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Antihypertensive Treatment in Type 2 Diabetic Patients

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1. Introduction

Hypertension is an heterogeneous disease in which both genetic and environmental factors play a relevant role. Among the major environmental determinants of essential hypertension are high alcohol consumption, physical inactivity, overweight, smoking and dietary factors, in particular animal fats, salt, and potassium intake (Binder A, 2007; Staessen et al, 2003). Worldwide prevalence estimates for hypertension may be as much as 1 billion individuals, and approximately 7.1 million deaths per year may be attributable to hypertension (World Health Report, 2002).

Hypertension is a highly prevalent risk factor for cardiovascular diseases throughout the industrialized world; data from several studies show that Hypertension plays a relevant etiologic role in the development of cerebrovascular attack, ischemic heart disease, cardiac and renal failure (Yusuf et al., 2001). The relationship between high blood pressure and cardiovascular events is continuous, consistent, and independent of other risk factors. It is becoming an increasingly common health problem worldwide because of growing longevity and prevalence of contributing factors such as obesity, physical inactivity and an unhealthy diet.

High blood pressure often coexists with other cardiovascular risk factors, such as obesity, dyslipidemia, impaired glucose tolerance, and type 2 diabetes, which compound the cardiovascular risk attributable to hypertension. The concordance of hypertension and type 2 diabetes is increased in the population; hypertension is disproportionately higher in diabetics, while persons with elevated blood pressure are two and a half times more likely to develop diabetes within 5 years (Gress et al., 2000; Sowers & Bakris, 2000).

The present chapter focuses on the most recent and significant literature that explored the possible pathogenetic links between essential hypertension and type 2 diabetes, and it reviews the evidences for "optimal" antihypertensive treatment in type 2 diabetic patients and concomitant hypertension, discussing in detail some areas of uncertainty, such as the selection of antihypertensive drugs of choice in these patients.

2. High blood pressure and type 2 diabetes

The association of hypertension with diabetes is particularly bad for the health and the evidences that the association of type 2 diabetes with hypertension markedly increases

cardiovascular and renal risk are incontrovertible (Fagan & Sowers, 1999): it has been shown that hypertension in type 2 diabetic patients increases the risk for macrovascular and microvascular complications (Adler et al., 2000), thus predisposing patients to stroke, cardiac death, congestive heart failure, coronary heart disease, peripheral vascular diseases, progression of nephropathy and retinopathy (Sowers & Haffner, 2002; Adler et al., 2000; Kohner et al., 1998). Hypertension in type 2 diabetes is one of the most widespread, important, and treatable cardiovascular risk factors in clinical practice; thus, good management of hypertensive diabetic patients is essential.

2.1 Pathogenetic links

Although there is a large evidence that shows the relationship between essential hypertension and type 2 diabetes, the precise mechanism of this link is still unclear. In 1966, Welborn and colleagues studied 19 normoglycemic patients with essential hypertension and demonstrated that these individuals had significantly higher plasma insulin concentrations compared with a normotensive control group (Welborn et al., 1966). This observation suggested that the prevalence of resistance to insulin would be increased in patients with essential hypertension. The relationship between essential hypertension, insulin resistance, and compensatory hyperinsulinemia, that occurs as a response to insulin resistance, has been extensively studied in the following years. Several research groups supported the hypothesis that insulin resistance, well known cause of type 2 diabetes, could play a key role in the pathogenesis of essential hypertension (Ferrannini et al., 1987; Shen et al., 1988; Swislocki et al., 1989; Pollare T, 1990). In 1992, the European Group for the Study of Insulin Resistance revealed that, in normotensives, blood pressure was directly related to both insulin resistance and insulin concentration; these relationships were independent of differences in age, gender, and degree of obesity (Ferrannini et al., 1992).

Several studies showed that the relation between insulinemia and/or insulin resistance and blood pressure appears to vary among ethnic groups. Nearly all studies showing a strong association between insulin and blood pressure were conducted among non-Hispanic whites (Saad et al., 1991); studies in African Americans (Mbanya et al., 1988; Falkner B et al., 1990), Hispanics (Haffner et al., 1988), Pima Indians (Saad et al., 1990), and Asian Indians (Nagi et al., 1990) showed a weak or no association. At the same time, Shamiss et al. demonstrated that the prevalence of insulin resistance was not increased in patients with secondary forms of hypertension (Shamiss et al., 1992); in addition, other studies revealed insulin resistance and hyperinsulinemia in normotensive, first-degree relatives of patients with essential hypertension (Ferrari P, 1992; Allemann Y, 1993).

