.
Gong et al. (2015)	Atherosclerosis	40 patients	Olmesartan (20 mg/day)	Treatment with olmesartan promoted the mobilization of endothelial progenitor cells and increased the serum levels of eNOS and NO.

Hirohata et al. (2010)	Atherosclerosis	247 patients	Olmesartan (10-40 mg/day)	Treatment with olmesartan significantly reduced TAV and percent change in PAV.
Hirohata et al. (2012)	Atherosclerosis	247 patients	Olmesartan (10-40 mg/day)	Administration of olmesartan in stable angina pectoris patients was associated with reduced incidence of long-term cardio- and cerebrovascular events.
Stumpe et al. (2007)	Atherosclerosis	165 patients	Olmesartan (20–40 mg/day) or atenolol (50–100 mg/day)	Olmesartan decreased carotid IMT and reduced the volume of larger atherosclerotic plaques.
Ramadan et al. (2016)	Atherosclerosis	120 patients	Valsartan (160-320 mg/day)	Treatment with valsartan was associated with regression in carotid atherosclerosis.
Rahman et al. (2002)	Atherosclerosis	38 patients	Eprosartan (600 mg/day) or hydrochlorothiazide (50 mg/day)	Eprosartan, compared with hydrochlorothiazide, effectively reduced systemic blood pressure, neutrophil superoxide anion generating capacity, soluble MCP-1, VCAM-1.
Yamamoto et al. (2011)	Atherosclerosis	57 patients	Losartan (50 mg/day) or amlodipine (2.5 mg/day)	Losartan was more effective than amlodipine in protecting the progression of atherosclerosis.
Yano et al. (2012)	Atherosclerosis	116 patients	Captopril (9 mg/day) and/or valsartan (10 mg/day)	Additional ARB therapy had minimal impact on the progression of coronary atherosclerosis as compared with an ACE inhibitor alone.
Dandona et al. (2003)	Atherosclerosis	32 patients	Valsartan (160 mg/day) or simvastatin (80 mg/day) or quinapril (40 mg/day)	Short-term treatment with valsartan inhibited ROS generation, suppressed NF-κB while induced IκB and suppressed plasma CRP concentration.
Janic et al. (2014)	Atherosclerosis	130 patients	Valsartan (20 mg/day) and/or fluvastatin (10 mg/day)	A low-dose combination of fluvastatin and decreased inflammatory parameters (hs-CRP and VCAM-1) and increased antioxidant defenses (total antioxidant status and glutathione peroxidase) more effective than low-dose valsartan alone.
Flammer et al. (2008)	Rheumatoid arthritis	11 patients	Ramipril (2.5-10 mg/day)	ACE inhibition with 10 mg/day ramipril markedly improved endothelial function in patients with RA.
Perry et al. (2008)	Rheumatoid arthritis	138 patients	Losartan or ramipril	Patients taking an ARB had significantly lower ESR levels compared with controls.
Yokohama et al. (2004)	Steatohepatitis	7 patients	Losartan (50 mg/day)	Treatment with losartan significantly decreased plasma TGF-β1 and serum ferritin concentration concurrently with an improvement in serum aminotransferase levels as well as hepatic necroinflammation and fibrosis.

Fogari et al. (2012)	Steatohepatitis	150 patients	Losartan (100 mg/day)	Six-month treatment with losartan significantly decreased the steatosis degree, SAT and VAT diameter compared with amlodipine therapy.
Alam et al. (2016)	Steatohepatitis	50 patients	Telmisartan (40-80 mg/day)	Telmisartan improved NAS and fibrosis score in NASH with insignificant adverse events.
Hidaka et al. (2011)	Steatohepatitis	48 patients	Olmesartan (10-40 mg/day)	Olmesartan significantly reduced TGF- β 1, which is the key cytokine for liver fibrosis.
Woo et al. (2008)	Nephritis	226 patients	Losartan (100 mg/day or 200 mg/day) or enalapril (10 mg/day or 20 mg/day)	High dose losartan was more efficacious in reducing proteinuria as well as preserving renal function when compared with normal dose losartan and enalapril.
Qiu et al. (2014)	Nephritis	479 patients	Irbesartan (150 mg/day)	Irbesartan significantly reduced proteinuria in patients with primary chronic glomerulonephritis.
Tylicki et al. (2005)	Nephritis	34 patients	Enalapril (10 mg/day) and losartan (25 mg/day)	Enalapril and losartan equally reduced proteinuria in patients with primary glomerulonephritis.
Tsuruoka et al. (2013)	Nephritis	29 patients	Irbesartan (100-200 mg/day)	Treatment with irbesartan significantly decreased proteinuria and improved the concentrations of adiponectin and hsCRP.

