pagepress

Monaldi Archives for Chest Disease 2021; volume 91:1570

Effects of inhibition of the renin-angiotensin system on hypertension-induced target organ damage: clinical and experimental evidence

Maria Rosaria De Luca[1], Daniela Sorriento[2], Domenico Massa[2], Valeria Valente[1], Federica De Luise[2], Emanuele Barbato[2], Carmine Morisco[2]

[1]Department of Translational Medical Science; [2]Department of Advanced Biomedical Sciences, Federico II University of Naples, Italy

Abstract

The dysregulation of renin-angiotensin-system (RAS) plays a pivotal role in hypertension and in the development of the related target organ damage (TOD). The main goal of treating hypertension is represented by the long-term reduction of cardiovascular (CV) risk. RAS inhibition either by angiotensin converting enzyme (ACE)-inhibitors or by type 1 Angiotensin II receptors blockers (ARBs), reduce the incidence of CV events in hypertensive patients. Actually, ACE-inhibitors and ARBs have been demonstrated to be effective to prevent, or delay TOD like left ventricular hypertrophy, chronic kidney disease, and atherosclerosis. The beneficial effects of RAS blockers on clinical outcome of hypertensive patients are due to the key role of angiotensin II in the pathogenesis of TOD. In particular, Angiotensin II through an inflammatory-mediated mechanism plays a role in the initiation, progression and vulnerability of atherosclerotic plaque. In addition, Angiotensin II can be considered the hormonal transductor of the pressure overload in cardiac myocytes, and through an autocrine-paracrine mechanism plays a role in the development of left ventricular hypertrophy. Angiotensin II by modulating the redox status and the immune system participates to the development of chronic kidney disease. The RAS blocker should be considered the first therapeutic option in patients with hypertension, even if ACE-inhibitors and ARBs have different impact on CV prevention. ARBs seem to have greater neuro-protective effects, while ACE-inhibitors have greater cardio-protective action.

Correspondence: Prof. Carmine Morisco, Dipartimento di Scienze Biomediche Avanzate, Università degli Studi Federico II, Via S. Pansini n. 5, 80131 Napoli, Italy.
Email: carmine.morisco@unina.it

Key words: Left ventricular hypertrophy; chronic kidney disease; atherosclerosis; ACE-inhibitors; Type 1 angiotensin II receptor antagonists; myocardial infarction; stroke.

Authors' contributions: DLMR, MC, study concept; MD, SD, FDL, VV, literature search; MC, manuscript original draft; BE, critical revision. All the authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: The authors declare that they have no competing interests, and all authors confirm accuracy.

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

Ethics approval: Not applicable.

Received for publication: 13 August 2020.
Accepted for publication: 3 October 2020.

Monaldi Archives for Chest Disease 2021; 91:1570
doi: 10.4081/monaldi.2021.1570

Introduction

Essential hypertension is one of the major cardiovascular (CV) risk factor. The main objective of treating hypertension is long-term reduction of cardiovascular (CV) risk. This goal can be achieved through: i) the optimal control of blood pressure (BP) [1]; ii) the prevention of hypertension-related target organ damage (TOD) with related metabolic complications; and ii) the reduction of CV events. The dysregulation of renin-angiotensin-system (RAS) plays a pivotal role not only in the genesis of hypertension, but also in the development of TOD, diabetes, obesity, atherosclerosis and occurrence of major CV events. In fact, it has been documented that angiotensin II (Ang II), the effector of RAS, is involved in the regulation of endothelial function, tissue remodeling, inflammation, oxidative stress, differentiation of adipocytes, glucose metabolism and electrolytes homeostasis (Figure 1). Blocking the RAS either with angiotensin converting enzyme (ACE)-inhibitors, or with the type 1 Ang II (AT_1) receptors blockers (ARBs), reduce the incidence of CV events in hypertensives and in patients with high CV risk [2-5]. ACE-inhibitors block the conversion of angiotensin-I into Ang II reducing the circulating and local levels of Ang II. ACE-inhibitors also reduce the release of aldosterone and vasopressin, decrease the activity of sympathetic nervous system, as well as the trophic effects of Ang II on cardiac muscle and vessels. The inhibition of ACE results into an increase in plasma bradykinin levels, which in turn, stimulates type 2 bradykinin receptors leading to the release of nitric oxide

pagepress

(NO) and vasoactive prostaglandins (prostacyclin and prostaglandin E2). These pharmacological effects are translated in several biological actions like a BP reduction associated with a decrease in plasma levels of epinephrine, norepinephrine and vasopressin. There is also an interference with development of vascular and cardiac hypertrophy and extracellular matrix proliferation, and a decrease in renal vascular resistances. Finally, pharmacological intervention might result into an increase of renal blood flow, which in turn, promotes Na^+ and water excretion, and in the modulation of fibrinolytic balance favoring antithrombotic pathways.

AT_1 receptors belong to the superfamily of G-protein–coupled receptors, characterized by 7 trans-membrane regions, and are localized in the kidney, heart, endothelium, vascular smooth muscle cells, brain, adrenal gland, platelets, adipocytes, and placenta. The AT_1 receptors mediate most of the detrimental effects of Ang II on CV system. ARBs act by blocking the AT_1 receptors and thus prevent the pathophysiological effects mediated by Ang II binding to the AT_1 receptor. Moreover, as a consequence of AT_1 blockade, ARBs increase systemic and local levels of Ang II. Increased levels of Ang II result in the unopposed stimulation of the AT_2 receptors. It has been proposed that stimulation of AT_2 receptors exerts an important role in counterbalancing some of the detrimental effects of Ang II on CV system: e.g. the inhibition cell growth, the promotion of cell differentiation, and the synthesis of NO. Finally, for some ARBs has been documented an agonist action on PPAR-γ receptors. Of note, these pharmacologic effects contribute to the improvement of insulin sensitivity. Altogether the latter pharmacological properties contribute to prevent the development of hypertension-induced TOD, and of associated diseases such as diabetes, atherosclerosis, and renal disease. These effects appear to be independent from ARBs-induced BP reduction.

RAS inhibition and hypertension-related TOD

Heart, kidney, arteries, brain are target organs of hypertension. Hypertension-induced TODs are important determinants of CV risk and represent a key target of antihypertensive therapy. Notably the combination of different TODs like LVH plus chronic kidney disease (CKD) has an additive effect on the incidence of CV events [6]. Ang II plays a critical role in the pathogenesis and progression of TODs and, in general, in the continuum of CV diseases (Figure 2). Thus, the RAS blockade must be considered as the first choice therapy of hypertensive patients with evidence of TODs.