Furthermore, results of several prospective studies support the view that insulin resistance and compensatory hyperinsulinemia are causally linked to the development of essential hypertension (Lissner et al., 1992; Zavaroni et al., 1994; Raitakari et al., 1995). In this regard, the most relevant study was performed by Skarfors et al., who evaluated risk factors for the development of hypertension in 2130 men observed over a 10-yr period; in individuals who subsequently developed hypertension, the analysis showed that independent predictors of the progression to hypertension were overweight, fasting and post-glucose challenge plasma insulin concentrations, and a family history of hypertension (Skarfors et al., 1991).

Recently, in some studies carried out in Japanese (Kanauchi et al., 2004), Indian (Sathiyapriya et al., 2006) and American (Player et al., 2007) populations has been reported the association between insulin resistance and prehypertension. Prehypertension is a new

category of blood pressure classification, introduced by The Seven Joint National Commission on the Prevention, Detection, Evaluation and Treatment of Hypertension to identify individuals with systolic blood pressure in the range of 120–139 mmHg or diastolic blood pressure between 80 and 89 mmHg (The Seventh Report of the Joint National Committee [JNC 7], 2004); it is not a benign condition, as it is strong predictor for the development of hypertension (Wang W, et al., 2006).

Prehypertension is not a disease category, but it is a condition at high risk of developing hypertension; so that both patients and clinicians are alerted to this risk and encouraged to prevent or delay hypertension. Prehypertensive individuals don't need drug therapy, however they should practice lifestyle modification in order to reduce their risk of developing hypertension in the future. Instead, individuals with prehypertension, who also have diabetes or kidney disease, should be considered candidates for appropriate drug therapy, if a trial of lifestyle modification fails (JNC-7).

Although some population-based studies have not been able to discern a significant relationship between insulin resistance and hyperinsulinemia, or showed only a weak association, at present there is substantial evidence that a large number of patients with essential hypertension are insulin resistant and hyperinsulinemic compared with normotensive individuals.

The mechanism through insulin resistance is associated with hypertension and blood pressure is not known. Skeletal muscle appears to be the primary site of insulin resistance in essential hypertension (Cepaldo et al., 1991; Natali et al., 1991); other organs, such as the kidney (Zheng et al., 2005; Strazzullo et al., 2006) may respond abnormally to insulin and adipocytes also appear to be a site of insulin resistance (Sironi et al., 2004). Thus, the putative interrelationship between insulin resistance and high blood pressure may involve organ-specific insulin resistance.

It is thought that insulin resistance could cause hypertension through compensatory hyperinsulinemia (Reaven & Hoffman, 1987). Insulin has been shown to increase renal sodium retention, stimulate the sympathetic nervous system, modulate membrane cation transport, and induce hypertrophy of vascular smooth muscle cells (Passa, 1992; Edelson & Sowers, 1993). In addition, insulin resistance has been associated with impaired endothelium-dependent vasodilatation, which could contribute to increased blood pressure (Wheatcroft et al., 2003). Moreover, there is a growing body of evidence indicating that Angiotensin II is also involved in the development of insulin resistance in vascular and skeletal muscle tissue, possibly by oxidative stress production (Sowers, 2004). It is plausible that insulin resistance, through the concomitant compensatory hyperinsulinemia, could contribute to the pathogenesis of hypertension by one or more of these mechanisms.

It has been hypothesized that insulin can increase renal sodium reabsorption in the proximal tubules and stimulate sympathetic tone, thus hyperinsulinemia could increase the blood pressure by inducing salt retention and central sympathetic overactivity (Galleti et al., 1997; Strazzullo et al., 2006). This hypothesis is strengthened by a interesting ex vivo study using the proximal tubules of both insulin receptor substrate-1 and insulin receptor substrate-2 deficient mice, in which while both mice showed insulin resistance and hyperinsulinemia, only the former showed hypertension. Administration of insulin, probably, increased the sodium reabsorption in the proximal tubules of the insulin receptor substrate-1 deficient mice, by the activation of $NaHCO_3^-$ co-transport, but not in the proximal tubules of the insulin receptor substrate-2 deficient mice, suggesting that the renal action of insulin is

mediated by insulin receptor substrate-2. Consequently, insulin receptor substrate-1 deficient mice showed higher blood pressure than insulin receptor substrate-2 deficient mice, possibly mediated by the greater sodium retention in the body. Thus, insulin resistance in the muscle, which is attributable to derangements of insulin receptor substrate-1, induces glucose intolerance and dyslipidemia; in turn, hyperinsulinemia induces sodium retention via insulin receptor substrate-2 phosphorylation in the kidney, resulting in volume-dependent salt-sensitive hypertension (Zheng et al., 2005). Lending support to this concept, the Olivetti Heart Study revealed that obese insulin-resistant individuals with metabolic syndrome showed a higher fractional sodium reabsorption in the proximal tubules (Strazzullo et al., 2006).