Table 2. Anti-inflammatory effects of ACE inhibitors in preclinical studies

	Expression/ production	Quinapril/ Quinaprilat	Enalapril/ Enalaprilat	Ramipril	Captopril	Fosinopril	Alacepril	Lisinopril
ICAM-1	Decrease		(Da Cunha et al., 2005)				(Shimozawa et al., 2004)	
VCAM-1	Decrease	(Ochiai et al., 2002)	(Da Cunha et al., 2005)				(Shimozawa et al., 2004)	
E-selectin	Decrease		(Da Cunha et al., 2005)					
MCP-1	Decrease	(Hernández-Presa et al., 1998)	(Da Cunha et al., 2005) (Husain et al., 2010)					
IL-8	Decrease	(Hernández-Presa et al., 1998)						
TNF-α	Decrease	(Dalbeth et al., 2004)	(Husain et al., 2010) (Spencer et al., 2007)	(Shi et al., 2012)	(Liu and Wang, 2014) (Amirshahrokhi et al., 2010) (Jahovic et al., 2005)			(Jahovic et al., 2005)
IL-6	Decrease	(Ochiai et al., 2002)		(Grothusen et al., 2005)	(Li et al., 2015a) (Agha and Mansour, 2000)			
IL-12	Decrease				(Li et al., 2015a)			
IL-10	Increase				(Li et al., 2015a) (Amirshahrokhi et al., 2010)			
NF-κB	Decrease	(Ochiai et al., 2002)	(Lee et al., 2014)			(Yang et al., 2013)		

STAT-3	Decrease					(Zhang et al., 2005)		
PPAR-α	Increase		(Da Cunha et al., 2005)					
PPAR-γ	Increase		(Da Cunha et al., 2005)					
MMP-9	Decrease				(Chen et al., 2006)			
MPO	Decrease			(Wahba et al., 2015)				
COX-2	Decrease		(Husain et al., 2010)					
iNOS	Decrease		(Husain et al., 2010)					
eNOS	Increase	(Ochiai et al., 2002)	(Husain et al., 2010)	(Hayek et al., 1999)				
CRP	Decrease			(Wahba et al., 2015)				
PGE2	Decrease			(Shi et al., 2012)				
LTB4	Decrease				(Agha and Mansour, 2000)			
TGF-β	Decrease		(Koga et al., 2008)		(Wengrower et al., 2004)			(Kuno et al., 2003) (Shinosaki et al., 2002)
	Increase				(Li et al., 2015a)			
TLR-4	Decrease					(Yang et al., 2013)		

Table 3. Anti-inflammatory effects of ARBs in preclinical studies

	Expression/ production	Candesartan	Losartan	Olmesartan	Telmisartan	Irbesartan	Valsartan
ICAM-1	Decrease	(Torres et al., 2014)					
MCP-1	Decrease	(Hadi et al., 2013)					
TNF-α	Decrease	(Hadi et al., 2013)	(Refaat et al., 2013) (Silveira et al., 2013)	(Guerra et al., 2016)	(Fujita et al., 2007)	(Kato et al., 2012)	(Fujita et al., 2007)
IL-1β	Decrease	(Hadi et al., 2013)	(Refaat et al., 2013) (Silveira et al., 2013)				
IL-6	Decrease	(Hadi et al., 2013)					
IL-17	Decrease			(Guerra et al., 2016)			
NF-κB	Decrease	(Hadi et al., 2013) (Chen et al., 2008)	(Xu et al., 2007)				
PPAR-γ	Increase				(Kuwashiro et al., 2011)	(Zhao et al., 2014)	
MPO	Decrease			(Guerra et al., 2016)			
COX-2	Decrease			(Guerra et al., 2016)			
iNOS	Decrease				(Arab et al., 2014)		
CRP	Decrease		(Refaat et al., 2013)				
TGF-β	Decrease	(Yamada et al., 2003)	(Yoshiji et al., 2009)	(Kurita et al., 2008)	(Fujita et al., 2007)		
TLR-2	Decrease	(Dasu et al., 2009)					
TLR-4	Decrease	(Dasu et al., 2009)					