Left ventricular hypertrophy

Left ventricular hypertrophy (LVH) is an independent risk factor for morbidity and mortality for CV diseases. BP is an important determinant of LVH, and a substantial percentage of patients with hypertension develop this complication. However, the development of LVH is complex and multifactorial involving genetic and metabolic abnormalities, neuro-hormonal stimulation, mechanical

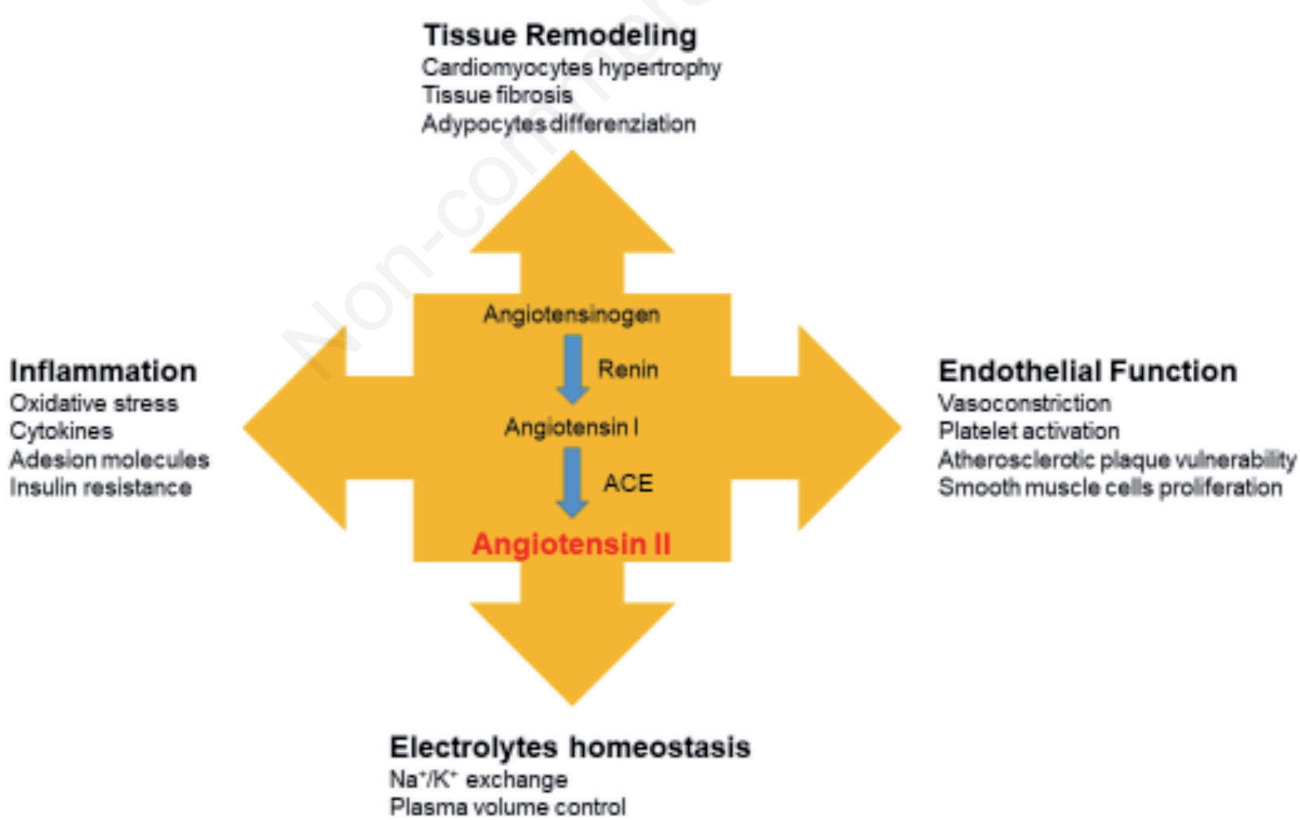

Figure 1. Pleiotropic effects of Angiotensin II. Angiotensin II plays a key role in the control of several pathogenic mechanisms that ultimately are involved in the development of hypertension-induced target organ damage. ACE, angiotensin converting enzyme.

forces, and inflammatory response (Figure 3). For instance, in newly diagnosed hypertensive patients, naïve to therapy, metabolic and anthropomorphic abnormalities together with systolic BP values were shown to be independent predictors of LVH [7].

Clinical evidence: Several studies analyzed the effects of different classes of antihypertensive drugs on LVH. The first meta-analysis assessing the ability of various antihypertensive agents to reduce left ventricular hypertrophy was published in 1996 by Schmieder *et al*. [8]. After adjustment for different treatment durations, left ventricular mass decreased by 13% with ACE inhibitors, 9% with calcium channel blockers, 6% with beta-blockers, and 7% with diuretics. There was a significant difference between classes of drugs: e.g. ACE inhibitors reduced left ventricular mass more than beta-blockers and diuretics, suggesting ACE inhibitors might be the first-line drugs to reduce LVH. Note, ARBs were not yet commercially available at the time. In 2003 was published another meta-analysis including also clinical trials investigating ARBs [9]: here, ARBs, calcium antagonists, and ACE-inhibitors were shown to be the most effective drugs to reducing left ventricular mass in patients with essential hypertension (Figure 4). In 2009 a metaregression-analysis [10] showed that ARBs induce the largest regression of LVH. In addition, ARBs are able also to interfere with the development of myocardial fibrosis. In fact, a sub-analysis of the LIFE study showed that ARBs decreased myocardial collagen content, whereas other drugs did not [11]. These studies indicate that RAS inhibition with both ACE-inhibitors or ARBs represents a valid pharmacologic strategy to prevent or reduce LVH.

Experimental data: The results of several experimental and pioneering studies suggest that Ang II plays a key role in the pathogenesis of LVH. For instance, treatment with an ACE inhibitor or ARBs causes regression or prevents the development of LVH [12,13] in animal models of pressure overload. Moreover, ACE inhibitor treatment is able to ameliorate the survival in a murine model of pressure overload [14]. These results are consistent with

