Chapter 10

The Effects of Antihypertensive Agents in Metabolic Syndrome – Benefits Beyond Blood Pressure Control

Nadya Merchant and Bobby V. Khan

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/54292

1. Introduction

Vascular dysfunction is a highly complex biological process, and cardiovascular diseases are a leading cause of morbidity and mortality in the United States [1]. It is estimated that approximately 80 million US adults (>1 in 3) have one or more types of cardiovascular (CV) disease, including hypertension, atherosclerosis, and congestive heart failure. CV disease has been estimated to account for 34.3% of all deaths in the United States in 2006 [1]. Vascular or endothelial dysfunction is caused by many interrelated factors including oxidative stress, hypertension, diabetes mellitus, renal disease, smoking, inflammation and atherosclerosis.

In this chapter we will review results from large-scale clinical trials to determine if inhibitors of the renin–angiotensin system (RAS), including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin type II receptor blockers (ARBs) and calcium channel blockers (CCBs), may have beneficial effects on central aortic pressure (CAP) and the biomarkers high-sensitivity C-reactive protein (hsCRP), adiponectin, cystatin C, homeostasis model assessment of insulin resistance (HOMA-IR), procollagen, tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6).

Biomarkers are playing an increasing role in the study of CV disease and we attempt to define their function in improving clinical management and outcomes [2, 3]. By definition, biomarkers are objectively measured indicators of biological processes, and to be of use, they must be relevant, predictable, accurate, and reproducible [3]. They provide readily quantifiable surrogate endpoints and allow accurate assessment of the effects of therapy on particular pathological processes, thereby allowing for prompt diagnosis and more timely initiation of appropriate treatment, improved monitoring, and treatment augmentation [4].

Some of the benefits of inhibiting RAS with ARBs and ACEIs have been shown to be independent of blood pressure (BP) reduction [5] [6]. Surrogate biomarkers are diverse, and they may provide a viable means of measuring the response to treatment. This chapter will focus on the following eight biomarkers, which have been used as predictors of vascular outcome in patients with hypertension and those with metabolic syndrome: CAP, hsCRP, adiponectin, cystatin C, HOMA-IR, procollagen, TNF-α, and IL-6.

Anti-inflammatory, anti-atherogenic, and/or improved metabolic homeostasis, independent of BP lowering, which is seen with some antihypertensives, may benefit high-risk patient populations or those who do not achieve adequate BP control. These include ethnic groups such as African Americans, obese patients, and patients with renal disease, metabolic syndrome, diabetes mellitus, and/or existing vascular disease. Improvements in inflammatory and other biomarkers has been reported with ARBs and ACEIs in obese patients with metabolic syndrome [7, 8] and in hypertensive patients with and without type 2 diabetes mellitus (T2DM) [9, 10]. Similarly, CCBs have been shown to improve markers of inflammation in patients with hypertension [11, 12], while β-blockers such as nebivolol were shown to modify markers of inflammation and obesity in obese African Americans with hypertension [13]. As a class, ARBs are known to have anti-inflammatory properties, which may contribute to their pharmacologic effects. Biomarker studies in hypertensive patients have demonstrated the effects of ARBs on inflammatory and other biomarkers [7, 14], including CAP [15, 16], hsCRP [14, 17-19], adiponectin [20], cystatin [21, 22], HOMA-IR [23-25], procollagen [26-28], TNF-α [29-31], and IL-6 [32-34].

This chapter summarizes the role of biomarkers as surrogate endpoints in the treatment of hypertensive patients and discusses the evidence for the effects of ARBs and other antihypertensive drugs on biomarkers and their correlation with clinical efficacy. The source material for this review was derived from a MEDLINE literature search, performed from 1999 to 2011, to identify published studies investigating the use of selective antihypertensive agents using at least one of the eight previously mentioned biomarkers. The agents specified in the search were amlodipine, olmesartan medoxomil, combination amlodipine plus olmesartan medoxomil, losartan, hydrochlorothiazide (HCTZ), and combination losartan plus HCTZ.

2. A review of anti-hypertensive drugs

Hypertension is a strong contributor to cardiovascular disease in patients with the cardiometabolic syndrome. It has been shown to not only be an independent risk factor, but it also contributes to the development of other risk factors for cardiovascular disease. Over the last few decades, a number of classes of anti-hypertensive drugs have been used to treat hypertension, with the ultimate goal of reducing the incidence of endpoints such as heart attacks and stroke. Some of the broad categories of antihypertensives include thiazide diuretics, ARBs, ACEIs, CCBs and β-blockers.

The first step in atherosclerosis is endothelial dysfunction. It has been shown that the RAS is involved in the development of atherosclerosis through many different mechanisms including increasing oxidative stress, vasoconstriction, inflammation and reduced ability of

the endothelium to regenerate itself (reviewed in [35]). The blockage of the RAS through ACEIs and ARBs, aids in slowing down the processes of endothelial dysfunction and subsequent atherosclerosis. ACEIs reduce angiotensin II production and suppress the degradation of bradykinin. This results in reduced oxidative stress, improved vasodilation and improved endothelial function [36, 37]. Some common ACEIs include ramipril, enalapril, lisinopril, perindopril and fosinopril. The Heart Outcomes Prevention Evaluation (HOPE) study evaluated the benefits of ramipril as compared to placebo [38]. Ramipril (10mg/day) resulted in a reduction of cardiovascular death (26% RR), nonfatal myocardial infarction (MI) (20% RR) and stroke (32% RR). Ramipril was shown to be beneficial in all subgroups of patients in the HOPE Study. The Efficacy of Perindopril in Reduction of Cardiovascular Events Among Patients with Stable Coronary Artery Disease (EUROPA) study, Perindopril Protection Against Recurrent Stroke (PROGRESS) study and the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) study are some other large, outcome trials which also showed a positive effect of ACEIs on cardiovascular events and mortality [39-41].

ARBs also block the RAS. This is accomplished through blocking of the angiotensin I receptor which leads to an upregulation of the angiotensin II receptor and the conversion of of angiotensin II to angiotensin $_{(1\text{-}7)}$ which has vasodilatory, antioxidant and pro-apoptotic properties [42, 43]. Some common ARBs include losartan, telmisartan, valsartan, olmesartan, candesartan and irbesartan. Large outcome trials such as the Renal Outcomes with Telmisartan, Ramipril, or Both, in People at High Vascular Risk (ONTARGET) study, and the Valsartan in Acute Myocardial Infarction (VALIANT) study have shown that ARBs are comparable to ACEIs in reducing cardiovascular risk, without the side effect of excess coughing that is frequently experienced by patients who are taking ACEIs [44] [45]. Combination of ARBs with β-blockers or statins have also shown positive results [46, 47].

CCBs are another class of antihypertensives which provide similar blood pressure lowering effects of ACEIs and ARBs, but they provide better protection against stroke and heart failure [48]. CCBs inhibit the flow of extracellular calcium through ion-specific channels that span the cell wall. This causes vascular smooth muscle cells to relax and thereby results in vasodilation, blood pressure lowering and reduced peripheral arterial resistance. Commonly prescribed CCBs include amlodipine, benidipine, azelnidipine and manidipine.

β-blockers are another group of antihypertensives which are divided into two main categories. Traditional (non-vasodilatory) β-blockers such as atenolol, metropolol and propanolol reduce blood pressure by reducing cardiac output [49]. These β-blockers are effective at lowering brachial blood pressure, however data from studies including the Conduit Artery Function Evaluation (CAFÉ) study suggests that these compounds do not adequately control central aortic pressure [50]. This can then lead to an increase in vascular events including stroke [51]. Additionally, these agents have been shown to increase plasma triglyceride levels [52] and the risk of new-onset diabetes by about 20-30% [53, 54]. The other group of β-blockers are the vasodilatory β-blockers which includes labetalol, carvediol and nebivolol. These drugs reduce systemic vascular resistance while maintaining cardiac

output. Additionally, these agents do not negatively affect glycemic control and may even provide beneficial metabolic effects [55-57].

Diuretics include HCTZ , chlorthalidone and the loop diuretics such as furosemide. According to the Joint National Committee on Prevention, Detection, Evaluation , and Treatment of High Blood Pressure (JNC 7) guidelines, diuretics are recommended as the first line of therapy for hypertension [58]. Chlorothalidone is more potent at 25mg dosing than 50mg of HCTZ. Also, chlorothalidone has been shown to improve cardiovascular outcomes [59]. Certain subpopulations, including diabetics, the elderly and blacks have lower renin levels and they respond favorably to diuretic therapy [60]. Diuretics, particularly HCTZ, are often combined with antihypertensives from another class, such as ARBs and ACEIs, to provide enhanced therapeutic benefits [61].

The newest category of anytihypertensives include direct renin inhibitors (DRIs). Aliskiren is the most common DRI. This class of drugs works by inhibiting the first rate-limiting step in the RAS, resulting in a more complete inhibition of the RAS cascade as compared to ACEIs and ARBs [62]. Additionally, DRIs reduce the production of aldosterone, which in addition to its sodium retension effects, also is a mediator in oxidative stress and inflammation [63] [64]. The Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) study and the Aliskiren Observation of Heart Failure Treatment (ALOFT) trial show that aliskiren has renal and cardio protective effects in addition to blood pressure regulation [65, 66].

