

# The effect of angiotensin receptor blockers on C-reactive protein and other circulating inflammatory indices in man

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**Abstract:** Anti-inflammatory properties may contribute to the pharmacological effects of angiotensin II receptor blockers (ARBs), a leading therapeutic class in the management of hypertension and related cardiovascular and renal diseases. That possibility, supported by consistent evidence from *in-vitro* and animal studies showing pro-inflammatory properties of angiotensin II, has been evaluated clinically by measuring the effect of ARBs on C-reactive protein and other circulating indices of inflammation (e-selectin, adhesion molecules, interleukin-6, tissue necrosis factor-alpha, monocyte chemoattractant protein-1) of potential clinical relevance, a body of evidence that this paper aims to review.

**Keywords:** renin-angiotensin system, angiotensin II type 1 receptor blockers, vascular inflammation, C-reactive protein, circulating inflammatory markers

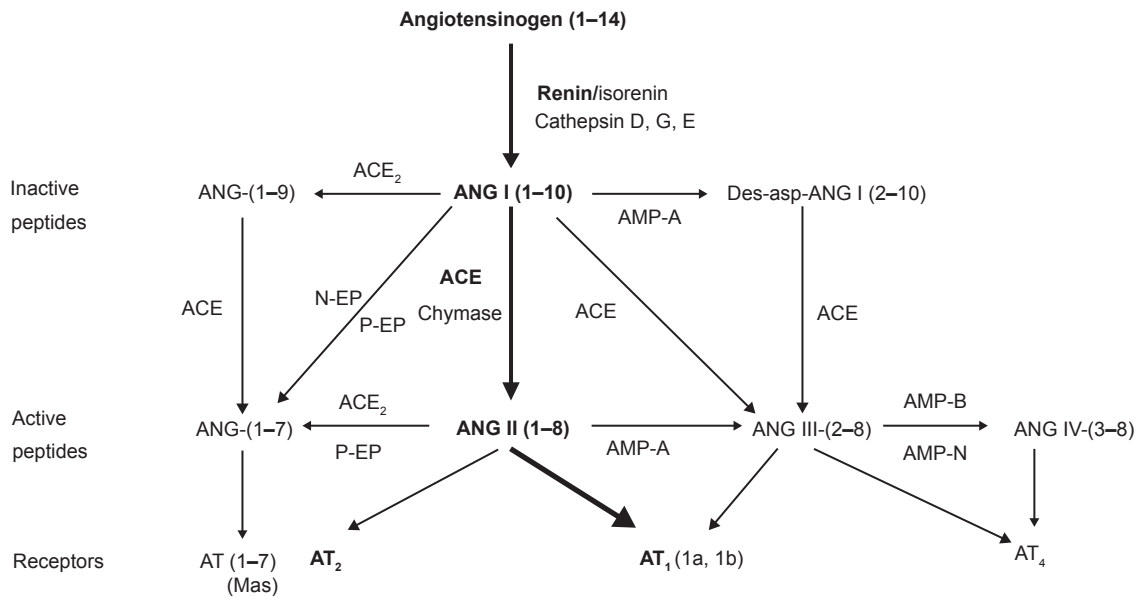
## Introduction

The renin-angiotensin system (RAS; Figure 1) is a multi-step peptidergic system by which circulating angiotensinogen, a liver-derived  $\alpha$ -glycoprotein derived from liver and other sources such as the kidney, adipose tissue and the heart,<sup>1</sup> is cleaved by renin, the rate limiting step in the biological cascade, to form the decapeptide angiotensin (Ang) I. In turn, Ang I is transformed by angiotensin-converting enzyme (ACE), a membrane-bound metalloproteinase expressed in high concentrations on the surface of pulmonary endothelial cells,<sup>1</sup> into the octapeptide AngII, the final effector of the RAS. The endocrine RAS, as above summarized, works in concert with local RASs, ie, self-contained, functionally autonomous AngII-generating systems in the heart, the nervous system, reproductive organs, and in interaction with other biological systems, eg, endothelins or nitric oxide.<sup>2</sup>

Most of the cardiovascular effects of AngII are mediated by G coupled type 1 receptors (AT1Rs) expressed in the vascular wall and organs such as liver, adrenals, brain, lung, kidney and the heart, that coexist with type 2 receptors mediating vasodilatation, inhibition of cell growth/proliferation and proapoptosis.<sup>3</sup> (Pro)renin receptors, which accelerate renin catalytic properties, activate circulating prorenin and stimulate AngII-independent intracellular signaling pathways, have recently been identified<sup>4</sup> whose more thorough understanding will likely unveil additional pathophysiologic facets of the RAS as a whole (Figure 2).