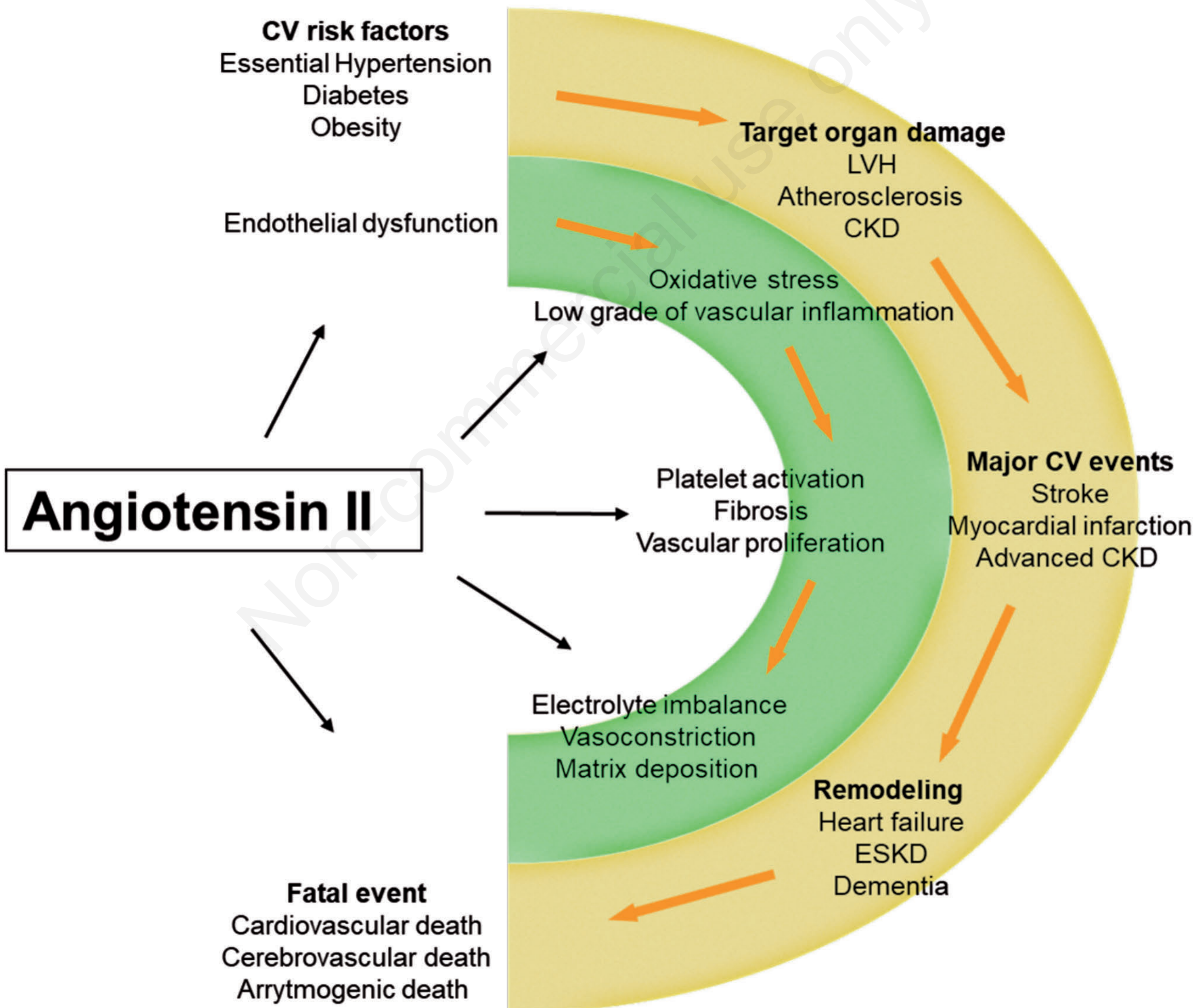

Figure 2. The key role of angiotensin II in the continuum of cardiovascular disease. Angiotensin II plays a key role in the pathogenesis of conventional cardiovascular risk factors, in the development and progression of target damage, in pathogenesis of major cardiovascular events and in their remodeling in final organ damage, and in the occurrence of death. CV, cardiovascular; LVH, left ventricular hypertrophy; CKD, chronic kidney disease; ESKD, end-stage kidney disease.

the involvement of RAS in the pathogenesis of LVH, and its activation by the hemodynamic loading in vivo. The role of Ang II as a critical mediator of stretch-induced hypertrophy has been shown in the neonatal rat cardiac myocyte system *in vitro*. Ang II receptor antagonists like [Sar1 Ile8]-Ang II (antagonist for the Ang II type I and II receptors) and losartan and TCV11974 (antagonists for the Ang II type I receptor) inhibit the stretch-induced hypertrophy of cardiac myocytes [15], suggesting that Ang II plays a critical role in stretch-induced hypertrophy. In addition, several data are consistent with the concept that cardiac RAS is chronically upregulated in loading-induced hypertrophy. In fact, mRNA expression of angiotensinogen, of renin, of ACE, and of Ang II receptors results into an upregulated cardiac hypertrophy induced by pressure overload and ischemia [16]. The upregulation of the cardiac RAS was also observed *in vitro*, in neonatal rat cardiac myocytes in response to mechanical stretch [17]. Treatment of cultured cardiac myocytes with exogenous Ang II also upregulates mRNA expression of angiotensinogen, renin, and ACE, but not of Ang II receptor [18]. This suggests that mechanical stretch initially causes acute secretion of preformed Ang II, and that secreted Ang II through an autocrine-paracrine mechanism may initiate a positive feedback, thereby upregulating the local RAS over the time (Figure 5). Further studies demonstrated an additive molecular mechanism that account for Ang II-mediated development of LVH. In particular, Bendall *et al*. demonstrated, in transgenic mice lacking the gp91^{phox} subunit of NADPH oxidase, that 2 week-stimulation of subpressor doses of Ang II stimulation failed to induce LVH, this was associated with inhibition to superoxide production [19]. The result of this study indicated that oxidative stress is centrally involved in the direct cardiac hypertrophic response to Ang II.

Chronic kidney disease

Development of CKD is one of the TODs secondary to essential hypertension. Ang II plays a key role in the pathogenesis of CKD. In particular, Ang II stimulation induces endothelial dysfunction, which in the kidneys can evolve to glomerulosclerosis, tubulointerstitial fibrosis and vascular sclerosis. These abnormalities are responsible of the development of overt nephropathy that can evolve to end-stage renal disease (ESRD). Clinical manifestations of hypertension-induced nephropathy are: i) macroalbuminuria or proteinuria; ii) decrease of glomerular filtration rate (GFR); iii) increase in serum creatinine levels. In the last decades, the role of microalbuminuria has also emerged as an important determinant of CV events [20,21]. Although the achievement of a tight BP control is an important goal to prevent CKD, this strategy alone often is not enough to prevent the development and progression of CKD. The benefit of ACE inhibitor therapy in reducing proteinuria and