3. Role of biomarkers and mechanisms in specific patient groups

3.1. CAP

While brachial BP is easily measured and has been shown to be predictive of CV morbidity and mortality, it is an imperfect surrogate measure of CAP. Peripheral systolic BP (SBP) measured at the brachial artery does not accurately reflect CAP, particularly in youths, as a result of peripheral amplification of the pulse pressure wave [67-69]. This amplification difference decreases with age and arterial stiffness. Central aortic systolic pressure or pulse pressure has been shown to be a powerful and more robust predictor of end organ damage and CV mortality than brachial BP, irrespective of whether the central pressures were derived from noninvasive pulse wave analysis or measured directly during routine catheterization [68]. Although techniques have been developed to a stage where direct noninvasive measurement of CAP could be readily applied to routine clinical practice, the studies conducted to-date, assessing the predictive value of CAP, have been relatively small. Thus, additional data from large interventional studies of clinical outcomes and larger-scale longitudinal epidemiological studies of clinical outcomes are required to confirm the utility of CAP as a predictor of vascular risk before it becomes part of routine clinical practice [67-69].

Noninvasive assessment of the central pulse pressure waveform is performed by applanation tonometry, which involves applying a pressure sensor (tonometer) with mild

pressure over the radial or carotid artery. The recorded waveform is then used to algorithmically derive central pressure indices from a peripheral brachial BP measurement [69]. In addition, aortic pulse wave velocity (PWV), which is usually recorded between the carotid and femoral arteries, is used to determine vessel distensibility; the velocity of the pulse wave increases with decreasing vessel distensibility (increased arterial stiffness) [67]. Increased PWV, an indication of arterial stiffness, appears to be associated with endothelial dysfunction, inflammation, and atherosclerosis, and has been shown to be an independent predictor of coronary events and CV mortality [67]. Hence, arterial stiffness is an emerging biomarker for therapeutic interventions.

3.2. hsCRP

C-reactive protein (CRP), an acute phase reactant predominantly produced in the liver in response to IL-6, interleukin-1β, and TNF-α, is a marker of the general inflammatory response. Current technology permits the quantification of CRP through a high-sensitivity assay, therefore this marker is referred to as hsCRP. Epidemiological studies have established that individuals with higher levels of hsCRP have increased CV risk [70]. The nature of the relationship between hsCRP and CV disease is unclear, but hsCRP provides a useful measure of risk and the effects of interventions [70, 71].

Studies have shown a continuous independent association between serum CRP levels and elevated BP [72]. In elderly, normotensive individuals, higher baseline CRP levels were associated with a higher incidence of new-onset hypertension after 2 years [73]. Moreover, in apparently healthy adults representative of the US population, a 10-mmHg increase in pulse pressure was associated with significant increases of 12%–15% in the odds of having an elevated CRP level, independent of SBP or diastolic BP (DBP), or demographic factors [74]. There are even suggestions that hsCRP may be a better marker of coronary artery disease (CAD) than low-density lipoprotein cholesterol (LDL-C) [2, 75]. Evidence suggests that inhibition of the RAS with certain agents, particularly ARBs and ACEIs, may improve CV outcomes by reducing vascular inflammation and remodeling independently of BP reductions [76].

3.3. Adiponectin

Adiponectin is one of the adipocyte-derived hormones that has profound anti-inflammatory and anti-atherogenic properties. It is also thought to play an important role in the modulation of glucose and lipid metabolism [2, 77]. Reduced adiponectin levels have been noted in males, obese subjects, and patients with hypertension, CAD, or T2DM [78]. Reduced adiponectin levels are predictive of CAD and MI [79]. Animal studies have shown that increased adiponectin levels are protective against atherosclerosis, while clinical studies with antihypertensive drugs, including ARBs, ACEIs, and CCBs, have associated improvements in BP and insulin resistance with increased adiponectin levels [78, 80]. In obese subjects, serum adiponectin levels were inversely associated with intima-media thickness, a surrogate measure of subclinical atherosclerosis, and positively associated with

arterial compliance [79]. The mechanism behind the beneficial effects of adiponectin is uncertain; one hypothesis suggests that adiponectin increases nitric oxide activity, thereby inhibiting platelet activation, while another hypothesis suggests it suppresses monocyte activation [78].

3.4. Cystatin C

The serum cystatin C level directly correlates with the glomerular filtration rate (GFR) and is produced constantly, independent of muscle mass, age, or sex. It is therefore an easily obtained biomarker for renal dysfunction that may be more reliable than measurement of creatinine levels in certain patient populations, particularly in children [81-83]. However, there are concerns over the cost of the immunoassay, intraindividual variability, and its sensitivity in transplant patients or its suitability in patients with cancer, where cystatin C production may vary [82]. Notably, a study in patients after heart transplantation found that cystatin C was superior to creatinine as a prognostic indicator of early renal dysfunction during 4 years of follow-up [84].

Cystatin C is a predictor of CV morbidity and mortality, and it has been suggested that this association may be independent of renal function [85, 86]. In one study, cystatin C, but not creatinine or GFR, was closely associated with left ventricular (LV) mass in patients with hypertension, suggesting utility as a marker for cardiac hypertrophy [86].

3.5. HOMA-IR

HOMA-IR is a mathematical model prediction that provides an accurate quantitative assessment of insulin resistance [87], which is associated with hypertension, obesity, and diabetes, and an increased risk of CAD [88].

Many CV drugs adversely affect glucose and lipid homeostasis, and insulin resistance is an important mediator of these adverse effects on glucose metabolism [88]. Direct RAS inhibitors (ARBs and ACEIs) and some other antihypertensives provide beneficial effects in terms of glucose homeostasis [88].

3.6. Procollagen

Collagen fractions in the extracellular matrix are intimately involved in the atherosclerotic process and the vascular remodeling that occurs in CV disease [89]. There is evidence that altered collagen metabolism (eg, elevated serum levels of tissue inhibitor of metalloproteinase-1) is associated with hypertension [89], and that plasma markers of collagen metabolism are positively correlated with arterial stiffness measured by PWV in hypertensive patients with LV hypertrophy [90].

Therefore, measurement of serum procollagen fractions as indicators of myocardial fibrosis may be useful in the clinical assessment of CV risk [91].

3.7. TNF-α

TNF-α is a marker of inflammation and is believed to promote the development of insulin resistance and hyperinsulinemia, and thereby affect BP [29]. TNF-α is released from mast cells and macrophages in the myocardial endothelium during acute MI, and from cardiomyocytes during persistent ischemia. The released TNF-α contributes to ischemic and/or reperfusion injury and is believed to contribute to cardiac contractile dysfunction after MI via a local inflammatory reaction [31]. Surprisingly, low levels of TNF-α may be beneficial and display a cardioprotective effect, reducing infarct size [31]. TNF-α is also believed to play a role in the development of atherosclerosis by up-regulating cell surface receptors for advanced glycation end products that promote the release of inflammatory mediators in the endothelium [30]. The differential effects are possibly related to which of the two tumor necrosis receptor types (TNF-R1 or TNF-R2) the TNF-α molecule interacts.

3.8. IL-6

IL-6 is an inflammatory cytokine that, along with TNF-α, is one of the main inducers of acute phase reactants, such as CRP. It has been positively correlated with CV risk. For instance, in elderly subjects without known CV disease, serum levels of IL-6 were significantly associated with CAD, stroke, and congestive heart failure events, and to a greater extent than CRP or TNF-α levels [92]. Similarly, in older men without CAD, IL-6 was found to be more discriminating than CRP and fibrinogen in predicting a first coronary artery ischemic event, being associated with MI/coronary death but not CAD endpoints (angina) [33]. However, not all studies have found strong correlations between IL-6 and CAD [34].

4. Antihypertensive drugs: benefits beyond just blood pressure lowering

Clinical evidence that many current antihypertensive agents have a beneficial effect on putative biomarkers of CV pathology or risk continues to accumulate and indicates that not all drugs or patient subpopulations are equal.

4.1. CAP

Of the various antihypertensive drug classes, RAS inhibitors (ARBs and ACEIs) and CCBs generally appear to have greater effects on CAP than β-blockers and thiazide diuretics. Despite similar brachial BP reductions, the combination of amlodipine plus perindopril was associated with greater reductions in CAP than atenolol plus a thiazide diuretic [93]. Lisinopril also significantly reduced central SBP, central pulse pressure, and the augmentation index, while bisoprolol only significantly lowered central DBP and actually increased the augmentation index [94]. The combination of olmesartan and azelnidipine was compared to olmesartan and amlodipine [95]. While both combinations had similar brachial BP lowering effects, there was a greater reduction in CAP with the olmesartan/azelnidipine combination. Another study showed significant reductions in both brachial and central BP

reductions with different drug classes in the following order: CCBs > diuretics (HCTZ) > ACEIs [96]. β-blockers did not significantly lower peripheral or central BP.

Similar brachial BP and CAP reductions were achieved with valsartan plus HCTZ versus amlodipine; however, valsartan plus HCTZ provided a greater reduction in arterial stiffness (estimated by aortic PWV) [97]. Reductions in central SBP were greater with fosinopril plus HCTZ than with indapamide or amlodipine; this correlated with 24-hour and nighttime SBP reductions, but not with seated cuff SBP [98].

Recent studies have shown that PWV is significantly reduced with candesartan or benidipine treatment, as compared to amlodipine [99, 100]. Arterial stiffness, measured through cardioankle vascular index was significantly decreased with combination of olmesartan and azelnidipine, but not with olmesartan monotheraphy [101]. However, arterial index decreased significantly with monotheraphy and combination therapy in this study. On the other hand, another recent study showed that monotheraphy with olmesartan does significantly decrease arterial stiffness [102].

The effects of antihypertensives on flow mediated dilation (FMD) has also been measured. Olmesartan has been shown to positively impact FMD and while amlodipine treatment has no effect on FMD [103], the combination of amlodipine and atorvastatin has significant improvements on this marker, even more than atorvastatin alone [104]. Another study found the same effects of amlodipine and atorvastatin combination on patients with hypertension and hyperglycemia [105]. The combination of amlodipine and valsartan was also found to improve FMD in diabetics with early hypertension, even more than the effects of the individual drugs [106].