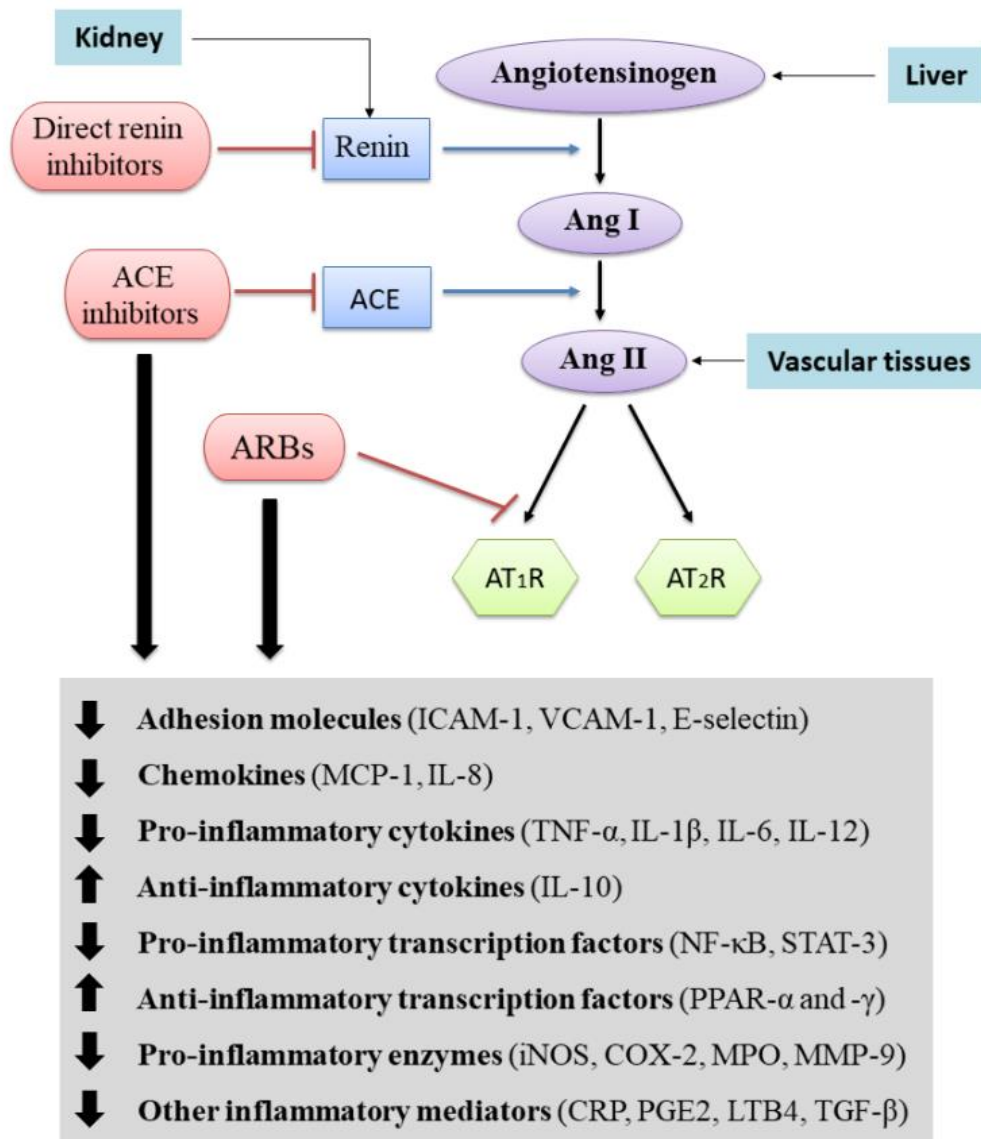


Figure 1