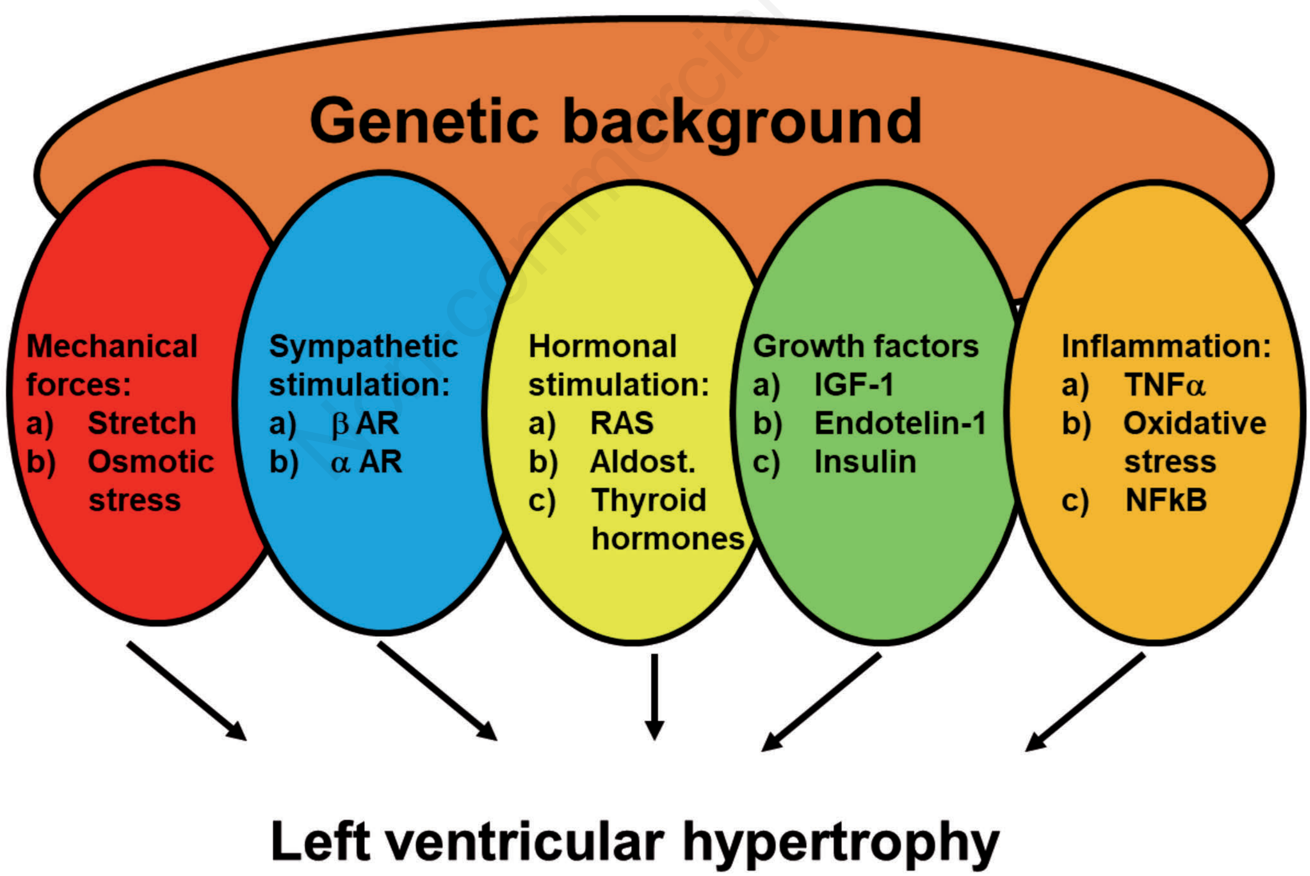

Figure 3, Determinants of left ventricular hypertrophy. Development of left ventricular hypertrophy is complex and multifactorial biological process involving genetic background, mechanical forces, sympathetic, hormonal, and growth factors stimulation, and inflammatory response. AR, adrenergic receptors; RAS, renin-angiotensin system; Aldost., aldosterone; IGF-1, insulin like growth factor-1; TNF , tumor necrosis factor- ; NFkB, nuclear factor kappa B.

the progression of CKD in non-diabetic patients are known since 1990s; similarly, beneficial effects were demonstrated also for ARBs in nondiabetic nephropathies [22]. Thus, antihypertensive drugs that interfere with RAS confer renal protection with other classes of antihypertensive agents.

Clinical evidence: The first convincing demonstration of the ability of ACE-inhibitors to interfere with the progression of CKD comes from the REIN study. This study showed that patients who had proteinuria of ≥3 g/day and were treated with the ACE inhibitor showed a significant lower rate of decline in GFR and a reduced risk of doubling serum creatinine or end-stage renal failure as compared with patients who received the conventional therapy [23]. The favorable effects of ACE-inhibitors in the delay of CKD were confirmed by several meta-analyses [24-26]. CKD represents also an independent risk factor for the development of LVH and heart failure; at this regard, it is noteworthy that in patients with ESRD, ARBs reduce LVH [27]. The beneficial effects of ARBs were also documented in diabetic nephropathy, as well as in patients with non-diabetic nephropathy. The Japanese Losartan Therapy Intended for the Global Renal Protection in HyperTensive Patients (JLIGHT) study examined the effect of Losartan in comparison with Amlodipine. This study showed that although Losartan and Amlodipine had a comparable antihypertensive effect, Losartan based treatment significantly reduced the severity of proteinuria [28]. In addition, the Angiotensin II Receptor Antagonist Micardis in Isolated Systolic hypertension (ARAMIS) study compared the antihypertensive efficacy of Telmisartan versus Hydrochlorothiazide or placebo in patients with isolated systolic hypertension. This study showed that, despite comparable reductions in systolic BP with both drugs, Telmisartan treatment significantly reduced urinary albumin excretion than hydrochlorothiazide [29].

There is compelling evidence that RAS blockade obtained with either ACE-inhibitors or ARBs reduce proteinuria, halting or slowing the decline of GFR in patients with hypertension, even in those with ESRD. However, not all patients treated with ACE inhibitors or ARBs achieve an adequate nephroprotective effect. This phenomenon might be explained by an incomplete blockade of RAS, due to the escape of Ang II. In particular, different pathways (mainly chymases), especially in diabetic nephropathy, can account for an alternative pathway of Ang II synthesis. The combination of ACE inhibitor plus ARBs may potentially help to overcome the escape of Ang II. The nephro-protective effects of dual RAS blockade with both ACE inhibitor and ARBs were evaluated by two meta-analyses [30,31] showing favorable synergistic actions in reducing proteinuria and slowing CKD progression. However, these actions were not confirmed by the ONTARGET study [4] in which patients were randomized to receive ACE-inhibitor (ramipril 10 mg daily) or ARB (telmisartan 80 mg daily) or both drugs. In particular, this study reported an increased incidence of dialysis, doubling of serum creatinine and of death during the combined therapy of ACE inhibitor and ARBs compared with the monotherapy. Nowadays there are no