4.2. hsCRP

Several antihypertensive drug classes, such as ARBs, ACEIs, and CCBs, lower serum hsCRP in addition to BP, indicating a reduction in the inflammatory processes involved in the progression of atherosclerosis. ARBs, in particular, seem to have a strong depressor effect on this marker of inflammation. Patients with chronic kidney disease (CKD), who have higher baseline levels of inflammation than control subjects with normal renal function, displayed significant reductions in hsCRP and brachial BP with olmesartan medoxomil treatment [107]. In a small study of 10 patients with mild-to-moderate hypertension, olmesartan medoxomil did not reduce BP significantly, but did produce significant reductions in hsCRP and appeared to improve myocardial function independent of BP lowering [19]. In another study, hsCRP levels significantly dropped in hypertensive patients who were treated with olmesartan for 6 month [102]. In non-diabetic patients with hypertension and the metabolic syndrome, both olmesartan medoxomil plus amlodipine and olmesartan medoxomil plus HCTZ effectively reduced BP and CRP with no differences between groups. However, olmesartan plus amlodipine produced greater reductions in all other inflammatory markers [108]. Olmesartan treatment was compared to candesartan treatment in hypertensive patients with T2DM [109]. BP and hsCRP reductions were similar in both treatment groups. In a separate

study, these researchers also found that monotherapy with either losartan or ramapril is equally beneficial in lowering hsCRP [109].

In a study comparing the CCB azelnidipine or the thiazide diuretic trichlormethiazide added to an ARB, the ARB plus azelnidipine combination produced significantly greater reductions in hsCRP than the ARB plus thiazide combination; this reduction mirrored the BP-lowering effects [110]. Similar data were shown in a 4-month crossover study comparing olmesartan medoxomil plus azelnidipine or trichlormethiazide [111]. Azelnidipine was shown to be superior to amlodipine with regards to hsCRP lowering in nondiabetic hypertensive patients and the beneficial effects of azelnidipine also included improved glucose tolerance and insulin sensitivity [112]. When combined with atorvastatin, amlodipine therapy reduces plasma hsCRP significantly [104]. In the recent Effects of Manidipine and its Combination with an ACE Inhibitor on Insulin Sensitivity and Metabolic, Inflammatory and Prothrombotic Markers in Hypertensive Patients with Metabolic Syndrome: the MARCADO Study, a number of monotherapies (manidipine, amlodipine, teimisartan) and combination therapy (manidipine/lisionpril) were compared for treatment of non-diabetic, hypertensive patients with the metabolic syndrome. Levels of hsCRP reduced with all of these treatments, but the most significant reduction was with the manidipine/lisinopril combination therapy [113]. Comparison of 12 weeks of combination therapy with enalapril plus add-on losartan with higher dose enalapril monotherapy showed a significant reduction in hsCRP with combination therapy, but not with high-dose enalapril alone; BP reductions were significant and similar in both groups [114]. In another study, patients who were on olmesartan therapy received additional HCTZ or azelnidipine therapy for 24 weeks. HsCRP levels dropped significantly with the azelnidipine add-on therapy but there was no change with HCTZ therapy [115].

Evidence suggests that ARBs may differ in their anti-inflammatory effects. For instance, in patients with CAD, olmesartan medoxomil and valsartan both produced significant reductions in BP, but only olmesartan medoxomil induced a significant reduction in hsCRP [116]. Losartan has also been shown to reduce hsCRP in newly diagnosed hypertensive patients who are at CV disease risk [117]. Studies comparing the hsCRP-lowering effects of ARBs and CCBs have shown variable results. One study found no difference in hsCRP reductions after 8 weeks of therapy with losartan or amlodipine regimens [118]. The effects on hsCRP and other inflammatory markers did not explain the greater improvements in insulin sensitivity seen with ARBs over CCBs. However, in patients with hypertension and other CV risk factors, therapy with valsartan plus HCTZ was significantly more effective than amlodipine in reducing hsCRP. These biomarker results correlated with BP reductions [119]. HsCRP improvement did not correlate with endothelial function in a study comparing candesartan with amlodipine; both treatments significantly improved endothelial function (assessed by changes in forearm blood flow in reactive hyperemia), whereas significant reductions in hsCRP levels were seen only with candesartan and not amlodipine therapy [120]. The study investigators concluded that the anti-inflammatory effects observed with candesartan may be related to observed improvement in insulin sensitivity. In a study of patients with CAD, treatment with irbesartan did not lower hsCRP levels. [121] The lack of

effect of irbesartan may have been due to low levels of hsCRP at study baseline. Patients were also receiving statin and aspirin therapy, which also lower levels of this marker. In a recent study, olmesartan reduced hsCRP levels in patients with essential hypertension while amlodipine had no effects on hsCRP [103].

As with ARBs, CCBs seem to differ in their ability to reduce inflammatory markers. In hypertensive patients with the metabolic syndrome, similar significant reductions in hsCRP and BP were seen with manidipine and amlodipine, but these data did not correlate with changes in other biomarkers, such as adiponectin, HOMA-IR, and TNF-α, which showed greater improvements with manidipine than with amlodipine [122]. In a different study in patients with arterial hypertension and insulin resistance who were already receiving at least two antihypertensive agents, neither moxonidine nor amlodipine showed significant changes in hsCRP, whereas both treatments resulted in significant BP lowering [123].

Adding a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor (atorvastatin) to amlodipine therapy produced significantly greater reductions in BP and hsCRP than was seen with amlodipine alone [124], but losartan plus simvastatin achieved similar reductions in hsCRP compared with losartan or simvastatin alone [47]. BP reductions were significantly greater with losartan or losartan plus simvastatin than with simvastatin alone. The combination of rosuvastatin and a number of ARBs was studied as treatment in adults with the metabolic syndrome [125]. While rosuvastatin and telmisartan reduced hsCRP by 44% after 24 weeks of therapy, there was less reduction in hsCRP with the combination of rosuvastatin and irbesartan or rosuvastatin and olmesartan.

These observations suggest that RAS antagonists such as ARBs and ACEIs have a significant anti-inflammatory effect, and there may be variations within these classes. As diseases such as diabetes mellitus and atherosclerosis are inflammatory processes, the clinical benefits seen with these classes of antihypertensives may be a combination of the suppression of inflammation and the reduction of BP.

4.3. Adiponectin

Studies assessing the effect of the selected antihypertensive drugs on the serum levels of adiponectin are discussed here. Antihypertensive agents do not uniformly influence metabolic parameters in patients with hypertension. In a comparison of telmisartan and irbesartan in obese, insulin-resistant, hypertensive patients, increases were significantly greater with telmisartan, although both treatments resulted in significant increases in adiponectin levels [126]. Adiponectin changes correlated inversely with changes in BP for telmisartan, but not for irbesartan. The investigators speculate that the differences between the two agents may be partly due to partial peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist activity exhibited by telmisartan, although a study by Kintscher et al in 14,200 patients confirmed that irbesartan also activates PPAR-γ [127]. Despite similar reductions in BP, olmesartan medoxomil plus amlodipine produced significant increases in adiponectin levels in patients with hypertension and the metabolic syndrome, whereas olmesartan medoxomil plus HCTZ did not [108]. The increase in adiponectin correlated

with a lower risk for developing T2DM and paralleled reductions (improvements) in HOMA-IR index and fasting plasma insulin levels.

In nondiabetic, proteinuric patients, treatment with losartan plus HCTZ reduced BP, proteinuria, and LDL-C, and increased adiponectin, but the change in adiponectin correlated with adverse reductions in high-density lipoprotein cholesterol (HDL-C) levels [128]. In a crossover study that investigated possible factors to explain improvements in insulin sensitivity with ARB therapy compared with CCB therapy in patients with hypertension, between group differences were not noted for increases in adiponectin levels or reductions in BP after 8 weeks of therapy with losartan or amlodipine [118]. In contrast, although both telmisartan and amlodipine increased adiponectin levels in patients with hypertension and T2DM, the increases were higher with telmisartan than with amlodipine [129]. Both groups showed a similar significant decrease in BP. Similarly, in patients with prediabetes, losartan produced greater increases in adiponectin than a CCB, whereas BP reduction was similar and significant in both groups [130]. Within CCBs, candesartan, but not olmesartan therapy, over the period of a year resulted in increased adiponectin and insulin sensitivity in T2DM hypertensive patients, even though BP lowering was similar in both treatment groups [109]. When compared to the ACEI ramipril, losartan treatment significantly improved adiponectin levels and overall metabolic parameters while ramipril had no effect on adiponectin or any other metabolic markers [131]. In obese hypertensive patients, telmisartan, but not losartan raised serum adiponectin levels [132].

ARBs and statins have additive effects on adiponectin. Losartan plus simvastatin or losartan alone resulted in significantly greater increases in adiponectin levels from baseline than with simvastatin alone [47]. This correlated with BP reductions, which were greater with losartan or losartan plus simvastatin than with simvastatin alone. A correlation was also observed with LDL reductions, which were greater with simvastatin or simvastatin with losartan relative to losartan alone.

There were no changes in adiponectin levels with the aldosterone blocker spironolactone or the CCB amlodipine in patients with diabetic nephropathy or in controls. However, spironolactone, but not amlodipine, increased adiponectin in a subgroup of patients with poor baseline glycemic control, i.e. glycosylated hemoglobin (HbA_{1c}) ≥8%. A significant decrease in SBP, but not DBP, was observed in both treatment groups [133]. This link between the renin-angiotensin cascade and aldosterone suggests a possible mechanism by which spironolactone provides an increased level of adiponectin in hyperglycemia.