In this regard it has been supposed that high-salt intake could be a common cause of hypertension and insulin resistance. Actually, several experimental studies, involving various species and genetically modified animals, have demonstrated that a prolonged increase in salt intake leads to an increase in blood pressure (Denton et al., 1995; Elliott et al., 2007). Evidence of a positive association between sodium intake and the level of blood pressure has been also obtained in humans (Rose & Stamler, 1989; Frost et al., 1991; Khaw et al., 2004). Moreover, it has been shown that a high-salt diet not only increases the blood pressure, but also decreases the insulin sensitivity in Dahl salt-sensitive rats (Ogihara et al., 2002). In this regard, several studies showed an intimate relationship between salt-sensitivity and insulin sensitivity in hypertensive patients (Galleti et al., 1997; Suzuki et al., 2000); accordingly, the Finnish epidemiological study showed that the prevalence of diabetes was higher among obese people on a high-salt diet (Hu et al., 2005). It has been hypothesized that salt-induced insulin resistance might be attributable to the overproduction of reactive oxygen species (Aviv, 2002); in contrast to sodium, potassium possesses antihypertensive and anti-oxidant effects (Ogihara et al., 2002) associated with the normalization of reactive oxygen species overproduction.

In addition, in Dahl salt-sensitive rats, a high salt intake induced cardiac diastolic dysfunction, because of increased reactive oxygen species production in the heart, but potassium supplementation could reverse this abnormality through the inhibition of reactive oxygen species production (Matsui et al., 2006). At the vascular level, increased sodium intake has been reported to induce pronounced structural alterations of arteries, such as cerebral or renal arteries, independently of blood pressure levels; through changes in shear stress and endothelial function, high sodium intake can induce pressure-independent effects on the vascular wall, affecting the vascular content of collagen and elastin fibres (Tobian, 1991; Avolio, 1985). Thus, dietary salt and potassium stimulate and inhibit reactive oxygen species production, respectively; in turn, overproduction of reactive oxygen species might induce insulin resistance and cardiac dysfunction. Taken together, reactive oxygen species might play a critical role not only in the development of insulin resistance and hypertension, but also in that of salt-induced cardiovascular damage (Aviv, 2002).

Insulin has been also shown to stimulate sympathetic nervous system activity (Reaven et al., 1996); however, the neural mechanisms and pathways that mediate the sympathoexcitatory effects of insulin are poorly understood. These actions could be mediated by a central mechanism, because intracerebroventricular administration of insulin causes a similar selective increase in lumbar sympathetic nerve activity (Muntzel et al., 1994). It is well known that the rostral ventrolateral medulla plays a pivotal role in the regulation of

sympathetic nerve activity and blood pressure (Guyenet, 2006). Rostral neurons support basal sympathetic activity and its excitability is regulated by a number of neurotransmitters including L-glutamate. Injection of L-glutamate into the rostral ventrolateral medulla increases neuronal discharge, sympathetic activity, and blood pressure, while blockade of local glutamate receptors eliminates many sympathoexcitatory reflexes and lowers blood pressure in multiple experimental models of hypertension (Bergamaschi et al., 1995; Ito et al., 2000; Guyenet, 2006). Based on this evidence, it has been hypothesized that glutamate receptor activation in the rostral ventrolateral medulla mediates the sympathoexcitatory response to hyperinsulinemia. In addition to glutamate, several evidences suggest that the brain renin-angiotensin and melanocortin systems mediate the sympathoexcitatory response to insulin (Song et al., 1991; Adan et al., 2000). In this regard, rostral neurons express Angiotensin II-AT_1 receptors, and injection of Angiotensin II into the rostral ventrolateral medulla increases sympathetic activity and blood pressure (Dampney et al., 2002), whereas blockade of brain AT_1 receptors blunts the pressor response to hyperinsulinemia (Nakata et al., 1998); thus, blockade of the renin-angiotensin system could prevent insulin-induced hypertension (Brands et al., 1997). On the other hand, rostral neurons express melanocortin receptors (Adan et al., 2000), and injection of a melanocortin agonist into the rostral ventrolateral medulla increases sympathetic activity and blood pressure (Kawabe et al., 2006). Interestingly, the sympathoexcitatory effect to insulin is abolished in melanocortin knockout mice (Rahmouni et al., 2003). Therefore, it is plausible that one or more of these systems may contribute to the sympathoexcitatory response during hyperinsulinemia.