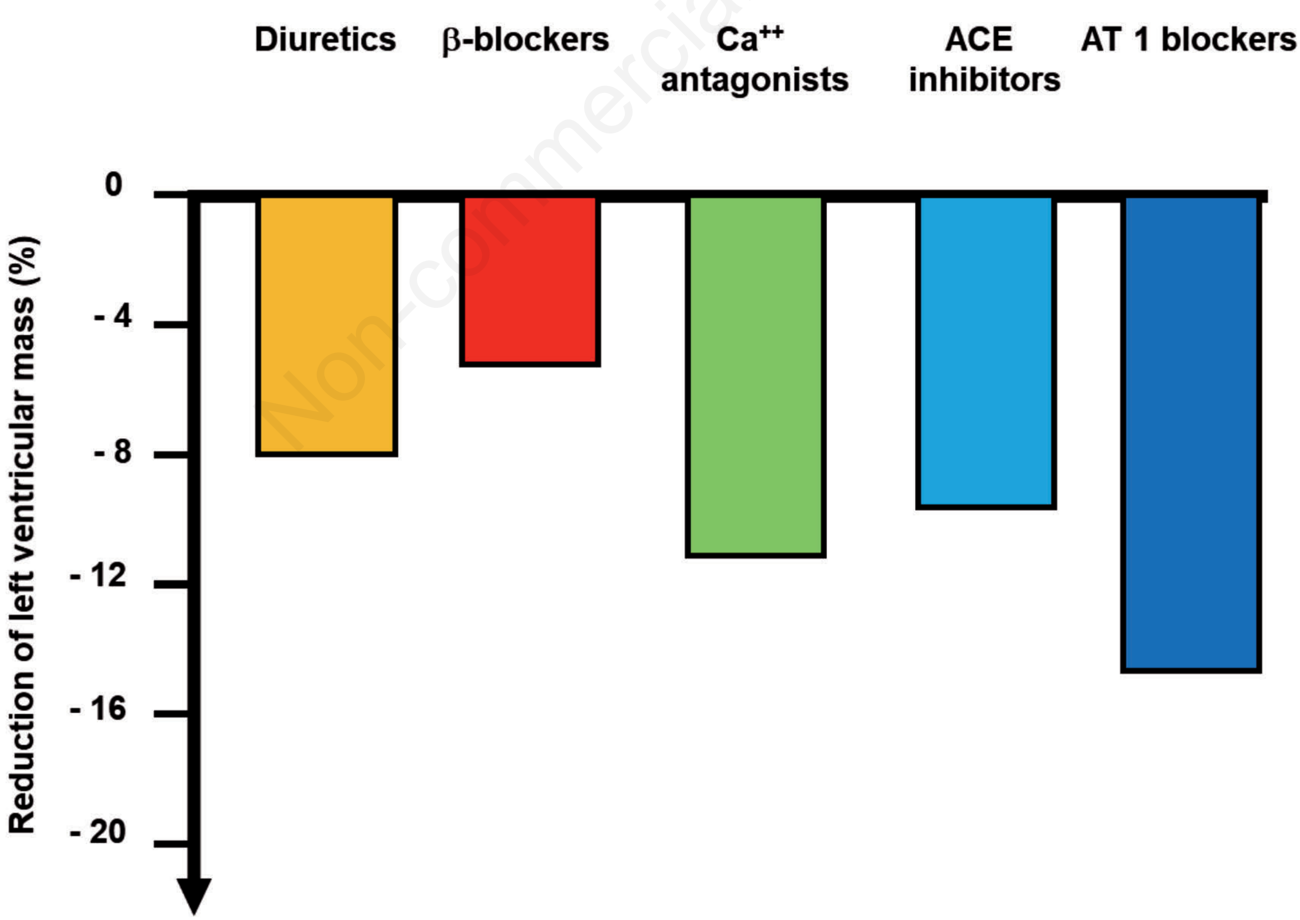

Figure 4. Effects of different classes of antihypertensive drugs on regression on left ventricular hypertrophy.

clinical evidence that the combination of ACE inhibitors plus ARBs has an additive effect in terms of nephroprotection, and this association is not recommended.

Experimental data: the main pathogenic mechanism responsible for the development of CKD involves chronic inflammation, oxidative stress, endothelial dysfunction, and vascular calcification. Ang II exerts in the kidney a control on cell growth, inflammation, and fibrosis [32]. These experimental data indicate that Ang II plays a pivotal role in the genesis of CKD by modulating the redox status and the immune system. In fact, Ang II increases tumor necrosis factor-alpha production and upregulates other pro-inflammatory mediators, including interleukin-6, monocyte chemotactic protein-1, and nuclear factor-kB [33]. In addition, Ang II is involved into the pathogenesis of CKD by also modulating the activation and infiltration of immunocompetent cells. Altogether these actions result in a complex network of glomerular stresses. There is some evidence demonstrating that the beneficial effects of the RAS blockade may be related to anti-inflammatory properties of ACE-inhibitors and ARBs [34]. In particular, the exposure of monocytes to captopril affects the cytokine-induced translocation of nuclear factor-kB translocation from the cytoplasm to the nucleus [35]. Furthermore, in patients with ESRD, ACE-inhibitor-based treatment reduces plasma levels of tumor necrosis factor-alpha and C-reactive protein.

These studies indicate that the main pathogenic mechanism that account of development of CKD in hypertension is an Ang II-evoked inflammatory response, and the blockade of RAS reduces the mediators of this response.

Atherosclerosis

Essential hypertension is an established risk factor for the development of atherosclerosis. Both clinical and experimental data indicate that hypertension promotes and accelerates the atherosclerotic process through Ang II-mediated mechanisms. In particular, Ang II promotes the inflammatory processes and oxidative stress that lead to the formation of atherosclerotic plaques and increases its vulnerability. Interference with RAS has been demonstrated to reduce the progression of the atherogenic process.

Clinical evidence: The first large, randomized trial that demonstrated the beneficial effects of ACE-inhibitor on CV morbidity and mortality was the HOPE study. Although many patients included in this study were not affected by essential hypertension, this study demonstrated in high-risk patients that the addition of ramipril to the standard therapy significantly reduced the rate of the primary composite endpoint [36]. Interestingly, in this study the use of ramipril reduced not only the cardio- and cerebro-vascular events, but also interfered with the progression of atherosclerotic disease. In fact, the SECURE study, a substudy of the HOPE trial, demonstrated that the rate of progression of the maximum carotid artery intima-media thickness (IMT) was significantly lower in the group randomized to Ramipril compared with placebo ($p=0.028$) [37]. In hypertensive patients, candesartan and losartan [38,39] respectively slow the progression of carotid artery remodeling. The effects of RAS blockade were repeatedly shown to impact on the mechanisms involved in the development and progression of atherosclerosis. In particular, Candesartan significantly decreases plasma levels of plasminogen activator inhibitor type-1 (PAI-1), as well as monocyte chemoattractant protein-1 [40] and circulating levels of adhesion molecules ICAM-1 and VCAM-1 [41]. Similar actions have been reported for ibesartan, valsartan and losartan. In addition, Olmesartan medoxomil-based therapies interfere with the vascular inflammation and progression of atherosclerosis not only in carotids, but also in coronary arteries. In particular, the OLIVUS study showed that olmesartan medoxomil decreased the rate of coronary atheroma progression in patients with stable angina pectoris [42].

The beneficial effects of RAS inhibition on the development

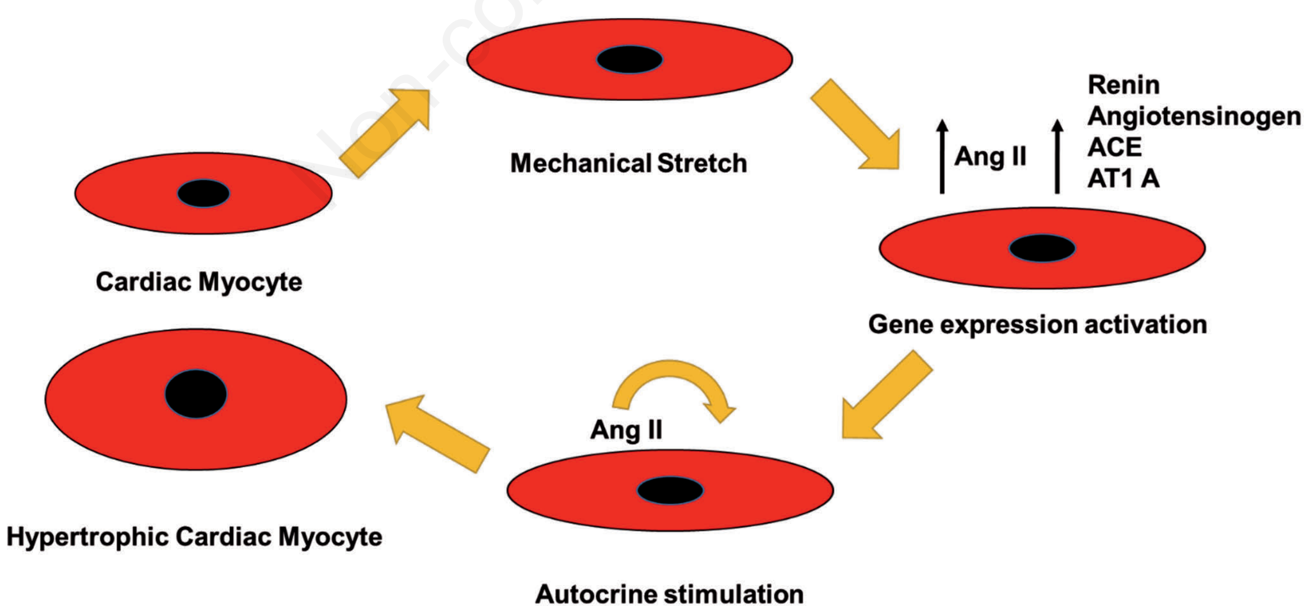

Figure 5. The role of renin angiotensin system in stretch-induced cardiac myocytes hypertrophy. Mechanical stretch initially causes acute secretion of preformed Angiotensin II, simultaneously stimulates gene expression of all components of tissue renin angiotensin system like angiotensinogen, renin, ACE, and Ang II receptor. Together these adaptive responses initiate a positive feedback mechanism that is responsible for the hypertrophic growth. Ang II, angiotensin II; ACE, angiotensin converting enzyme; AT1, Type 1 Ang II receptor.