In a comparison of enalapril, metoprolol, amlodipine, and indapamide, no changes in adiponectin level were seen with enalapril, amlodipine, or metoprolol, whereas a reduction in adiponectin was seen with indapamide. This reduction in adiponectin with the thiazide-like diuretic correlated with increased insulin resistance [134]. In a comparison of metoprolol, amlodipine, ramipril, doxazosin, and valsartan in hypertensive patients with the metabolic syndrome, both ramipril and valsartan resulted in significantly higher increases in adiponectin than the other regimens; adiponectin levels inversely correlated

with SBP [135]. In a study comparing manidipine, amlodipine, telmisartan, and the combination therapy of manidipine and lisinopril, adiponectin levels increased with all of the treatments except amlodipine. The greatest increase in adiponectin was seen with manidipine [113]. The combination of amlodipine and atorvastatin resulted in a greater increase in adiponectin than treatment with amlodipine alone [104]. Similar results were seen in patients with hypertension and hyperglycemia that were treated with amlodipine and atorvastatin [105].

In a small study in patients with hypertension, ramipril, candesartan, and amlodipine were associated with greater increases in adiponectin levels while thiazide and atenolol were associated with a decrease in adiponectin. There were no correlations with BP lowering, which was greatest with atenolol, amlodipine, and candesartan therapies than with ramipril [136].

Unlike the situation with hypertensive, obese, or diabetic patients, where adiponectin levels are reportedly reduced, the levels of adiponectin are raised in patients with renal disease when compared with healthy controls. Thus, in patients with renal disease, a positive correlation between adiponectin and insulin resistance is seen, and increased adiponectin levels are associated with increased all-cause and CV mortality (the opposite of that seen in obese patients or those with T2DM without renal disease). Paradoxically, short-term losartan therapy in patients with T2DM nephropathy was associated with a significant decrease in adiponectin levels compared with amlodipine therapy [137].

Adiponectin, secreted by fat cells, regulates the insulin response and has a favorable effect on glucose and lipid metabolism. Insulin resistance is a hallmark for the progression of vascular disease. The quantitative changes in adiponectin provide insight into how antihypertensive agents such as ARBs may be effective in attenuating or reversing the pathogenesis of atherosclerosis and diabetes mellitus.

4.4. Cystatin C

Only three studies have assessed the effect of the selected antihypertensive drugs on serum cystatin C levels. In one study, a significant decrease in cystatin C with olmesartan medoxomil therapy correlated with improvements in BP, LV mass index, and LV hypertrophy at 6 months [138]. Another study found that cystatin C levels decreased in patients who were on olmesartan or olmesartan with HCTZ, but in this study, there was no correlation between cyctatin C and BP levels [139]. However, the third study found no significant decrease in cystatin C with enalapril/losartan combination therapy or with high-dose enalapril, despite significant reductions in BP [114].

The use of cystatin C as an early marker for CKD may be helpful in longitudinal follow-up analyses. The findings in the above studies are preliminary but suggest that BP reduction may be associated with lower cystatin C levels. It is too early to determine whether inhibition of the RAS (in the form of ACEIs or ARBs) may have an effect on cystatin C that is superior to other antihypertensive drugs.

4.5. HOMA-IR

HOMA-IR is a model and calculation to determine quantification of insulin resistance. Antihypertensive drugs appear to have differing effects on insulin resistance, with ARBs foremost among those improving insulin sensitivity, although considerable variability has been observed and not all ARBs may be equal in this regard. RAS inhibitors generally have greater effects on glucose homeostasis than CCBs, which are usually considered to have neutral effects.

In hypertensive patients, a significantly greater reduction in HOMA-IR was seen with losartan/amlodipine therapy than with high-dose amlodipine [118]. The addition of losartan therapy to chronic heart failure patients who were on ACEIs resulted in a reduction of HOMA-IR as well as inflammatory cytokines after 24 weeks of therapy [140]. The MARCADOR Study compared the effects of manidipine, amlodipine, telmisartan, and manidipine combined with lisinopril. While BP lowering was similar with all of these treatments, HOMA-IR levels improved in all of the treatments except for amlodipine, and the greatest change in HOMA-IR was seen with manidipine treatment [113]. In contrast to previous results, both losartan and telmisartan had neutral effects on insulin resistance in 42 hypertensive patients with the metabolic syndrome, with no significant reductions in HOMA-IR in either group; BP reductions were similar for both ARBs [141]. In a more recent study, obese hypertensive patients were treated with telmisartan or olmesartan. While olmesartan improved BP levels, only telmisartan improved insulin glucose and HOMA-IR levels in addition to improving BP levels [25]. Others have also shown that telmisartan therapy helps to reduce HOMA-IR levels as compared to other ARBs and CCBs [132, 142]. Researchers studied the effects of irbesartan as compared to olmesartan in obese hypertensive females and found that while both treatments improved BP and lipid levels, only olmesartan resulted in HOMA-IR changes [143]. Olmesartan was also found to reduce HOMA-IR in hypertensive patients with sleep disordered breathing. Positive changes in BP level and left ventricular ejection fraction were also seen in these patients with olmesartan treatment [144].

Non-diabetic CKD patients have a high prevalence of insulin resistance, metabolic syndrome, and chronic inflammation. Treatment with olmesartan medoxomil for 16 weeks was associated with a significant reduction in HOMA-IR, along with reductions in markers of inflammation [107]. Losartan therapy was associated with improvements in fasting plasma insulin and HOMA-IR in patients with T2DM nephropathy, in parallel with reductions in adiponectin levels [137]. Both olmesartan medoxomil and telmisartan were shown to improve HOMA-IR in patients with nonalcoholic fatty liver disease and chronic hepatitis C, conditions with a greater incidence of insulin resistance than other liver diseases [145].

In a study investigating the effect of combination therapy with amlodipine plus olmesartan medoxomil on HOMA-IR in hypertensive patients with the metabolic syndrome, HOMA-IR was significantly reduced with olmesartan medoxomil/amlodipine, whereas no significant changes were seen with olmesartan medoxomil/HCTZ. The reductions in the HOMA-IR

index strongly correlated with the increases in adiponectin level in the group treated with olmesartan medoxomil/amlodipine [108].

In a crossover study of amlodipine with or without atorvastatin therapy in obese patients with hypertension and normal lipid profiles, combination amlodipine/atorvastatin therapy produced a significantly greater reduction in HOMA-IR than amlodipine monotherapy; there was no correlation with BP reduction with either treatment [29]. The combination of rosuvastatin with telmisartan significantly lowered HOMA-IR and fasting serum insulin levels in metabolic syndrome patients, but when irbesartan or olmesartan was combined with rosuvastatin, HOMA-IR and fasting insulin levels increased [125]. In non-diabetic patients with the metabolic syndrome, manidipine, but not amlodipine, significantly reduced HOMA-IR [122].

In patients with hypertension and insulin resistance, neither moxonidine nor amlodipine produced changes in HOMA-IR. Both treatments significantly lowered BP and increased HDL-C, but only moxonidine reduced serum triglycerides. Neither drug affected serum CRP levels [123].

In patients with T2DM nephropathy, losartan, but not amlodipine, reduced HOMA-IR from baseline, but the between-group difference was not significant. However, other parameters of glucose metabolism (eg, fasting blood glucose, HbA_{1c}, and insulin sensitivity) were improved to a greater extent with losartan than with amlodipine [146]. In patients with hypertension and T2DM, telmisartan resulted in greater improvements in HOMA-IR than amlodipine [129].

Similar results with losartan and amlodipine were seen in patients with prediabetes, with greater improvements in HOMA-IR with losartan than with amlodipine; the two agents resulted in similar BP reductions [130].

In a study in hypertensive patients, both candesartan and amlodipine significantly improved endothelial function, but significant decreases in HOMA-IR and CRP were only observed with candesartan [120].

In a comparison of losartan and amlodipine in Japanese patients with hypertension, with or without diabetes, losartan provided greater increases in adiponectin than amlodipine. These increases correlated with HOMA-IR changes [147].

In agreement with the adiponectin results discussed earlier, indapamide treatment increased HOMA-IR in patients with hypertension, whereas no changes in HOMA-IR were seen with enalapril, metoprolol, or amlodipine [134]. In patients with hypertension and the metabolic syndrome, doxazosin, amlodipine, ramipril, and valsartan produced significant reductions in HOMA-IR, whereas no changes were seen with metoprolol [135].

Insulin resistance is a central force in the pathogenesis of vascular diseases, and HOMA-IR provides a reasonable assessment of the quantification of insulin resistance. Several long-term clinical studies have demonstrated the clinical benefit of ARBs in diabetic kidney disease, both in late stage [the Reduction of Endpoints in NIDDM with Angiotensin II

Antagonist Losartan (RENAAL) study and the Irbesartan Diabetic Nephropathy Trial (IDNT) study] and early stage [The Effect of Irbesartan on the Development of Diabetic Nephropathy in Patients with Type 2 Diabetes (IRMA-2) study]. The role of HOMA-IR may be beneficial in clinical practice, and quantitative and longitudinal analysis could provide long-term follow-up of disease management.

4.6. Procollagen

Several studies have assessed the effect of antihypertensive agents on procollagen fractions as a marker of atherogenesis and vascular remodeling. Valsartan and ramipril, but not amlodipine, were associated with reductions in procollagen. Despite similar BP lowering, valsartan and ramipril were more effective than amlodipine in preventing new episodes of atrial fibrillation [148].

Another study showed a significant difference in procollagen type I carboxy-terminal peptide (PICP) lowering between candesartan and amlodipine. Although BP control was similar, 24-hour SBP was significantly lower and LV mass index significantly decreased with amlodipine, while the effect of ARBs on procollagen indicate that they protect against CV fibrosis and renal injury [149].