Each step of the biological cascade leading to AngII, the biological effector of the system, can be pharmacologically inhibited by renin inhibitors such as aliskiren, ACE inhibitors (ACEIs) and All AT1R blockers (ARBs) (Figure 2), these latter triggering a compensatory renin rise due to the disruption of the feedback inhibition of renin production.<sup>1-4</sup> The increase in renin activity stimulates the conversion of Ang I and Ang II, which may limit the efficacy of RAS inhibition<sup>3</sup> and the increased renin can also activate the prorenin/renin

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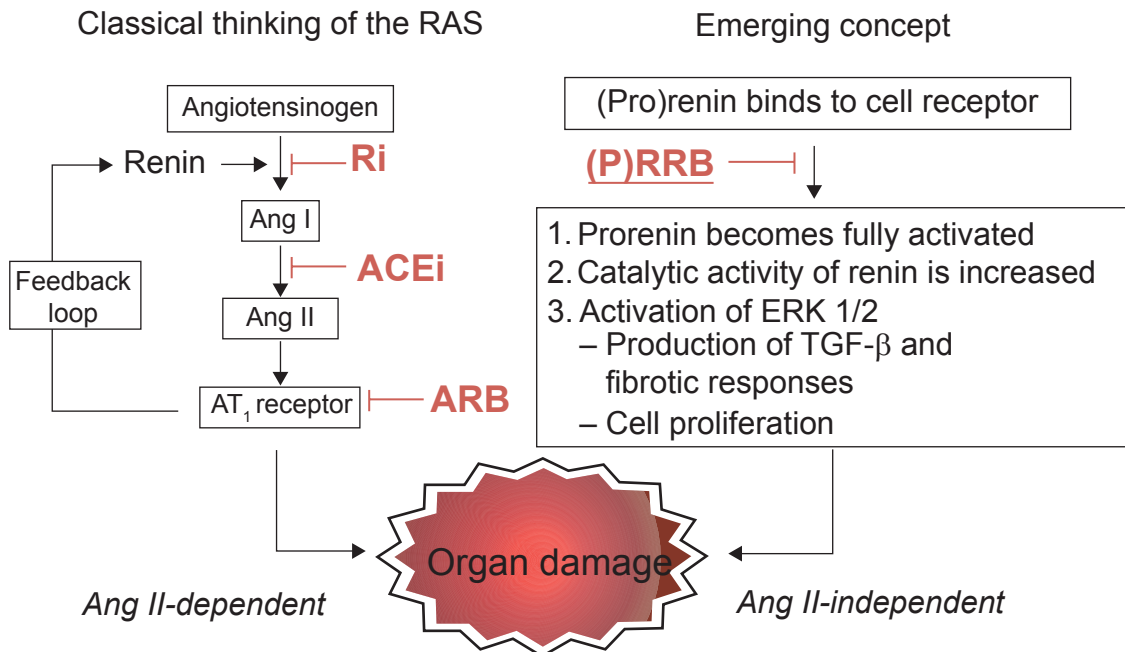
**Figure 1** The renin-angiotensin system and cascade of bioactive angiotensins.

**Abbreviations:** ACE<sub>2</sub>, ACE-related carboxypeptidase; AMP-A, aminopeptidase A; AMP-B, aminopeptidase B; AMP-N, aminopeptidase N; N-EP, neutral endopeptidase; P-EP, prolylen-dopeptidase.

receptor causing renal and cardiovascular damages independent of Ang II<sup>4</sup> (Figure 2). ARBs constitute a heterogeneous pharmacological class (Table 1) sharing AT<sub>1</sub>R antagonism<sup>5,6</sup> as a common feature whose clinical profile has been clarified by several published randomized clinical trials<sup>7-29</sup> (Table 2) in hypertension, cardio-, cerebrovascular disease, diabetes, and

others either completed<sup>30</sup> or on their way to completion<sup>31,32</sup> will further expand our knowledge on this topic.

Although primarily ascribable to AT<sub>1</sub>R antagonism of the vascular, neurohormonal and renal effects of blood-borne and locally produced AngII,<sup>1,2</sup> the therapeutic effect of ARBs may be compounded by “pleiotropic” mechanisms related



**Figure 2** Schematic representation of the classical renin-angiotensin system (RAS) and of the emerging concept integrating the (pro)renin receptor and the blocking of the system at different steps by pharmacological compounds.