Altered cation transport is another of several mechanisms by which insulin resistance might raise blood pressure. Both sodium/potassium-ATPase (Ewart & Klip, 1995; Sweeney & Klip, 1998) and calcium-ATPase pumps (Levy et al., 1989; Zemel et al., 1993) are insulin sensitive; thus, when insulin resistance is present, the activity of these pumps in the smooth muscle of the arterial wall might be reduced. This would lead to an intracellular accumulation of sodium and calcium, thereby sensitizing the vascular wall to pressor substances (Resnick, 1993). Nevertheless, several data have demonstrated a significant vasodilating effect of insulin (Zemel et al., 1990; Kim & Zemel, 1993; Kahn et al., 1993); to reconcile these discordant observations, it was suggested that vascular smooth muscle resistance to this action may be the cause of hypertension in insulin resistance. This concept is supported by the observation that pharmacological amplification of peripheral insulin sensitivity results in reduced arterial pressure (Morgan et al., 1992; Dubey et al., 1993). Therefore, although insulin attenuates vasoconstrictor responses to pressor agonists and accelerates vascular smooth muscle relaxation, these effects are blunted in obesity and insulin resistance (Laakso et al., 1990). In addition, insulin is also a growth factor and therefore might have a trophic effect on the vessel wall, one that could initiate and sustain hypertension as well as atherosclerosis (DeFronzo & Ferrannini, 1991).

There are several lines of evidence showing that also endothelial function is compromised in situations of reduced sensitivity to endogenous insulin. For example, the increase of blood flow in the legs in response to methacholine, a measure of endothelium-dependent vasorelaxation, is reduced in non diabetic insulin-resistant individuals (Steinberg et al., 1996); moreover, nitric oxide–dependent flow-mediated dilatation of the brachial artery is impaired in hypertensive (Higashi et al., 1997) and normotensive (Balletshofer et al., 2000) subjects with insulin resistance. It is well established that a decreased bioavailability of nitric oxide contributes to endothelial dysfunction (Singh et al., 2010); furthermore, nitric

oxide may modulate insulin sensitivity (Pitocco et al., 2010). Activation of nitric oxide synthase augments blood flow to insulin-sensitive tissues, such as skeletal muscle, liver, and adipose tissue, and its activity is impaired in insulin resistance; whereas inhibition of nitric oxide synthase reduces the microvascular delivery of nutrients and blunts insulin-stimulated glucose uptake in skeletal muscle (Shi & Vanhoutte, 2009; Roberts & Sindhu, 2009). It has been shown that increased levels of asymmetric dimethylarginine, an endogenous inhibitor of nitric oxide synthase, are associated with endothelial vasodilator dysfunction and increased risk of cardiovascular diseases; moreover it has been found that plasma levels of asymmetric dimethylarginine are positively correlated with insulin resistance in non diabetic, normotensive people (Toutouzas et al., 2008).

However, the findings that plasma concentrations of plasminogen activator inhibitor 1 and endothelin 1 are elevated in the metabolic syndrome may indicate a more generalized endothelial dysfunction strongly related to insulin resistance (Ferri et al., 1997; Abbasi et al., 1999). Along the same lines, it has been shown that plasma concentrations of soluble adhesion molecules are increased in proportion to the degree of insulin resistance in healthy volunteers (Chen et al., 1999).