and progression of atherosclerosis are corroborated by several studies that evaluated the capability of ACE-inhibitors and ARBs to prevent the major cerebrovascular and cardiovascular events (i.e. stroke and myocardial infarction). The beneficial effects of RAS inhibition on the incidence of stroke in hypertensive patients is well documented. The first meta-analysis was published by Turnbull *et al*. in 2003 [43]. This showed that ACE-inhibitors reduced the risk of stroke compared with placebo by 28%; while ARBs reduced the risk of stroke compared with control regimens by 21%. In 2008, Reboldi *et al*. showed that the administration of ARBs was associated with a small but statistically significant reduction in the risk of stroke compared with the administration of ACE-inhibitors [44]. This last meta-analysis seems to indicate that ARBs compared with ACE-inhibitors, have a slightly greater protective effect on stroke. However, in 2009 it was published a further meta-analysis that showed no difference in terms of neuroprotection between ACE-inhibitors and ARBs [45].

The effects of RAS inhibition on prevention of myocardial infarction are still debated and in some cases controversial. This controversy started from the publication of results of the VALUE study [46] in which a significant increase of myocardial infarction was detected in the Valsartan group compared with the Amlodipine group. On these bases, Verma and Strauss raised the hypothesis that ARBs, unlike ACE inhibitors, might increase the rates of myocardial infarction despite their beneficial effects on reducing BP [47]. This theory, called "ARB-myocardial infarction paradox" was not confirmed by the meta-analysis of Bangalore *et al*. [48]. Here, ARBs were not associated with any increase in the risk of myocardial infarction. These authors concluded that ARBs do not increase the risk of myocardial infarction; however, they do not have any beneficial effect on both myocardial infarction and cardiovascular mortality. However, further meta-analyses showed opposite results. In particular, Stauss and Hall [49] showed that only incidence of stroke was lower in patients treated with ARBs compared with placebo. Overall death was not reduced by ARBs whereas myocardial infarction was significantly increased by 8%. The results of this meta-analysis clearly demonstrate that compared with placebo, ACE inhibitors reduce the incidence of myocardial infarction and CV death, whereas there is no evidence than an ARBs are better than placebo. The same authors 10 years later, in a point of view underlined the current clinical relevance of their meta-analysis [50]. These observations are consistent with the concept that the use of ACE-inhibitors is more effective in reducing overall and cardiovascular death as compared with ARBs [51].

Experimental evidence: Vascular inflammation is considered nowadays the principal pathogenic mechanism of atherosclerosis [52]. Ang II plays a pivotal role not only in the development of atherosclerosis but also in the vulnerability of atherosclerotic plaques through the modulation of inflammation state. In fact, Ang II regulates the gene expression and synthesis of adhesion molecule (VCAM-1, ICAM-1, P-selectin), cytokine, chemokine, and growth factor of the arterial wall. In addition, RAS positively regulates the complement system, resulting in vascular inflammation and mobilization/and activation of inflammatory cells. The RAS stimulates also coagulation cascade and platelet aggregation. In particular, Ang II is a potent stimulator of tissue factor in monocytes and vascular endothelial cells [53], which in concert with further mediators contribute to the pathogenesis of coronary heart disease in patients with hypertension [54]. Bench tests indicate that RAS blockade exerts potent antiatherosclerotic effects, through anti-inflammatory, antiproliferative, and antioxidant actions [55]. Treatment with the ACE-inhibitor trandolapril reduces endothelial dysfunction in hyperlipidemic rabbits [56]. In addition, administration of quinapril to rabbits reduced macrophage infiltration in atherosclerotic lesions in femoral arteries through the direct inhibition of macrophage chemoattractant protein (MCP)-1 expression. The favorable effects of RAS blockade were also reported in animal models of hypertension. In particular, in stroke prone spontaneously hypertensive rats (SHR-SP) administration of ramipril reduced mortality and improved LVH, cardiac and endothelial functions [57]. These pharmacological effects in SHR-SP rats were documented also for ARBs as losartan, and telmisartan [58]. Of note, these experimental data indicate that ARBs compared to ACE-inhibitors might have a greater and specific cerebral protective effect, independently from their antiatherosclerotic action. In fact, pretreatment of rats with low doses of candesartan but not ramipril, significantly reduced the stroke extension and improved the neurological outcome after induction of acute cerebral ischemia by middle cerebral artery occlusion. In addition, post-stroke mRNA and protein expression of the neurotrophin receptor, TrkB, were significantly elevated in animals treated with candesartan, compared with ramipril [59].

ACE inhibitors seem to be more effective than ARBs in terms of cardiac protection. In fact, the inhibition of breakdown of bradykinin exerted by ACE inhibitors represents an 'adjunctive' mechanism. Bradykinin inhibits both platelet aggregation and circulating PAI-I levels and is one of the most potent stimulators of tissue plasminogen activator. Furthermore, bradykinin promotes the vasodilatation via the release of prostacyclin, NO, and endothelium-derived hyperpolarizing factor. On the other hand, bradikinin is also a mediator of ischemic preconditioning [60]. Ischemic preconditioning has great pathophysiological relevance, since it confers protection against ischemia-induced cell death to those organs that are composed of terminally differentiated cells, like the brain and heart. To further explain the lack of cardioprotective effects of ARBs it should be considered that experimental evidence indicates that AT2 receptor stimulation, rather than to be beneficial, as previously proposed, seems to be detrimental for cardiovascular system. In particular, under certain circumstances, stimulation of AT2 receptors has pro-atherogenic and pro-inflammatory effects. To corroborate this hypothesis there is the evidence that in human myocytes Ang II may promote plaque rupture by augmenting matrix metalloproteinase-1 in an AT2-dependent fashion and by preventing growth of vascular smooth muscle cells with reduced collagen deposition and additional cellular apoptosis within advanced plaques [61].

Highlights and clinical implications

- Hypertension-induced TODs account for enhanced CV risk.
- RAS through the inflammatory response in an important pathogenic mechanism of TODs.
- Inhibition of RAS with ACE-inhibitors or with ARS is able to prevent or delay the development of TOD.
- ACE-inhibitors and ARBs have different impact on CV prevention. ARBs seem to have greater neuroprotective effects, while ACE-inhibitors have greater cardioprotective action.