**Abbreviations:** Ri, renin inhibitor; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; (P)RRB, (pro)renin receptor blocker.<sup>4</sup>

**Table 1** Main pharmacokinetic characteristics of the available ARBs

Drug	Tmax <sub>(h)</sub>	Dose range (mg)	Bioavailability (%)	Half-life <sub>(h)</sub>	Vd (L)	Elimination (feces/urine)	Antagonism
Losartan*	1 (3–4)	50–100	33	2 (6–9)	34 (12)	60/35	Competitive
Valsartan	2	80–160	23	6	17	83/13	Competitive
Irbesartan	1–2	150–300	60–80	11–15	53–93	80/20	Insurmountable
Candesartan	3–5	8–32	42	9–12	9	67/33	Insurmountable
Eprosartan	2–6	400–800	13	5–7	13	90/10	Insurmountable
Telmisartan	1	20–80	43	24	500	98% fecal	Insurmountable
Olmесartan	1.4–2.8	20–40	26	13	17	35%–49% urine	Insurmountable

**Abbreviations:** ARBs, angiotensin II receptor blockers; Tmax, time to reach peak serum concentration; Vd, distribution volume.

**Note:** \*Values in parentheses refer to EXP3174, the active metabolite of losartan.

to modulation of the multiform effects of AngII on vascular cells (Figure 3) by which the peptide may accelerate the onset and progression of atherosclerotic vascular disease.<sup>33</sup> Growing evidence, in fact, demonstrates the cytokine-like potential of locally-synthesized AngII to act in a paracrine, autocrine, and possibly intracrine manner to promote vascular inflammation, a main component of the atherogenic process (see below). That interesting possibility, generated by a consistent series of *in-vitro* and animal studies, has stimulated a number of clinical studies focusing on the effect of ARBs on circulating inflammatory indices<sup>34–78</sup> that this paper will discuss.

## AngII and vascular inflammation

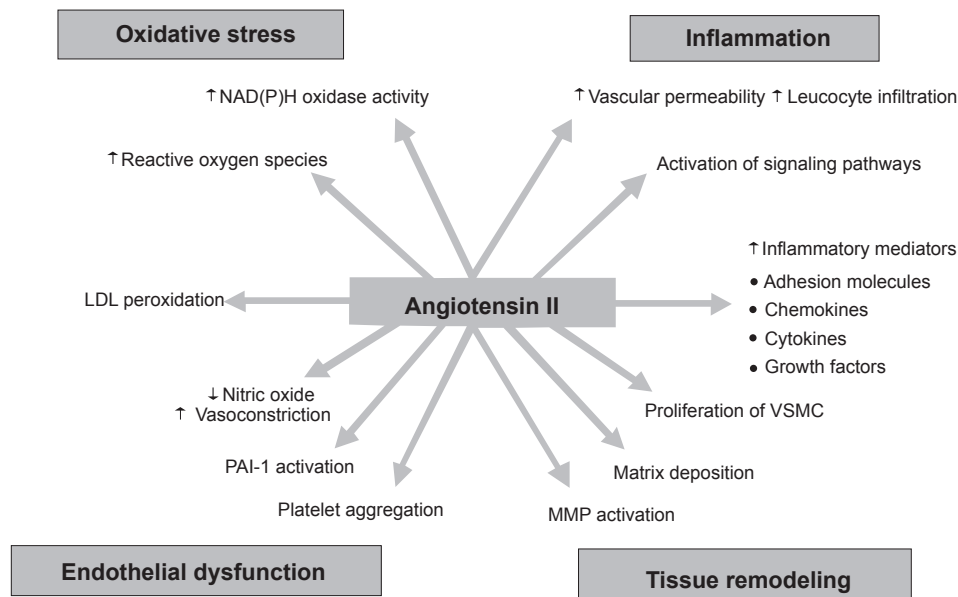
The classical view of atherosclerosis as a lesion composed by lipid deposits has now been changed to that of a chronic inflammatory disorder triggered and maintained by the production of inflammatory mediators and immune cells involved in the initiation, progression, and rupture of the plaque.<sup>79</sup> AngII may promote and amplify that process through the congeries of mechanisms summarized in Figure 3. In fact, All facilitates

adhesion of monocytes and neutrophils to endothelial cells through AT1R-stimulated upregulation of P- and E-selectin expression, thus capturing free-flowing leukocytes from the blood and allowing endothelial rolling. The peptide also stimulates the expression of intercellular (ICAM-1) and vascular (VCAM-1) cellular adhesion molecules by which leukocytes accumulate at the sites of inflammation and infiltrate the endothelial layer by production of chemokines such as monocyte chemoattractant protein-1 (MCP-1) in endothelial and vascular smooth muscle cells, monocytes/macrophages, and cardiac myocytes. AngII also increases the expression of cytokines such as interleukin-6 (IL-6) that activates macrophages and adhesion molecule expression and increases local angiotensinogen generation and thereby local AngII formation in the vascular wall, further amplifying vascular inflammation. AngII, by stimulating platelet binding to endothelial cells and/or leukocytes, contributes to thrombin release, the main effector of platelets, that augments the expression of P-selectin, E-selectin, VCAM-1, and ICAM-1.<sup>79,80</sup> It should, however, be clear that the vascular effects of AngII are complex