Angiotensin II, which is generated from angiotensinogen, is also well known to be a key substance influencing endothelial function and involved in the development of cardiovascular disease, through the activation of NADPH oxidase; oxidative stress may play an important role also in Angiotensin II-induced insulin resistance (Houstis et al., 2006). It has been reported that Angiotensin II-induced reactive oxygen species up-regulation affects several levels of the intracellular insulin signaling pathways (Ogihara et al., 2002). In vitro, reactive oxygen species has been shown to impair insulin receptor substrate-1 phoshorylation and insulin receptor substrate-1-induced phosphatidylinositol 3-kinase activation in cultured adipocytes, leading to impaired translocation of GLUT-4 glucotransporters to the membrane and consequently insulin resistance (Ogihara et al., 2004). Angiotensin II may also influence the development of type 2 diabetes via direct effects on the endocrine pancreas (Leung & de Gasparo, 2006; Leung, 2007). Local rennin-angiotensin system is known to be present in the pancreas, and AT1 receptors are expressed in islet beta-cells and upregulated in states of insulin resistance. By reducing blood flow to the pancreas and its islet cells, angiotensin II has the potential to alter the first phase of glucose-stimulated insulin secretion. Additionally, angiotensin II-promoted reactive oxygen species synthesis has been shown to induce islet cell fibrosis and apoptosis and ultimately beta-cell dysfunction (Leung & de Gasparo, 2006).

At last, in hypertensive obese patients, visceral obesity plays a critical role in the development of insulin resistance; in support of this contention, there is a growing body of evidence indicating that adipocytes produce several cytokines, the so-called adipokines, such as leptin, tumor necrosis factor-alpha, non esterified fatty acids, adiponectin, resistin and angiotensinogen, which can influence insulin sensitivity (Galic et al., 2010). According to the contribution of visceral fat to insulin resistance, a recent study revealed that mice fed with a high-fat diet showed up-regulation of the angiotensinogen gene expression in the visceral fat (Rahmouni et al., 2004). In obese humans the levels of the circulating components of the renin-angiotensin system are elevated, however weight loss is associated with a decrease in the levels of these components (Engeli et al., 2005). Therefore, the adipocyte-related renin-angiotensin system may fill an important role in the pathogenesis of insulin resistance. Several other adipokines, such as tumor necrosis factor-α, resistin, leptin

and non esterified fatty acids have the potential to decrease insulin sensitivity (Houstis et al., 2006), while adiponectin (Ziemke & Mantzoros, 2010) and adrenomedullin (Shimosawa et al., 2002) produced by adipocytes increase insulin sensitivity.
Alternatively, insulin resistance and hypertension may be linked indirectly through mechanisms of an inherited or acquired nature. Ethnic or racial differences in sympathetic nervous system activity might explain the differences in the relation of insulin resistance to blood pressure; a further possibility is that a cellular or structural defect, genetic or acquired, may constitute the link between insulin resistance and blood pressure. Racial differences in cation regulation have been described and could account for the observed variation in the relation of insulin resistance to blood pressure (Aviv & Gardner, 1989).
In conclusion, there is a large body of experimental evidence that the prevalence of insulin resistance and compensatory hyperinsulinemia is increased in patients with essential hypertension, and similar changes can be seen in normotensive first-degree relatives of patients with essential hypertension. In addition, insulin resistance and hyperinsulinemia have also been shown in several large, prospective, population-based studies to be independent predictors of the development of essential hypertension. However, not all patients with essential hypertension are insulin resistant/hyperinsulinemic, and it is obvious that the increase in blood pressure in these individuals is unrelated to any change in insulin action. The fact that insulin resistance does not provide an unitarian hypothesis to account for the etiology of essential hypertension should not obscure the wide evidences of the importance of insulin resistance, and its metabolic consequences, in the pathogenesis of perhaps as many as half of the patients with essential hypertension.

2.2 Therapeutic blood pressure target and treatment

Treating high blood pressure has been associated with about a 40% reduction in the risk of stroke, about a 20-25% reduction in the risk of myocardial infarction, and heart failure, averaging 50% (Collins et al., 1990).
Although the treatment of hypertension has been shown to prevent cardiovascular diseases and to extend and enhance life, hypertension remains inadequately managed everywhere (Trilling & Froom, 2000; Berlowitz et al., 1998). The World Health Organization reports that suboptimal blood pressure is responsible for 62% of cerebrovascular disease and 49% of ischemic heart disease, with little variation by sex. For this reason, suboptimal blood pressure is recognized the number one attributable risk factor for death throughout the world (World Health Organization, 2002).
Thus, International Guidelines for the management of hypertension provides that, in hypertensive patients, the treatment should be initiated before significant cardiovascular damage develops, and the primary goal of treatment is to achieve maximum reduction in the long-term total risk of cardiovascular diseases; in order to this aim systolic/diastolic blood pressure should be reduced to at least below 140/90mmHg, and to lower values if tolerated, in all hypertensive patients.
In individuals with high blood pressure and additional risk factors, is essential the effective management for controlling the coexisting problems that contribute to overall cardiovascular risk (JNC-7, 2004; Mancia et al., 2007).
The United Kingdom Prospective Diabetes Study (Adler et al, 2000) demonstrated that each 10 mmHg decrease in systolic blood pressure was associated with average reductions in rates of diabetes-related mortality, myocardial infarction, and microvascular complications