There were no differences in procollagen markers with losartan- or atenolol-based regimens after the first year of treatment; changes in PICP during the first year of treatment were related to subsequent changes in LV mass index after 2 and 3 years of treatment in patients randomized to losartan, but not atenolol [26]. Losartan-related reduction in procollagen was shown to be greater in patients with higher baseline levels (those with hypertension and severe myocardial fibrosis) [150] and was significantly associated with symptom improvement [151].

4.7. TNF-α and IL-6

The effects of antihypertensive drugs on the inflammatory biomarker TNF-α have been somewhat variable. In patients with hypertension, olmesartan medoxomil reduced TNF-α levels in one study [152], but in another study in Japanese patients, neither losartan nor the CCB amlodipine significantly affected TNF-α levels [147]. In obese hypertensive patients, telmisartan, but not losartan treatment, was shown to reduce serum TNF-α levels [132]. Conversely, another study showed that in newly diagnosed hypertension patients, losartan lowers TNF-α levels [117]. In chronic heart failure patients, the addition of losartan to ACEI therapy resulted in a significant reduction of TNF-α levels [140]. Amlodipine was effective in reducing TNF-α, but was significantly more effective when combined with atorvastatin [153]. Another study found no difference between losartan and amlodipine in TNF-α levels after treatment, but the investigators did not appear to perform baseline assessments in order to determine if either drug reduced TNF-α from baseline levels [118]. Manidipine and lisinopril combination therapy was shown to have a highly significant effect on TNF-α levels in non-diabetic, hypertensive patients with the metabolic syndrome [113].

Losartan therapy significantly reduced TNF-α in patients with hypertension and T2DM [154]. However, olmesartan medoxomil combined with HCTZ had no effect on TNF-α in patients with hypertension and the metabolic syndrome (without diabetes), but when olmesartan medoxomil was combined with amlodipine, the combination did significantly reduce TNF-α levels [108]. Amlodipine was shown to reduce serum TNF-α levels, as well as mRNA expression of TNF-α in hypertensives with and without diabetes [155]. Interestingly, amlodipine alone was shown in another study to have no effect on TNF-α levels in patients with hypertension and the metabolic syndrome, whereas manidipine monotherapy was effective in lowering TNF-α [122]. Olmesartan medoxomil had no effect on TNF-α levels in patients with stage 3 or 4 CKD [107], and TNF-α was unaffected by amlodipine or spironolactone in patients with diabetic nephropathy [133].

Studies investigating the effect of antihypertensive drugs on IL-6 levels are summarized here. In an open-labeled study, losartan therapy reduced IL-6 levels in recently diagnosed hypertension without other CV disease risk factors [117]. Olmesartan medoxomil reduced IL-6 levels in one study in patients with hypertension [152], but had no effect in patients with stage 3 or 4 CKD [107]. Olmesartan medoxomil was ineffective when combined with HCTZ in patients with hypertension and the metabolic syndrome, but was effective in these patients when combined with amlodipine [108]. Valsartan combined with HCTZ was more effective than amlodipine alone in reducing IL-6 [156]. Another study showed that diabetics with hypertension have higher IL-6 levels than non-diabetics with hypertension, and amlodipine reduced serum IL-6 as well as mRNA expression of IL-6 in diabetics and non-diabtetics [155]. In a crossover study with non-diabetic hypertensive patients, IL-6 levels were reduced with azelnidipine therapy, but not with amlodipine [112]. In the MARCADOR study, the greatest reduction in IL-6 was achieved with a combination of manidipine and lisinopril, while there was no change in IL-6 with amlodipine [113]. Another study found a greater reduction in IL-6 with benidipine treatment as compared to amlodipine treatment [100]. Losartan, as add-on therapy has also been shown to reduce IL-6 levels [140].

These cytokines are rather non-specific for quantification of inflammation; however, these studies do reflect the general state of inflammation in the vasculature. Clinical studies that measure the level of the cytokines demonstrate variable results. Multiple studies with antihypertensives indicate a general reduction in the levels of cytokines, suggesting a decrease in vascular inflammation. In context with the clinical situation and other risk factors, the measurement of these biomarkers may be useful.

5. Conclusions

It can be expected that biomarkers will continue to play an increasing role in the management of CV disease. Their importance or significance is likely to increase in direct proportion to the growth in our knowledge of disease pathophysiology and the mechanisms of drug action. The use of biomarkers does, however, depend upon the markers being accurate, relevant to the purpose, easy to measure, and consistently reproducible.

There is a wealth of evidence for improvement of validated biomarkers of vascular disease with most classes of antihypertensive treatment in a range of high-risk patient populations. These include obese patients, patients with diabetes, patients with renal disease and/or metabolic syndrome, existing vascular disease, and African American patients. Benefits have also been observed in those with normal BP, but with other CV risk factors. There is some evidence to suggest that at least part of the effect seen with some antihypertensives on these biomarkers may be independent of BP reduction. Different drugs may have quite different effects on biomarkers, despite very similar or equivalent effects on BP. However, with other drugs, the changes in certain biomarkers appear to parallel changes in BP. In addition, there appear to be clear associations between certain biomarkers, such as HOMA-IR and adiponectin, and the manner in which they are affected by certain antihypertensive drugs.

There is particularly compelling evidence that RAS inhibitors (ACEIs and ARBs) and CCBs may have beneficial effects beyond BP control, making them particularly attractive for either monotherapy or combination therapy. In contrast, other drugs, such as the thiazide diuretic HCTZ, appear to counter the beneficial effects on biomarkers normally observed with ARBs when they are used in combination.

Of the biomarkers selected for review in this chapter, the benefits of antihypertensive therapy on hsCRP, adiponectin, and HOMA-IR reflect a potential for quantifiable long-term vascular benefits. However, more evidence is required to elucidate the mechanisms involved and understand the variability and apparent anomalies observed. In addition, more information about any differences between specific antihypertensive agents within the same class is needed. Additional evidence is required to determine the relevance of improvements observed with antihypertensive therapy on CAP, cystatin C, procollagen, TNF-α, and IL-6 to a reduction in the risk of subsequent vascular events.

Further research is required to determine the extent to which these antihypertensive-related improvements in biomarkers contribute to the overall clinical outcome achieved in tandem with other CV risk reduction strategies and interventions. In addition, long-term studies with biomarkers are also required to show whether biomarkers correlate with long-term clinical outcomes.

Author details

Nadya Merchant and Bobby V. Khan
Atlanta Vascular Research Foundation, Atlanta, GA, USA

6. References

[1] Writing Group, M., et al., Heart disease and stroke statistics--2010 update: a report from the American Heart Association. Circulation, 2010. 121(7): p. e46-e215.

[2] Packard, R.R. and P. Libby, Inflammation in atherosclerosis: from vascular biology to biomarker discovery and risk prediction. Clin Chem, 2008. 54(1): p. 24-38.
[3] Maisel, A.S., Cardiovascular and renal surrogate markers in the clinical management of hypertension. Cardiovasc Drugs Ther, 2009. 23(4): p. 317-26.
[4] Vasan, R.S., Biomarkers of cardiovascular disease: molecular basis and practical considerations. Circulation, 2006. 113(19): p. 2335-62.
[5] Lambers Heerspink, H.J., V. Perkovic, and D. de Zeeuw, Renal and cardio-protective effects of direct renin inhibition: a systematic literature review. J Hypertens, 2009. 27(12): p. 2321-31.
[6] Novo, S., et al., Role of ARBs in the blood hypertension therapy and prevention of cardiovascular events. Curr Drug Targets, 2009. 10(1): p. 20-5.
[7] Sola, S., et al., Irbesartan and lipoic acid improve endothelial function and reduce markers of inflammation in the metabolic syndrome: results of the Irbesartan and Lipoic Acid in Endothelial Dysfunction (ISLAND) study. Circulation, 2005. 111(3): p. 343-8.
[8] Nagamia, S., et al., The role of quinapril in the presence of a weight loss regimen: endothelial function and markers of obesity in patients with the metabolic syndrome. Prev Cardiol, 2007. 10(4): p. 204-9.
[9] Persson, F., et al., Irbesartan treatment reduces biomarkers of inflammatory activity in patients with type 2 diabetes and microalbuminuria: an IRMA 2 substudy. Diabetes, 2006. 55(12): p. 3550-5.
[10] Derosa, G., et al., Candesartan effect on inflammation in hypertension. Hypertens Res, 2010. 33(3): p. 209-13.
[11] Shurtz-Swirski, R., et al., [The effect of calcium channel blocker lercanidipine on lowgrade inflammation parameters in essential hypertension patients]. Harefuah, 2006. 145(12): p. 895-9, 942.
[12] Komoda, H., T. Inoue, and K. Node, Anti-inflammatory properties of azelnidipine, a dihydropyridine-based calcium channel blocker. Clin Exp Hypertens, 2010. 32(2): p. 121-8.
[13] Merchant, N., et al., Effects of nebivolol in obese African Americans with hypertension (NOAAH): markers of inflammation and obesity in response to exercise-induced stress. J Hum Hypertens, 2011. 25(3): p. 196-202.
[14] Del Fiorentino, A., et al., The effect of angiotensin receptor blockers on C-reactive protein and other circulating inflammatory indices in man. Vasc Health Risk Manag, 2009. 5(1): p. 233-42.
[15] Polonia, J., et al., Different influences on central and peripheral pulse pressure, aortic wave reflections and pulse wave velocity of three different types of antihypertensive drugs. Rev Port Cardiol, 2003. 22(12): p. 1485-92.
[16] Karalliedde, J., et al., Valsartan improves arterial stiffness in type 2 diabetes independently of blood pressure lowering. Hypertension, 2008. 51(6): p. 1617-23.
[17] Ridker, P.M., et al., Valsartan, blood pressure reduction, and C-reactive protein: primary report of the Val-MARC trial. Hypertension, 2006. 48(1): p. 73-9.