**Table 2** Acronyms of completed and ongoing randomized controlled clinical trials with ARBs

Drug	HT	Stroke	Diabetes/renal	CHF	MI	AF
Candesartan	SCOPE <sup>15</sup>	ACCESS <sup>16</sup>	ALPINE <sup>19</sup> DIRECT <sup>27</sup>	CHARM <sup>17</sup>		
Eprosartan		MOSES <sup>22</sup>				
Irbesartan			IDNT <sup>8</sup> , IRMAII <sup>10</sup>	I-PRESERVE <sup>28</sup>		ACTIVE <sup>31</sup>
Losartan	LIFE <sup>12</sup>		RENAAL <sup>9</sup>	ELITE <sup>7</sup> , HEAAL <sup>32</sup>	OPTIMAL <sup>14</sup>	
Olmесartan			ROADMAP <sup>29</sup>			
Telmisartan	ONTARGET <sup>24</sup> TRANSCEND <sup>26</sup>	PROFESS <sup>25</sup>	DETAIL <sup>21</sup>			
Valsartan	VALUE <sup>20</sup> JIKEI <sup>23</sup>		MARVAL <sup>13</sup> NAVIGATOR	VALHEFT <sup>11</sup>	VALIANT <sup>18</sup>	GISSI-AF <sup>30</sup>

**Abbreviations:** AF, atrial fibrillation; ARBs, angiotensin II receptor blockers; CHF, congestive heart failure; HT, hypertension; MI, myocardial infarction.



**Figure 3** Effects of angiotensin II on vascular cellular biology.

**Abbreviations:** LDL, low-density lipoprotein; MMP, matrix metallo proteinases; PAI, plasminogen activator inhibitor; VSMC, vascular smooth muscle cells.

and multiform (Figure 3) and involve several intracellular pathways leading to inflammation and proliferation reviewed in detail elsewhere.<sup>33,79</sup>

Ang II directly act on NAD(P)H oxidase, an enzyme present in vascular wall cells consisting of membrane and cytoplasmic subunits and a small GTP-binding protein Rac.<sup>81</sup> NAD(P)H oxidase generates reactive oxygen species (ROS) that activate nuclear factor kappa B (NFkB), a transcription factor binding specific sequences in the promoter regions of target genes thus inducing transcription of proinflammatory cytokines, chemokines, mediators of inflammation, immune receptors, and adhesion molecules.<sup>82</sup> The effect of AngII on NFkB has been documented in endothelial and vascular smooth muscle, glomerular, tubular, and mononuclear cells and its overactivation in tissue of ANGII stimulated animals related to AT1R activation.<sup>81</sup> ROS excess also impairs endothelial function by decreasing NO bioavailability by both constitutive (eNOS) and inducible (iNOS) NO synthases, accelerates atherogenesis<sup>83</sup> and attenuates BP raise in response to AngII infusion,<sup>84,85</sup> a piece of evidence suggestive of a role of inflammatory components in the genesis of essential hypertension.

## The effect of ARBs on circulating inflammatory indices

### ARBs and C-reactive protein

C-reactive protein (CRP) is a protein synthesized by hepatocytes under the influence of IL-6 within 24–72 hrs after

infectious and noninfectious disorders, including myocardial infarction and other acute coronary syndromes. Detection of both CRP mRNA and protein in vascular smooth muscle cells and macrophages within atherosclerotic plaques suggests its de novo synthesis in the vessel wall in which CRP may activate the complement system and/or interact with macrophages and other resident vascular cells.<sup>86</sup> Due to its long-term stability during storage, long half-life, lack of diurnal variation as well as lack of age and sex dependence, circulating CRP represents a reliable long-term index of subclinical inflammation provided of predictive power for cardiovascular events in patients with both established coronary artery disease and in primary prevention independent of concomitant factors such as smoking status, diabetes, blood pressure, use of hormone-replacement therapy and low-density lipoprotein (LDL) cholesterol.<sup>87</sup>