References

1. Volpe M, Gallo G, Battistoni A, Tocci G. Highlights of ESC/ESH 2018 Guidelines on the management of hyperten-

sion: What every doctor should know. High Blood Press Cardiovasc Prev 2019;26:1-8. doi: 10.1007/s40292-018-00297-y
2. Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 2002;359:995-1003. doi: 10.1016/S0140-6736(02)08089-3
3. Heart Outcomes Prevention Evaluation Study Investigators, Yusuf S, Sleight P, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000;342:145-53. [Corrections in N Engl J Med 2000;342:1376 and 2000;342:748]. doi: 10.1056/NEJM200001203420301
4. ONTARGET Investigators, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547-59. doi: 10.1056/NEJMoa0801317
5. Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators, Yusuf S, Teo K, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. Lancet 2008;372:1174-83. [Correction in Lancet 2008;372:1384]. doi: 10.1016/S0140-6736(08)61242-8
6. Carpinella G, Pagano G, Buono F, et al. Prognostic value of combined target-organ damage in patients with essential hypertension. Am J Hypertens 2015;28:127-34. doi: 10.1093/ajh/hpu098
7. Buono F, Crispo S, Pagano G, et al. Determinants of left ventricular hypertrophy in patients with recent diagnosis of essential hypertension. J Hypertens 2014;32:166-73. doi: 10.1097/HJH.0b013e328365c87d
8. Schmieder RE, Martus P, Klingbeil A. Reversal of left ventricular hypertrophy in essential hypertension. A meta-analysis of randomized double-blind studies. JAMA 1996;275:1507-13.
9. Klingbeil AU, Schneider M, Martus P, et al. A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. Am J Med 2003;115:41-6. doi: 10.1016/s0002-9343(03)00158-x
10. Fagard RH, Celis H, Thijs L, Wouters S. Regression of left ventricular mass by antihypertensive treatment: a meta-analysis of randomized comparative studies. Hypertension 2009;54:1084-91. doi: 10.1161/HYPERTENSIONAHA.109.136655
11. Ciulla MM, Paliotti R, Esposito A, et al. Different effects of antihypertensive therapies based on losartan or atenolol on ultrasound and biochemical markers of myocardial fibrosis: results of a randomized trial. Circulation 2004;110:552-7. doi: 10.1161/01.CIR.0000137118.47943.5C
12. Bruckschlegel G, Holmer SR, Jandeleit K, et al. Blockade of the renin-angiotensin system in cardiac pressure-overload hypertrophy in rats. Hypertension 1995;25:250-9. doi: 10.1161/01.hyp.25.2.250
13. Kojima M, Shiojima I, Yamazaki T, et al. Angiotensin II receptor antagonist TCV-116 induces regression of hypertensive left ventricular hypertrophy in vivo and inhibits the intracellular signaling pathway of stretch-mediated cardiomyocyte hypertrophy in vitro. Circulation 1994;89:2204-11. doi: 10.1161/01.cir.89.5.2204
14. Weinberg EO, Schoen FJ, George D, et al. Angiotensin-converting enzyme inhibition prolongs survival and modifies the transition to heart failure in rats with pressure overload hypertrophy due to ascending aortic stenosis. Circulation 1994;90:1410-22. doi: 10.1161/01.cir.90.3.1410
15. Yamazaki T, Komuro I, Kudoh S, et al. Angiotensin II partly mediates mechanical stress-induced cardiac hypertrophy. Circ Res 1995;77:258-65. doi: 10.1161/01.res.77.2.258
16. Suzuki J, Matsubara H, Urakami M, Inada M. Rat angiotensin II (type 1A) receptor mRNA regulation and subtype expression in myocardial growth and hypertrophy. Circ Res 1993;73:439-47. doi: 10.1161/01.res.73.3.439
17. Malhotra R, Sadoshima J, Brosius FC 3rd, Izumo S. Mechanical stretch and angiotensin II differentially upregulate the renin-angiotensin system in cardiac myocytes in vitro. Circ Res 1999;85:137-46. doi: 10.1161/01.res.85.2.137
18. Shyu KG, Chen JJ, Shih NL, et al. Angiotensinogen gene expression is induced by cyclical mechanical stretch in cultured rat cardiomyocytes. Biochem Biophys Res Commun 1995;211:241-8. doi: 10.1006/bbrc.1995.1802
19. Bendall JK, Cave AC, Heymes C, et al. Pivotal role of a gp91(phox)-containing NADPH oxidase in angiotensin II-induced cardiac hypertrophy in mice. Circulation 2002;105:293-6. doi: 10.1161/hc0302.103712
20. Bigazzi R, Bianchi S, Baldari D, Campese VM. Microalbuminuria predicts cardiovascular events and renal insufficiency in patients with essential hypertension. J Hypertens 1998;16:1325-33. doi: 10.1097/00004872-199816090-00014
21. Meccariello A, Buono F, Verrengia E, et al. Microalbuminuria predicts the recurrence of cardiovascular events in patients with essential hypertension. J Hypertens 2016;34:646-53. doi: 10.1097/HJH.0000000000000846
22. Taal MW, Brenner BM. Renoprotective benefits of RAS inhibition: from ACEI to angiotensin II antagonists. Kidney Int 2000;57:1803-17. doi: 10.1046/j.1523-1755.2000.00031.x
23. [No authors listed]. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Lancet 1997;349:1857-63.
24. Kshirsagar AV, Joy MS, Hogan SL, et al. Effect of ACE inhibitors in diabetic and nondiabetic chronic renal disease: a systematic overview of randomized placebo-controlled trials. Am J Kidney Dis 2000;35:695-707. doi: 10.1016/s0272-6386(00)70018-7
25. Jafar TH, Schmid CH, Landa M, et al. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data Ann Intern Med 2001;135:73-87. [Correction in Ann Intern Med 2002;137:299]. doi: 10.7326/0003-4819-135-2-200107170-00007
26. Burnier M, Lin S, Ruilope L, et al. Effect of angiotensin receptor blockers on blood pressure and renal function in patients with concomitant hypertension and chronic kidney disease: a systematic review and meta-analysis. Blood Press 2019;28:358-74. doi: 10.1080/08037051.2019.1644155
27. Yang LY, Ge X, Wang YL, et al. Angiotensin receptor blockers reduce left ventricular hypertrophy in dialysis patients: a meta-analysis. Am J Med Sci 2013;345:1-9. doi: 10.1097/MAJ.0b013e318249d387
28. Iino Y, Hayashi M, Kawamura T, et al. Renoprotective effect of losartan in comparison to amlodipine in patients with chronic kidney disease and hypertension--a report of the Japanese Losartan Therapy Intended for the Global Renal Protection in