[18] Bloch, M.J., Do angiotensin receptor antagonists decrease hsCRP independent of blood pressure - and does it matter? J Clin Hypertens (Greenwich), 2007. 9(1): p. 57-9.
[19] Futai, R., et al., Olmesartan ameliorates myocardial function independent of blood pressure control in patients with mild-to-moderate hypertension. Heart Vessels, 2009. 24(4): p. 294-300.
[20] Moriuchi, A., et al., Induction of human adiponectin gene transcription by telmisartan, angiotensin receptor blocker, independently on PPAR-gamma activation. Biochem Biophys Res Commun, 2007. 356(4): p. 1024-30.
[21] Schepke, M., et al., Hemodynamic effects of the angiotensin II receptor antagonist irbesartan in patients with cirrhosis and portal hypertension. Gastroenterology, 2001. 121(2): p. 389-95.
[22] Watanabe, S., et al., Valsartan reduces serum cystatin C and the renal vascular resistance in patients with essential hypertension. Clin Exp Hypertens, 2006. 28(5): p. 451-61.
[23] Derosa, G., et al., Metabolic effects of telmisartan and irbesartan in type 2 diabetic patients with metabolic syndrome treated with rosiglitazone. J Clin Pharm Ther, 2007. 32(3): p. 261-8.
[24] Usui, I., et al., Telmisartan reduced blood pressure and HOMA-IR with increasing plasma leptin level in hypertensive and type 2 diabetic patients. Diabetes Res Clin Pract, 2007. 77(2): p. 210-4.
[25] de Luis, D.A., et al., Effects of telmisartan vs olmesartan on metabolic parameters, insulin resistance and adipocytokines in hypertensive obese patients. Nutr Hosp, 2010. 25(2): p. 275-9.
[26] Christensen, M.K., et al., Does long-term losartan- vs atenolol-based antihypertensive treatment influence collagen markers differently in hypertensive patients? A LIFE substudy. Blood Press, 2006. 15(4): p. 198-206.
[27] Muller-Brunotte, R., et al., Myocardial fibrosis and diastolic dysfunction in patients with hypertension: results from the Swedish Irbesartan Left Ventricular Hypertrophy Investigation versus Atenolol (SILVHIA). J Hypertens, 2007. 25(9): p. 1958-66.
[28] Kawamura, M., et al., Candesartan decreases type III procollagen-N-peptide levels and inflammatory marker levels and maintains sinus rhythm in patients with atrial fibrillation. J Cardiovasc Pharmacol, 2010. 55(5): p. 511-7.
[29] Fogari, R., et al., Effects of amlodipine-atorvastatin combination on inflammation markers and insulin sensitivity in normocholesterolemic obese hypertensive patients. Eur J Clin Pharmacol, 2006. 62(10): p. 817-22.
[30] Fujita, M., et al., Blockade of angiotensin II receptors reduces the expression of receptors for advanced glycation end products in human endothelial cells. Arterioscler Thromb Vasc Biol, 2006. 26(10): p. e138-42.
[31] Schulz, R. and G. Heusch, Tumor necrosis factor-alpha and its receptors 1 and 2: Yin and Yang in myocardial infarction? Circulation, 2009. 119(10): p. 1355-7.
[32] Cesari, M., et al., Inflammatory markers and onset of cardiovascular events: results from the Health ABC study. Circulation, 2003. 108(19): p. 2317-22.

[33] Luc, G., et al., C-reactive protein, interleukin-6, and fibrinogen as predictors of coronary heart disease: the PRIME Study. Arterioscler Thromb Vasc Biol, 2003. 23(7): p. 1255-61.
[34] Pai, J.K., et al., Inflammatory markers and the risk of coronary heart disease in men and women. N Engl J Med, 2004. 351(25): p. 2599-610.
[35] Patarroyo Aponte, M.M. and G.S. Francis, Effect of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Antagonists in Atherosclerosis Prevention. Curr Cardiol Rep, 2012.
[36] Lonn, E., Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in atherosclerosis. Curr Atheroscler Rep, 2002. 4(5): p. 363-72.
[37] Shahin, Y., et al., Angiotensin converting enzyme inhibitors effect on endothelial dysfunction: a meta-analysis of randomised controlled trials. Atherosclerosis, 2011. 216(1): p. 7-16.
[38] Yusuf, S., [After the HOPE Study. ACE inhibitor now for every diabetic patient?. Interview by Dr. Dirk Einecke]. MMW Fortschr Med, 2000. 142(44): p. 10.
[39] Fox, K.M. and E.U.t.O.r.o.c.e.w.P.i.s.c.A.d. Investigators, Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet, 2003. 362(9386): p. 782-8.
[40] PROGRESS will change the way we view stroke treatment. Cardiovasc J S Afr, 2001. 12(5): p. 288.
[41] Dahlof, B., et al., Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet, 2005. 366(9489): p. 895-906.
[42] Dzau, V.J., Theodore Cooper Lecture: Tissue angiotensin and pathobiology of vascular disease: a unifying hypothesis. Hypertension, 2001. 37(4): p. 1047-52.
[43] Dzau, V.J., et al., The relevance of tissue angiotensin-converting enzyme: manifestations in mechanistic and endpoint data. Am J Cardiol, 2001. 88(9A): p. 1L-20L.
[44] Investigators, O., et al., Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med, 2008. 358(15): p. 1547-59.
[45] Velazquez, E.J., et al., VALsartan In Acute myocardial iNfarcTion (VALIANT) trial: baseline characteristics in context. Eur J Heart Fail, 2003. 5(4): p. 537-44.
[46] Dahlof, B., et al., Effects of losartan and atenolol on left ventricular mass and neurohormonal profile in patients with essential hypertension and left ventricular hypertrophy. J Hypertens, 2002. 20(9): p. 1855-64.
[47] Koh, K.K., et al., Additive beneficial effects of losartan combined with simvastatin in the treatment of hypercholesterolemic, hypertensive patients. Circulation, 2004. 110(24): p. 3687-92.
[48] Turnbull, F. and C. Blood Pressure Lowering Treatment Trialists, Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet, 2003. 362(9395): p. 1527-35.

[49] Messerli, F.H., Calcium antagonists and beta-blockers: impact on cardiovascular and cerebrovascular events. Clin Cornerstone, 2004. 6(4): p. 18-27.
[50] Williams, B., et al., Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation, 2006. 113(9): p. 1213-25.
[51] Terai, M., et al., Comparison of arterial functional evaluations as a predictor of cardiovascular events in hypertensive patients: the Non-Invasive Atherosclerotic Evaluation in Hypertension (NOAH) study. Hypertens Res, 2008. 31(6): p. 1135-45.
[52] Luna, B. and M.N. Feinglos, Drug-induced hyperglycemia. JAMA, 2001. 286(16): p. 1945-8.
[53] Bangalore, S., et al., A meta-analysis of 94,492 patients with hypertension treated with beta blockers to determine the risk of new-onset diabetes mellitus. Am J Cardiol, 2007. 100(8): p. 1254-62.
[54] Dahlof, B., 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(9311): p. 995-1003.
[55] Wright, J.T., Jr., et al., Lowering blood pressure with beta-blockers in combination with other renin-angiotensin system blockers in patients with hypertension and type 2 diabetes: results from the GEMINI Trial. J Clin Hypertens (Greenwich), 2007. 9(11): p. 842-9.
[56] Bakris, G.L., et al., Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. JAMA, 2004. 292(18): p. 2227-36.
[57] Agabiti Rosei, E. and D. Rizzoni, Metabolic profile of nebivolol, a beta-adrenoceptor antagonist with unique characteristics. Drugs, 2007. 67(8): p. 1097-107.
[58] Chobanian, A.V., et al., The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA, 2003. 289(19): p. 2560-72.
[59] Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. JAMA, 1991. 265(24): p. 3255-64.
[60] Sica, D.A., et al., Thiazide and loop diuretics. J Clin Hypertens (Greenwich), 2011. 13(9): p. 639-43.
[61] Materson, B.J., et al., Results of combination anti-hypertensive therapy after failure of each of the components. Department of Veterans Affairs Cooperative Study Group on Anti-hypertensive Agents. J Hum Hypertens, 1995. 9(10): p. 791-6.
[62] Fisher, N.D. and N.K. Hollenberg, Renin inhibition: what are the therapeutic opportunities? J Am Soc Nephrol, 2005. 16(3): p. 592-9.
[63] Brown, N.J., Aldosterone and vascular inflammation. Hypertension, 2008. 51(2): p. 161-7.
[64] Farquharson, C.A. and A.D. Struthers, Spironolactone increases nitric oxide bioactivity, improves endothelial vasodilator dysfunction, and suppresses vascular angiotensin