Because of those favorable characteristics for risk stratification, several studies listed in Table 3 have addressed the effect of ARBs on circulating CRP levels in hypertensive and diabetic patients. The Val-MARC (Valsartan-Managing blood pressure Aggressively and evaluating Reductions in hsCRP) study is probably the more important trial addressing the issue of whether BP reduction *per se* lowers CRP levels, or whether selective AT1R antagonism through valsartan may have independent effects to reduce CRP levels.<sup>69</sup> The study included 1668 patients with stage 2 hypertension randomly allocated to either valsartan alone (160–320 mg/day, n = 836) or valsartan/hydrochlorothiazide (HCTZ, 160–320 mg/12.5 mg/day, n = 832) for a period of six weeks. At the end of treatment, valsartan

**Table 3** Percent changes in high sensitivity (hs) C-reactive protein (CRP) during ARB treatment

Author	Type of ARB	Dose and duration of treatment	Clinical condition (n. patients)	Hs-CRP baseline (mg/L)	% Change
Wassmann <sup>42</sup>	C	16 mg × 6 wk	HC (17)	7.6 ± 2.7	-24% <sup>ns</sup> vs P
Dohi <sup>46</sup>	C	8 mg × 3 mo	HT (67)	0.7 ± 0.4	-14%* vs B
Koh <sup>47</sup>	C	16 mg × 3 mo	HT (45)	1.7 (0.11–2.6)	NS vs B
Rosei <sup>60</sup>	C	8–16 mg × 3 mo	HT (61)	3.1 ± 2.75	+5% <sup>ns</sup> vs B
Schram <sup>63</sup>	C	8 mg × 6–12 mo	HT + D (24)	1.97 (1.14–3.65)	NS vs B
White <sup>75</sup>	C	4–32 mg × 6 mo	CHF (41)	7 mg/L	-26%* vs P
Schieffer <sup>54</sup>	I	300 mg × 3 mo	CAD/HT (21)	NR	-2.5 mg/L* vs B
Biasucci <sup>57</sup>	I	300 mg × 1 mo	CAD (13)	3.1 (0.7–17.7)	-61%* vs P
Andersen <sup>34</sup>	L	50–100 mg × 2 mo	Type 1D (16)	1.0 (0.5–1.82)	+16% <sup>ns</sup> vs P
Prasad <sup>38</sup>	L	25–50 mg × 2 mo	CAD (31)	4.5 ± 1.1	+10% <sup>ns</sup> vs B
Koh <sup>52</sup>	L	100 mg × 2 mo	HT/HC (47)	0.85 (0.3–1.3)	+6% <sup>ns</sup> vs B
Fliser <sup>50</sup>	O	20 mg × 3 mo	HT/MS (100)	3.56 ± 3.17	-15%* vs B
Miura <sup>59</sup>	T	40 mg × 3 mo	Type 2D (18)	1.54 ± 1.55	-29%* vs B
Koulouris <sup>62</sup>	T	40 mg × 3 mo	Type 2D (37)	1.38 ± 1.0	-38%* vs P
Link <sup>65</sup>	T	40 mg × 3 mo	CAD/HT (21)	2.5 ± 0.6	-44%* vs B
Nagel <sup>66</sup>	T	40 mg × 3 mo	HT/MS (20)	5.3 ± 3.77	+8% <sup>ns</sup> vs B
Yano <sup>74</sup>	T	40 mg × 3 mo	HT/MS (30)	0.77	-22%* vs B
Galle <sup>77</sup>	T	40–80 mg × 1 yr	Type 2D + HT (255)	2.1 (0.28–15.8)	-3% <sup>ns</sup> vs B
Nakayama <sup>78</sup>	T	40 mg/2 mo	HT/DIAB (20)	0.76 ± 0.6	+90% vs B
Dandona <sup>45</sup>	V	160 mg × 1 wk	NS (8)	1.27 ± 1.54	-23%* vs B
Yasunari <sup>55</sup>	V	80 mg × 8 mo	HT (52)	NR	-29%* vs B
Anand <sup>56</sup>	V	160 mg × 1 yr	CHF (106)	3.23	-9.3%* vs B
Manabe <sup>58</sup>	V	40–80 × 1 mo	HT (29)	1.5 ± 1.1	-13% <sup>ns</sup> vs B
Ruilope <sup>61</sup>	V	160 mg × 6 mo	HT (720)	NR	-13%* vs B
Ridker <sup>69</sup>	V	80–160 mg × 6 wk	HT (836)	2.11	-8.9%* vs B
Rajagopalan <sup>73</sup>	V	160 mg × 4 mo	HT (107)	3	-5.3% <sup>ns</sup> vs B
Galle <sup>77</sup>	V	80–160 mg × 1 yr	DIAB + HT (255)	1.88 (0.28–12.59)	-3% <sup>ns</sup> vs B