Hypertensive Patients (JLIGHT) study. Hypertens Res 2004;27:21-30. doi: 10.1291/hypres.27.21
29. Vogt L, Navis G, Köster J, et al. The angiotensin II receptor antagonist telmisartan reduces urinary albumin excretion in patients with isolated systolic hypertension: results of a randomized, double-blind, placebo-controlled trial. J Hypertens 2005;23:2055-61. doi: 10.1097/01.hjh.0000186829.56372.04
30. Catapano F, Chiodini P, De Nicola L, et al. Antiproteinuric response to dual blockade of the renin-angiotensin system in primary glomerulonephritis: meta-analysis and metaregression. Am J Kidney Dis 2008;52:475-85. doi: 10.1053/j.ajkd.2008.03.008
31. Kunz R, Friedrich C, Wolbers M, Mann JF. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. Ann Intern Med 2008;148:30-48. doi: 10.7326/0003-4819-148-1-200801010-00190
32. Mezzano SA, Ruiz-Ortega M, Egido J. Angiotensin II and renal fibrosis. Hypertension 2001;38:635-8. doi: 10.1161/hy09t1.094234.
33. Ruiz-Ortega M, Lorenzo O, Suzuki Y, Rupérez M, Egido J. Proinflammatory actions of angiotensins. Curr Opin Nephrol Hypertens 2001;10:321-9. doi: 10.1097/00041552-200105000-00005
34. Stenvinkel P, Ketteler M, Johnson RJ, et al. IL-10, IL-6, and TNF-alpha: central factors in the altered cytokine network of uremia--the good, the bad, and the ugly. Kidney Int 2005;67:1216-33. doi: 10.1111/j.1523-1755.2005.00200.x
35. Andersson P, Cederholm T, Johansson AS, Palmblad J. Captopril-impaired production of tumor necrosis factor-alpha-induced interleukin-1beta in human monocytes is associated with altered intracellular distribution of nuclear factor-kappaB. J Lab Clin Med 2002;140:103-9. doi: 10.1067/mlc.2002.125905
36. Heart Outcomes Prevention Evaluation Study Investigators, Yusuf S, Sleight P, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000;342:145-53 [corrections in 2000;342:1376 and N Engl J Med 2000;342:748]. doi: 10.1056/NEJM200001203420301
37. Lonn E, Yusuf S, Dzavik V, et al. Effects of ramipril and vitamin E on atherosclerosis: the study to evaluate carotid ultrasound changes in patients treated with ramipril and vitamin E (SECURE). Circulation 2001;103:919-25. doi: 10.1161/01.cir.103.7.919
38. Baguet JP, Asmar R, Valensi P, Nisse-Durgeat S, Mallion JM. Effects of candesartan cilexetil on carotid remodeling in hypertensive diabetic patients: the MITEC study. Vasc Health Risk Manag 2009;5:175-183. doi: 10.2147/vhrm.s3409
39. Sonoda M, Aoyagi T, Takenaka K, Uno K, Nagai R. A one-year study of the antiatherosclerotic effect of the angiotensin-II receptor blocker losartan in hypertensive patients. A comparison with angiotensin-converting enzyme inhibitors. Int Heart J 2008;49:95-103. doi: 10.1536/ihj.49.95
40. Koh KK, Chung WJ, Ahn JY, et al. Angiotensin II type 1 receptor blockers reduce tissue factor activity and plasminogen activator inhibitor type-1 antigen in hypertensive patients: a randomized, double-blind, placebo-controlled study. Atherosclerosis 2004;177:155-60. doi: 10.1016/j.atherosclerosis.2004.07.008
41. Rosei EA, Rizzoni D, Muiesan ML, et al. Effects of candesartan cilexetil and enalapril on inflammatory markers of atherosclerosis in hypertensive patients with non-insulin-dependent diabetes mellitus. J Hypertens 2005;23:435-44. doi: 10.1097/00004872-200502000-00027
42. Hirohata A, Yamamoto K, Miyoshi T, et al. Impact of olmesartan on progression of coronary atherosclerosis a serial volumetric intravascular ultrasound analysis from the OLIVUS (impact of OLmesarten on progression of coronary atherosclerosis: evaluation by intravascular ultrasound) trial. J Am Coll Cardiol 2010;55:976-82. doi: 10.1016/j.jacc.2009.09.062
43. Turnbull F, Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet 2003;362:1527-35. doi: 10.1016/s0140-6736(03)14739-3
44. Reboldi G, Angeli F, Cavallini C, et al. Comparison between angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the risk of myocardial infarction, stroke and death: a meta-analysis. J Hypertens 2008;26:1282-9. doi: 10.1097/HJH.0b013e328306ebe2
45. Lu GC, Cheng JW, Zhu KM, et al. A systematic review of angiotensin receptor blockers in preventing stroke. Stroke 2009;40:3876-8. doi: 10.1161/STROKEAHA.109.559989
46. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 2004;363:2022-31. doi: 10.1016/S0140-6736(04)16451-9
47. Verma S, Strauss M. Angiotensin receptor blockers and myocardial infarction. BMJ 2004;329:1248-9. doi: 10.1136/bmj.329.7477.1248
48. Bangalore S, Kumar S, Wetterslev J, Messerli FH. Angiotensin receptor blockers and risk of myocardial infarction: meta-analyses and trial sequential analyses of 147 020 patients from randomised trials. BMJ 2011;342:d2234. doi: 10.1136/bmj.d2234
49. Strauss MH, Hall AS. Angiotensin receptor blockers may increase risk of myocardial infarction: unraveling the ARB-MI paradox. Circulation 2006;114:838-4. [Correction in Circulation 2006;114:e576]. doi: 10.1161/CIRCULATIONAHA.105.594986
50. Strauss MH, Hall AS. Angiotensin receptor blockers do not reduce risk of myocardial infarction, cardiovascular death, or total mortality: Further evidence for the ARB-MI paradox. Circulation 2017;135:2088-90. doi: 10.1161/CIRCULATIONAHA.117.026112
51. Salvador GL, Marmentini VM, Cosmo WR, Junior EL. Angiotensin-converting enzyme inhibitors reduce mortality compared to angiotensin receptor blockers: Systematic review and meta-analysis. Eur J Prev Cardiol 2017;24:1914-24. doi: 10.1177/2047487317728766
52. Fiordelisi A, Iaccarino G, Morisco C, Coscioni E, Sorriento D. NFkappaB is a Key Player in the Crosstalk between Inflammation and Cardiovascular Diseases. Int J Mol Sci 2019;20:1599. doi: 10.3390/ijms20071599
53. Celi A, Cianchetti S, Dell'Omo G, Pedrinelli R. Angiotensin II, tissue factor and the thrombotic paradox of hypertension. Expert Rev Cardiovasc Ther 2010;8:1723-9. doi: 10.1586/erc.10.161
54. Gigante B, Bellis A, Visconti R, et al. Retrospective analysis of coagulation factor II receptor (F2R) sequence variation and coronary heart disease in hypertensive patients. Arterioscler Thromb Vasc Biol 2007;27:1213-9. doi: 10.1161/ATVBAHA.107.140541
55. Schmieder RE, Hilgers KF, Schlaich MP, Schmidt BM. Renin-

angiotensin system and cardiovascular risk. Lancet 2007;369:1208-19. doi: 10.1016/S0140-6736(07)60242-6
56. Chobanian AV, Haudenschild CC, Nickerson C, Hope S. Trandolapril inhibits atherosclerosis in the Watanabe heritable hyperlipidemic rabbit. Hypertension 1992;20:473-7. doi: 10.1161/01.hyp.20.4.473
57. Linz W, Jessen T, Becker RH, Schölkens BA, Wiemer G. Long-term ACE inhibition doubles lifespan of hypertensive rats. Circulation 1997;96:3164-72. doi: 10.1161/01.cir.96.9.3164
58. Thoene-Reineke C, Rumschüssel K, Schmerbach K, et al. Prevention and intervention studies with telmisartan, ramipril and their combination in different rat stroke models. PLoS One 2011;6:e23646. doi: 10.1371/journal.pone.0023646
59. Krikov M, Thone-Reineke C, Müller S, Villringer A, Unger T. Candesartan but not ramipril pretreatment improves outcome after stroke and stimulates neurotrophin BNDF/TrkB system in rats. J Hypertens 2008;26:544-52. doi: 10.1097/HJH.0b013e3282f2dac9
60. Bellis A, Sorriento D, Fiordelisi A, et al. autocrine bradykinin release promotes ischemic preconditioning-induced cytoprotection in bovine aortic endothelial cells. Int J Mol Sci 2020;21:2965. doi: 10.3390/ijms21082965
61. Kim MP, Zhou M, Wahl LM. Angiotensin II increases human monocyte matrix metalloproteinase-1 through the AT2 receptor and prostaglandin E2: implications for atherosclerotic plaque rupture. J Leukoc Biol 2005;78:195-201. doi: 10.1189/jlb.1204715