I/angiotensin II conversion in patients with chronic heart failure. Circulation, 2000. 101(6): p. 594-7.
[65] Parving, H.H., et al., Aliskiren combined with losartan in type 2 diabetes and nephropathy. N Engl J Med, 2008. 358(23): p. 2433-46.
[66] Cleland, J.G., et al., Clinical trials update from the European Society of Cardiology Congress 2007: 3CPO, ALOFT, PROSPECT and statins for heart failure. Eur J Heart Fail, 2007. 9(10): p. 1070-3.
[67] Wang, X., et al., Assessment of arterial stiffness, a translational medicine biomarker system for evaluation of vascular risk. Cardiovasc Ther, 2008. 26(3): p. 214-23.
[68] Williams, B. and P.S. Lacy, Central aortic pressure and clinical outcomes. J Hypertens, 2009. 27(6): p. 1123-5.
[69] Nelson, M.R., et al., Noninvasive measurement of central vascular pressures with arterial tonometry: clinical revival of the pulse pressure waveform? Mayo Clin Proc, 2010. 85(5): p. 460-72.
[70] Paoletti, R., A.M. Gotto, Jr., and D.P. Hajjar, Inflammation in atherosclerosis and implications for therapy. Circulation, 2004. 109(23 Suppl 1): p. III20-6.
[71] Black, S., I. Kushner, and D. Samols, C-reactive Protein. J Biol Chem, 2004. 279(47): p. 48487-90.
[72] Bautista, L.E., et al., Association between C-reactive protein and hypertension in healthy middle-aged men and women. Coron Artery Dis, 2004. 15(6): p. 331-6.
[73] Dauphinot, V., et al., C-reactive protein implications in new-onset hypertension in a healthy population initially aged 65 years: the Proof study. J Hypertens, 2009. 27(4): p. 736-43.
[74] Abramson, J.L., W.S. Weintraub, and V. Vaccarino, Association between pulse pressure and C-reactive protein among apparently healthy US adults. Hypertension, 2002. 39(2): p. 197-202.
[75] Genest, J., Preventive cardiology: move over low density lipoprotein cholesterol, hello C-reactive protein? Can J Cardiol, 2004. 20 Suppl B: p. 89B-92B.
[76] Savoia, C. and E.L. Schiffrin, Reduction of C-reactive protein and the use of anti-hypertensives. Vasc Health Risk Manag, 2007. 3(6): p. 975-83.
[77] Montecucco, F. and F. Mach, Update on therapeutic strategies to increase adiponectin function and secretion in metabolic syndrome. Diabetes Obes Metab, 2009. 11(5): p. 445-54.
[78] Karthikeyan, V.J. and G.Y. Lip, Antihypertensive treatment, adiponectin and cardiovascular risk. J Hum Hypertens, 2007. 21(1): p. 8-11.
[79] Shargorodsky, M., et al., Adiponectin and vascular properties in obese patients: is it a novel biomarker of early atherosclerosis? Int J Obes (Lond), 2009. 33(5): p. 553-8.
[80] Makita, S., et al., Potential effects of angiotensin II receptor blockers on glucose tolerance and adiponectin levels in hypertensive patients. Cardiovasc Drugs Ther, 2007. 21(4): p. 317-8.
[81] Ylinen, E.A., et al., Cystatin C as a marker for glomerular filtration rate in pediatric patients. Pediatr Nephrol, 1999. 13(6): p. 506-9.

[82] Laterza, O.F., C.P. Price, and M.G. Scott, Cystatin C: an improved estimator of glomerular filtration rate? Clin Chem, 2002. 48(5): p. 699-707.
[83] Massey, D., Commentary: clinical diagnostic use of cystatin C. J Clin Lab Anal, 2004. 18(1): p. 55-60.
[84] Kniepeiss, D., et al., Serum cystatin C is an easy to obtain biomarker for the onset of renal impairment in heart transplant recipients. J Thorac Cardiovasc Surg, 2010.
[85] Mena, C., et al., Cystatin c and blood pressure: results of 24 h ambulatory blood pressure monitoring. Eur J Intern Med, 2010. 21(3): p. 185-90.
[86] Prats, M., et al., Cystatin C and cardiac hypertrophy in primary hypertension. Blood Press, 2010. 19(1): p. 20-5.
[87] Matthews, D.R., et al., Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia, 1985. 28(7): p. 412-9.
[88] Cooper-DeHoff, R.M., M.A. Pacanowski, and C.J. Pepine, Cardiovascular therapies and associated glucose homeostasis: implications across the dysglycemia continuum. J Am Coll Cardiol, 2009. 53(5 Suppl): p. S28-34.
[89] Szmigielski, C., et al., Metabolism of collagen is altered in hypertensives with increased intima media thickness. Blood Press, 2006. 15(3): p. 157-63.
[90] Ishikawa, J., et al., Collagen metabolism in extracellular matrix may be involved in arterial stiffness in older hypertensive patients with left ventricular hypertrophy. Hypertens Res, 2005. 28(12): p. 995-1001.
[91] Lopez, B., et al., The use of collagen-derived serum peptides for the clinical assessment of hypertensive heart disease. J Hypertens, 2005. 23(8): p. 1445-51.
[92] Cesari, M., et al., Inflammatory markers and cardiovascular disease (The Health, Aging and Body Composition [Health ABC] Study). Am J Cardiol, 2003. 92(5): p. 522-8.
[93] Williams, B., et al., Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation, 2006. 113(9): p. 1213-25.
[94] Neal, D.A., et al., Hemodynamic effects of amlodipine, bisoprolol, and lisinopril in hypertensive patients after liver transplantation. Transplantation, 2004. 77(5): p. 748-50.
[95] Takami, T. and Y. Saito, Effects of Azelnidipine plus OlmesaRTAn versus amlodipine plus olmesartan on central blood pressure and left ventricular mass index: the AORTA study. Vasc Health Risk Manag, 2011. 7: p. 383-90.
[96] Morgan, T., et al., Effect of different antihypertensive drug classes on central aortic pressure. Am J Hypertens, 2004. 17(2): p. 118-23.
[97] Kagota, S., et al., Peroxynitrite is Involved in the dysfunction of vasorelaxation in SHR/NDmcr-cp rats, spontaneously hypertensive obese rats. J Cardiovasc Pharmacol, 2007. 50(6): p. 677-85.
[98] Ferguson, J.M., et al., Effects of a fixed-dose ACE inhibitor-diuretic combination on ambulatory blood pressure and arterial properties in isolated systolic hypertension. J Cardiovasc Pharmacol, 2008. 51(6): p. 590-5.

[99] Ishii, H., T. Tsukada, and M. Yoshida, Angiotensin II type-I receptor blocker, candesartan, improves brachial-ankle pulse wave velocity independent of its blood pressure lowering effects in type 2 diabetes patients. Intern Med, 2008. 47(23): p. 2013-8.
[100] Nakamura, M., et al., Brachial-ankle pulse wave velocity as a risk stratification index for the short-term prognosis of type 2 diabetic patients with coronary artery disease. Hypertens Res, 2010. 33(10): p. 1018-24.
[101] Kinouchi, K., et al., Differential Effects in Cardiovascular Markers between High-Dose Angiotensin II Receptor Blocker Monotherapy and Combination Therapy of ARB with Calcium Channel Blocker in Hypertension (DEAR Trial). Int J Hypertens, 2011. 2011: p. 284823.
[102] Miyoshi, T., et al., Olmesartan reduces arterial stiffness and serum adipocyte fatty acid-binding protein in hypertensive patients. Heart Vessels, 2011. 26(4): p. 408-13.
[103] Takiguchi, S., et al., Olmesartan improves endothelial function in hypertensive patients: link with extracellular superoxide dismutase. Hypertens Res, 2011. 34(6): p. 686-92.
[104] Koh, K.K., et al., Additive beneficial effects of atorvastatin combined with amlodipine in patients with mild-to-moderate hypertension. Int J Cardiol, 2011. 146(3): p. 319-25.
[105] Li, M., et al., Impact of combination therapy with amlodipine and atorvastatin on plasma adiponectin levels in hypertensive patients with coronary artery disease: combination therapy and adiponectin. Postgrad Med, 2011. 123(6): p. 66-71.
[106] Yilmaz, R., et al., Impact of amlodipine or ramipril treatment on left ventricular mass and carotid intima-media thickness in nondiabetic hemodialysis patients. Ren Fail, 2010. 32(8): p. 903-12.
[107] de Vinuesa, S.G., et al., Insulin resistance, inflammatory biomarkers, and adipokines in patients with chronic kidney disease: effects of angiotensin II blockade. J Am Soc Nephrol, 2006. 17(12 Suppl 3): p. S206-12.
[108] Martinez-Martin, F.J., et al., Olmesartan/amlodipine vs olmesartan/hydrochlorothiazide in hypertensive patients with metabolic syndrome: the OLAS study. J Hum Hypertens, 2011. 25(6): p. 346-53.
[109] Derosa, G., et al., Differential effects of candesartan and olmesartan on adipose tissue activity biomarkers in type II diabetic hypertensive patients. Hypertens Res, 2010. 33(8): p. 790-5.
[110] Doi, M., et al., Combination therapy of calcium channel blocker and angiotensin II receptor blocker reduces augmentation index in hypertensive patients. Am J Med Sci, 2010. 339(5): p. 433-9.
[111] Ishimitsu, T., et al., Angiotensin-II receptor antagonist combined with calcium channel blocker or diuretic for essential hypertension. Hypertens Res, 2009. 32(11): p. 962-8.
[112] Fukao, K., et al., Effects of calcium channel blockers on glucose tolerance, inflammatory state, and circulating progenitor cells in non-diabetic patients with essential hypertension: a comparative study between Azelnidipine and amlodipine on glucose tolerance and endothelial function - a crossover trial (AGENT). Cardiovasc Diabetol, 2011. 10: p. 79.