**Abbreviations:** C, candesartan; I, irbesartan; L, losartan; O, olmesartan; T, telmisartan; V, valsartan; CHF, congestive heart failure; HC, hypercholesterolemia; HT, hypertension; CAD, coronary artery disease; T2D, type 2 diabetes; T1D, type 1 diabetes; NS, normal subjects; MS, metabolic syndrome; B, baseline; P, concurrent placebo; ns, not significant. **Note:** \*denotes statistical significance ( $p < 0.05$  or less) of changes from either baseline or concurrent placebo.

alone slightly but significantly reduced high sensitivity (hs)CRP levels, an effect maintained over an extended follow-up period albeit with a low level of association with achieved BP. As CRP levels were unchanged in the combined valsartan/HCTZ therapy group, the data were taken as suggestive of a negative interaction of thiazide diuretics with the anti-inflammatory effects of ARBs conclusion. That conclusion contrasts, though, with the results of the VAST (Valsartan/HCTZ versus Amlodipine in STage II hypertensive patients) trial whose primary objective was to determine whether valsartan 160 mg plus HCTZ 25 mg OD would be more effective than monotherapy with amlodipine 10 mg OD.<sup>61</sup> Modulation by valsartan of CRP levels was confirmed in other, small-sized studies in

patients with hypertension,<sup>55</sup> congestive heart failure<sup>56</sup> as well as normal subjects<sup>45</sup> although other reports did not confirm those data.<sup>58,73,77</sup> For example, Rajagopalan and colleagues<sup>73</sup> found no significant change in hs-CRP in 104 hypertensive patients randomized to 12 weeks valsartan (160 mg daily) as compared with significant reductions in those on combined statin treatment. Galle and colleagues in the VIVALDI trial (investigate the efficacy of telmisartan versus VALsartan in hypertensive type 2 Diabetic patients with overt nephropathy)<sup>77</sup> found no influence of valsartan (160 mg) as well as telmisartan (80 mg) on inflammatory parameters in 255 hypertensive patients with diabetic nephropathy and the study was unable to show any effect beyond that due to blood pressure

control. Nonsignificant changes in hsCRP were reported with candesartan<sup>42,47,60,63</sup> including the CENTRO (CandEsartaN on aTherosclerotic Risk factors) trial, a multicenter, randomized, double blind comparison of candesartan and enalapril, an ACEI, in hypertensive, diabetic patients showing no effect of the ARB (but also enalapril) on hsCRP.<sup>60</sup> Similar discrepancies also characterized the effect of telmisartan<sup>59,62,65,66,74,78</sup> including the already commented VIVALDI trial.<sup>77</sup> Positive results were reported for irbesartan in two studies in coronary heart disease patients,<sup>54,57</sup> but their small sample size precludes generalization. Olmesartan was tested in a well designed and carefully conducted prospective, placebo-controlled, double-blind multicenter study by Fliser and colleagues<sup>50</sup> who measured hs-CRP levels and other inflammatory markers in 199 patients with essential hypertension and obesity-related microinflammation. After 12 weeks of therapy, with additional HTCZ if needed, olmesartan decreased hs-CRP (−21.1%;  $P < 0.02$ ), TNF- $\alpha$  (−13.6%;  $P < 0.01$ ), IL-6 (−18.0%;  $P < 0.01$ ) and MCP-1 (−6.5%;  $P < 0.01$ ). Albeit gathered in a well designed and carefully conducted study, those results need confirmation in additional trials, however. A greater anti-inflammatory effect of olmesartan as compared with telmisartan was recently claimed by Nakayama and colleagues,<sup>78</sup> but the conclusion is flawed by the experimental design lacking adequate wash-out prior to randomization. Notably, losartan did not affect CRP in patients with diabetic nephropathy,<sup>34</sup> coronary artery disease,<sup>38</sup> and hypertension.<sup>54</sup> No data are available about the effect of eprosartan.