[113] Martinez-Martin, F.J., et al., Effects of manidipine and its combination with an ACE inhibitor on insulin sensitivity and metabolic, inflammatory and prothrombotic markers in hypertensive patients with metabolic syndrome: the MARCADOR study. Clin Drug Investig, 2011. 31(3): p. 201-12.
[114] Igarashi, M., et al., Dual blockade of angiotensin II with enalapril and losartan reduces proteinuria in hypertensive patients with type 2 diabetes. Endocr J, 2006. 53(4): p. 493-501.
[115] Matsui, Y., et al., Urinary albumin excretion during angiotensin II receptor blockade: comparison of combination treatment with a diuretic or a calcium-channel blocker. Am J Hypertens, 2011. 24(4): p. 466-73.
[116] Sugihara, M., et al., Safety and efficacy of antihypertensive therapy with add-on angiotensin II type 1 receptor blocker after successful coronary stent implantation. Hypertens Res, 2009. 32(7): p. 625-30.
[117] Sardo, M.A., et al., Effects of the angiotensin II receptor blocker losartan on the monocyte expression of biglycan in hypertensive patients. Clin Exp Pharmacol Physiol, 2010. 37(9): p. 933-8.
[118] Aksnes, T.A., et al., Improved insulin sensitivity by the angiotensin II-receptor blocker losartan is not explained by adipokines, inflammatory markers, or whole blood viscosity. Metabolism, 2007. 56(11): p. 1470-7.
[119] Ruilope, L.M., et al., Efficacy and tolerability of combination therapy with valsartan plus hydrochlorothiazide compared with amlodipine monotherapy in hypertensive patients with other cardiovascular risk factors: the VAST study. Clin Ther, 2005. 27(5): p. 578-87.
[120] Tomiyama, H., et al., Discrepancy between improvement of insulin sensitivity and that of arterial endothelial function in patients receiving antihypertensive medication. J Hypertens, 2007. 25(4): p. 883-9.
[121] Navalkar, S., et al., Irbesartan, an angiotensin type 1 receptor inhibitor, regulates markers of inflammation in patients with premature atherosclerosis. J Am Coll Cardiol, 2001. 37(2): p. 440-4.
[122] Martinez Martin, F.J., Manidipine in hypertensive patients with metabolic syndrome: the MARIMBA study. Expert Rev Cardiovasc Ther, 2009. 7(7): p. 863-9.
[123] Masajtis-Zagajewska, A., J. Majer, and M. Nowicki, Effect of moxonidine and amlodipine on serum YKL-40, plasma lipids and insulin sensitivity in insulin-resistant hypertensive patients-a randomized, crossover trial. Hypertens Res, 2010. 33(4): p. 348-53.
[124] Ge, C.J., et al., Synergistic effect of amlodipine and atorvastatin on blood pressure, left ventricular remodeling, and C-reactive protein in hypertensive patients with primary hypercholesterolemia. Heart Vessels, 2008. 23(2): p. 91-5.
[125] Rizos, C.V., et al., Combining rosuvastatin with sartans of different peroxisome proliferator-activated receptor-gamma activating capacity is not associated with different changes in low-density lipoprotein subfractions and plasma lipoprotein-associated phospholipase A(2). Metab Syndr Relat Disord, 2011. 9(3): p. 217-23.

[126] Negro, R., G. Formoso, and H. Hassan, The effects of irbesartan and telmisartan on metabolic parameters and blood pressure in obese, insulin resistant, hypertensive patients. J Endocrinol Invest, 2006. 29(11): p. 957-61.
[127] Kintscher, U., et al., Irbesartan for the treatment of hypertension in patients with the metabolic syndrome: a sub analysis of the Treat to Target post authorization survey. Prospective observational, two armed study in 14,200 patients. Cardiovasc Diabetol, 2007. 6: p. 12.
[128] Krikken, J.A., et al., Antiproteinuric therapy decreases LDL-cholesterol as well as HDL-cholesterol in non-diabetic proteinuric patients: relationships with cholesteryl ester transfer protein mass and adiponectin. Expert Opin Ther Targets, 2009. 13(5): p. 497-504.
[129] Negro, R. and H. Hassan, The effects of telmisartan and amlodipine on metabolic parameters and blood pressure in type 2 diabetic, hypertensive patients. J Renin Angiotensin Aldosterone Syst, 2006. 7(4): p. 243-6.
[130] Nishimura, H., et al., Losartan elevates the serum high-molecular weight-adiponectin isoform and concurrently improves insulin sensitivity in patients with impaired glucose metabolism. Hypertens Res, 2008. 31(8): p. 1611-8.
[131] Derosa, G., et al., Different actions of losartan and ramipril on adipose tissue activity and vascular remodeling biomarkers in hypertensive patients. Hypertens Res, 2011. 34(1): p. 145-51.
[132] Huang, Y.Y., et al., [Effect of losartan on renal expression of monocyte chemoattractant protein-1 and transforming growth factor-beta(1) in rats after unilateral ureteral obstruction]. Nan Fang Yi Ke Da Xue Xue Bao, 2011. 31(8): p. 1405-10.
[133] Matsumoto, S., K. Takebayashi, and Y. Aso, The effect of spironolactone on circulating adipocytokines in patients with type 2 diabetes mellitus complicated by diabetic nephropathy. Metabolism, 2006. 55(12): p. 1645-52.
[134] Piecha, G., et al., Indapamide decreases plasma adiponectin concentration in patients with essential hypertension. Kidney Blood Press Res, 2007. 30(3): p. 187-94.
[135] Yilmaz, M.I., et al., Effect of antihypertensive agents on plasma adiponectin levels in hypertensive patients with metabolic syndrome. Nephrology (Carlton), 2007. 12(2): p. 147-53.
[136] Koh, K.K., et al., Distinct vascular and metabolic effects of different classes of anti-hypertensive drugs. Int J Cardiol, 2010. 140(1): p. 73-81.
[137] Guo, L.L., Y. Pan, and H.M. Jin, Adiponectin is positively associated with insulin resistance in subjects with type 2 diabetic nephropathy and effects of angiotensin II type 1 receptor blocker losartan. Nephrol Dial Transplant, 2009. 24(6): p. 1876-83.
[138] Albayrak, S., et al., Effect of olmesartan medoxomil on cystatin C level, left ventricular hypertrophy and diastolic function. Blood Press, 2009. 18(4): p. 187-91.
[139] Koc, Y., et al., Effect of Olmesartan on serum cystatin C levels in the patients with essential hypertension. Eur Rev Med Pharmacol Sci, 2011. 15(12): p. 1389-94.
[140] Ogino, K., et al., Addition of losartan to angiotensin-converting enzyme inhibitors improves insulin resistance in patients with chronic heart failure treated without beta-blockers. Circ J, 2010. 74(11): p. 2346-52.

[141] Bahadir, O., et al., Effects of telmisartan and losartan on insulin resistance in hypertensive patients with metabolic syndrome. Hypertens Res, 2007. 30(1): p. 49-53.
[142] Lan, J., et al., The relationship between visfatin and HOMA-IR in hypertensive patients, and the effect of antihypertensive drugs on visfatin and HOMA-IR in hypertensive patients with insulin resistance. Diabetes Res Clin Pract, 2011. 94(1): p. 71-6.
[143] De Luis, D.A., et al., Effects of olmesartan vs irbesartan on metabolic parameters and visfatin in hypertensive obese women. Eur Rev Med Pharmacol Sci, 2010. 14(9): p. 759-63.
[144] Dohi, T., et al., Effects of olmesartan on blood pressure and insulin resistance in hypertensive patients with sleep-disordered breathing. Heart Vessels, 2011. 26(6): p. 603-8.
[145] Enjoji, M., et al., Therapeutic effect of ARBs on insulin resistance and liver injury in patients with NAFLD and chronic hepatitis C: a pilot study. Int J Mol Med, 2008. 22(4): p. 521-7.
[146] Jin, H.M. and Y. Pan, Angiotensin type-1 receptor blockade with losartan increases insulin sensitivity and improves glucose homeostasis in subjects with type 2 diabetes and nephropathy. Nephrol Dial Transplant, 2007. 22(7): p. 1943-9.
[147] Watanabe, S., et al., The effect of losartan and amlodipine on serum adiponectin in Japanese adults with essential hypertension. Clin Ther, 2006. 28(10): p. 1677-85.
[148] Fogari, R., et al., Effect of valsartan and ramipril on atrial fibrillation recurrence and P-wave dispersion in hypertensive patients with recurrent symptomatic lone atrial fibrillation. Am J Hypertens, 2008. 21(9): p. 1034-9.
[149] Ishimitsu, T., et al., Protective effects of an angiotensin II receptor blocker and a long-acting calcium channel blocker against cardiovascular organ injuries in hypertensive patients. Hypertens Res, 2005. 28(4): p. 351-9.
[150] Diez, J., et al., Losartan-dependent regression of myocardial fibrosis is associated with reduction of left ventricular chamber stiffness in hypertensive patients. Circulation, 2002. 105(21): p. 2512-7.
[151] Dziadzio, M., et al., Losartan therapy for Raynaud's phenomenon and scleroderma: clinical and biochemical findings in a fifteen-week, randomized, parallel-group, controlled trial. Arthritis Rheum, 1999. 42(12): p. 2646-55.
[152] Lorenzen, J.M., et al., Angiotensin II receptor blocker and statins lower elevated levels of osteopontin in essential hypertension--results from the EUTOPIA trial. Atherosclerosis, 2010. 209(1): p. 184-8.
[153] Fogari, R., et al., Hydrochlorothiazide added to valsartan is more effective than when added to olmesartan in reducing blood pressure in moderately hypertensive patients inadequately controlled by monotherapy. Adv Ther, 2006. 23(5): p. 680-95.
[154] Park, H., et al., Relationship between insulin resistance and inflammatory markers and anti-inflammatory effect of losartan in patients with type 2 diabetes and hypertension. Clin Chim Acta, 2006. 374(1-2): p. 129-34.

[155] Navarro-Gonzalez, J., et al., Serum and gene expression profile of tumor necrosis factor-alpha and interleukin-6 in hypertensive diabetic patients: effect of amlodipine administration. Int J Immunopathol Pharmacol, 2010. 23(1): p. 51-9.
[156] Ruilope, L.M., et al., 24-hour ambulatory blood-pressure effects of valsartan and hydrochlorothiazide combinations compared with amlodipine in hypertensive patients at increased cardiovascular risk: a VAST sub-study. Blood Press Monit, 2005. 10(2): p. 85-91.