## ARBs and circulating adhesion molecules, cytokines, and chemokines

A number of clinical studies have assessed the effect of ARBs on circulating inflammatory markers other than CRP such as E-selectin, a member of the selectin family expressed on the surface of stimulated endothelial cells, and ICAM-1 and VCAM-1, two immunoglobulin-like molecules acting as endothelial ligands to facilitate endothelial adhesion of circulating leukocytes.<sup>79</sup> Those biological products circulate in blood as a result of enzymatic cleavage or from shedding of damaged or activated endothelial cells under the influence of proatherogenic stimuli such as hypertension, type 2 diabetes, obesity as well as established peripheral and coronary artery disease.<sup>79,88</sup> While the prognostic power of raised s-eSEL is dubious,<sup>88</sup> circulating ICAM-1 predicted cardiovascular risk independent of traditional risk factors in the 14,916 healthy men enrolled in the Physicians' Health Study (PHS),<sup>89</sup> as well as in the elderly, apparently healthy subjects of the Atherosclerosis Risk in Communities (ARIC) study.<sup>90</sup> On the

other hand, VCAM-1 did not predict future cardiovascular risk,<sup>90</sup> suggesting important distinctions between the roles of different CAMs in atherogenesis. Evidence has also been gathered in support of the clinical relevance of inflammatory cytokines such as circulating IL-6 and TNF- $\alpha$ , and MCP-1, a chemokine that orchestrates the migration of leukocytes into the intima and within atherosclerotic lesions.<sup>79</sup> Increased plasma IL-6 levels were reported early after admission for acute coronary syndromes and associated with a complicated in-hospital course and higher IL-6 levels predicted acute coronary syndromes in apparently healthy men.<sup>91</sup> Post-MI elevations of circulating TNF- $\alpha$ <sup>92</sup> and MCP-1<sup>93</sup> also associated with an increased risk of recurrent coronary events.<sup>89</sup>

As summarized in Table 4, losartan did not affect circulating adhesion molecules in patients with diabetes and/or hypertension and/or coronary artery disease<sup>34,38,39,53</sup> while a significant decrease was reported only in two, small studies in normal subjects.<sup>41,51</sup> The effect of the drug on eSEL, on the other hand, was consistently negative.<sup>34,38,39,41,51</sup> The same discrepant behavior was shared by candesartan,<sup>35,42,60</sup> the other ARBs frequently used in studies of this kind, while either eprosartan<sup>40</sup> or telmisartan<sup>65</sup> treatment did not change VCAM-1 levels to a statistically significant extent. No data are available for irbesartan or olmesartan.

As shown in Table 4, similar considerations hold for the effect of ARBs on MCP-1, TNF- $\alpha$  and IL-6.<sup>42,47,75</sup>

## Conclusions

Despite a quite consistent evidence from basic research field, the anti-inflammatory effect of ARBs in man, at least to the extent derived from their effect on circulating inflammatory indices, is quite inconsistent, a conclusion that applies even to studies apparently adopting the same drug at similar dosages, comparable patient selection criteria and experimental design. Further limitations derive from the small sample sizes that characterize many of the available studies, heterogeneity of ARBs as a pharmacological class (see Table 1), lack of prospective studies evaluating the relationship between anti-inflammatory effects of ARBs and incident morbid events and the complexity of the effects of AngII on vascular biology (Figure 3). Additional difficulties derive from the inherent variability of circulating inflammatory indices, a pattern emerging quite clearly from Table 3 to which genetic factors acting at the individual<sup>94</sup> as well as the population<sup>95</sup> level may contribute. Not unlike ARBs, ACEIs showed divergent results,<sup>96</sup> sometimes in contrast with the effects of the ARBs. Thus, enalapril but not losartan reduced inflammatory markers in hypertensive and diabetic patients.<sup>39</sup>

**Table 4** Percent changes in circulating e-selectin (SEL), intercellular cellular adhesion molecule (ICAM)-I, vascular cellular adhesion molecule (VCAM)-I, interleukin-6 (IL-6), tumor necrosis factor (TNF)- $\alpha$ , monocyte chemoattractant protein (MCP)-I during ARB treatment

Author	Type of ARB	Clinical condition (n. patients)	e-SEL	sICAM-I	sVCAM-I	IL-6	TNF- $\alpha$	MCP-I
Tsutamoto <sup>35</sup>	C	CHF (14)	N/A	↓	↓	↓	↓	N/A
Wassmann <sup>42</sup>	C	HC (17)	N/A	-22.6%*	N/A	N/A	+6.8% <sup>ns</sup>	-18.1%*
Koh <sup>47</sup>	C	HT (47)	N/A	N/A	N/A	N/A	-24%*	-7%*
Rosei <sup>60</sup>	C	HT (61)	-5%*	-4.1%*	N/A	N/A	N/A	N/A
Schram <sup>63</sup>	C	HT (22)	N/A	ns	↓	N/A	N/A	N/A
Ogawa <sup>68</sup>	C/V	HT/T2D (33)	N/A	N/A	N/A	-29.4%	N/A	-25.7%
White <sup>75</sup>	C	CHF (41)	ns	ns	N/A	ns	N/A	Ns
Rahman <sup>40</sup>	E	HT (19)	N/A	N/A	-35%	N/A	N/A	-34%*
Lauten <sup>48</sup>	I	CAD (37)	N/A	N/A	N/A	↓	N/A	N/A
Schieffer <sup>54</sup>	I	CAD/HT (21)	N/A	N/A	N/A	↓	N/A	N/A
De Rosa <sup>64</sup>	I/T	T2D/MS (188)	N/A	N/A	N/A	↓	N/A	N/A
Andersen <sup>34</sup>	L	T1D (29)	-1% <sup>ns</sup>	+2% <sup>ns</sup>	-5%*	N/A	N/A	N/A
Prasad <sup>38</sup>	L	CAD (31)	+2% <sup>ns</sup>	+5% <sup>ns</sup>	+3% <sup>ns</sup>	N/A	N/A	N/A
Jilma <sup>39</sup>	L	HT (15)	-3% <sup>ns</sup>	-5% <sup>ns</sup>	-8% <sup>ns</sup>	N/A	+1% <sup>ns</sup>	+2% <sup>ns</sup>
Rajagopalan <sup>41</sup>	L	NS (18)	ns	-50%*	-24%*	N/A	N/A	-30%*
Graninger <sup>51</sup>	L	NS (7)	0% <sup>ns</sup>	-11%*	-11%*	N/A	N/A	N/A
Koh <sup>52</sup>	L	HT (47)	N/A	N/A	N/A	N/A	N/A	-7%*
Sardo <sup>53</sup>	L	HT (20)	N/A	-3% <sup>ns</sup>	N/A	N/A	-8% <sup>ns</sup>	N/A
Fliser <sup>50</sup>	o	HT (100)	N/A	N/A	N/A	-18%*	-14%*	-4%*
Link <sup>65</sup>	T	HT (21)	N/A	N/A	-14% <sup>ns</sup>	-38% <sup>ns</sup>	-39% <sup>ns</sup>	N/A
Nagel <sup>66</sup>	T	HT/MS (20)	N/A	N/A	N/A	-8% <sup>ns</sup>	N/A	N/A
Manabe <sup>58</sup>	V	HT (39)	N/A	N/A	N/A	-4%*	-33%*	N/A
Nomura <sup>67</sup>	V	HT/DIAB (28)	-6.1%*	-3.6%	N/A	N/A	-6.6%*	-4.7%*
Rajagopalan <sup>73</sup>	V	HT (107)	N/A	N/A	N/A	N/A	N/A	-15.6%*

**Abbreviations:** C, candesartan; I, irbesartan; L, losartan; O, olmesartan; T, telmisartan; V, valsartan; CHF, congestive heart failure; HC, hypercholesterolemia; HT, hypertension; CAD, coronary artery disease; T2D, type 2 diabetes; T1D, type 1 diabetes; NS, normal subjects; MS, metabolic syndrome; B, baseline; P, concurrent placebo; ns, not significant; N/A, not assessed.

**Notes:** ↓ Indicates significant reductions in absence of precise figures retrievable from the publication. \*Denotes statistical significance ( $p < 0.05$  or less).

It should also be noted that interference on inflammatory indices is not specific for RAS inhibitors since other classes of cardiovascular drugs such as beta-adrenoceptor blocking drugs,<sup>97,98</sup> statins<sup>99</sup> as well as nonpharmacological interventions such as exercise training, weight loss<sup>94</sup> and nutritional factors<sup>100</sup> may influence CRP levels. Suggestions have also been raised about a beneficial effect of intensive blood pressure and lipid treatment *per se*.<sup>101</sup> Moreover, the validity of circulating inflammatory markers as a surrogate end-point for an underlying inflammatory process is unclear since the relationship with their activity at the local level is unknown. Importantly, modifications in circulating CRP, even when highly consistent such as in the case of statins,<sup>99</sup> have dubious pathophysiological significance since decrements in hsCRP were associated with either no change,<sup>102,103</sup> or improved cardiovascular prognosis.<sup>104</sup> As a matter of fact, the LDL- and

CRP-lowering effect of statins<sup>99,105</sup> are closely intertwined, possibly as an expression of their metabolic effect on the liver. For these reasons, no firm conclusions can be drawn about their effect at this point and further studies are needed.

## Disclosure

The authors report no conflicts of interest in this work.

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