of retinopathy or nephropathy. Moreover, randomized controlled trials (Mann et al., 2001; Hansson et al., 1998; Tuomilehto et al., 1999) including large diabetic populations have demonstrated that adequate blood pressure control improves cardiovascular outcomes, especially stroke, when aggressive blood pressure targets are achieved (Arauz-Pacheco et al., 2003; Psaty et al., 2003).

Recommendations from both American Diabetes Association (Arauz-Pacheco et al., 2003) and International Diabetes Federation (IDF Clinical Guidelines Task Force; 2006) are consistent with International Guidelines for the management of hypertension which have provided that in hypertensive patients with type 2 diabetes and in high or very high risk patients, such as those with associated clinical conditions (stroke, myocardial infarction, renal dysfunction, proteinuria), target blood pressure should be at least < 130/80mmHg.

The treatment for hypertensive patients with type 2 diabetes should aim at achieving blood pressure target, reducing cardiovascular risk and at improving insulin resistance (Giles & Sander, 2005).

The therapeutic lifestyle change is the first step for treatment of hypertensive patients with type 2 diabetes; it includes: diet, regular aerobic physical activity such as brisk walking at least 30 minutes daily, weight loss, if the patients are obese, and behavioural treatment. Both smoking cessation and alcohol intake reduction - no more than 30 mL of ethanol per day - are also need. These non pharmacological interventions can decrease blood pressure and improve insulin sensitivity; they should be more strongly recommended to diabetic and non diabetic hypertensive patients, on account of their positive impact on cardiovascular diseases prevention (Wagh & Stone, 2004; JNC-7, 2004).

In several studies weight reduction has been shown to improve insulin resistance in obese patients, apparently associated with the reduction of visceral fat (Park & Lee, 2005; Buchwald et al., 2004; Busetto, 2001); benefits of moderate weight loss include decreased blood glucose, insulinemia, lipid levels, and blood pressure. In particular, the loss of one kilogram in body weight has resulted in decreases in mean arterial blood pressure of 1 mmHg (Wagh & Stone, 2004). However the role of very low calorie diets and pharmacologic agents that induce weight loss in the management of hypertension in diabetic patients has not been adequately studied.

Lifestyle change cannot leave aside dietary intervention, promoting salt restriction and increasing potassium intakes, that should be more systematically considered in the management and prevention of essential hypertension. In recent years, the benefits of lowering sodium and increasing potassium intakes have been reinforced by the demonstration that these non-pharmacological approaches to hypertension management enable the lowering of blood pressure and the reduction of target organ damage as well as cardiovascular events (Lawes et al., 2008).

A restriction in dietary salt intake reduced pulse pressure, suggesting an improvement in arterial distensibility (Gates et al., 2004); moreover, several interventional studies have been conducted to investigate the clinical impact of lowering dietary sodium intake on blood pressure and cardiovascular events (Elmer et al., 1991; Lasser et al., 1995; Whelton et al., 1998). Systolic and diastolic blood pressure resulted significantly reduced among individuals assigned to reduced sodium intake group; accordingly, a meta-analysis of randomized studies, which took into account only studies with a duration of at least one month and modest reductions of sodium intake (mean 4.4–4.6 g of salt daily), demonstrated that a reduction in salt intake is associated with a significant decrease in blood pressure,

both in normotensive and hypertensive individuals (He & MacGregor, 2002). In addition, based on the changes in blood pressure from the meta-analysis of randomized salt-reduction trials and the relationship between blood pressure and stroke and ischemic heart disease, it has been estimated that a 3 g daily reduction of dietary salt intake would reduce stroke by 13% and ischemic heart disease by 10% (He & MacGregor, 2003). Experimentally, a low sodium diet prevents also renal alterations in several models of hypertension and renal diseases (Lax et al., 1992; Bank, 1988). In humans, the long-term benefits of a low sodium intake on the progression of non-diabetic or diabetic nephropathies are less well documented; the most significant impact of dietary salt intake on renal function could be its effect on urinary albumin excretion. (Du Cailar et al., 2002; Verhave et al., 2004).

Regarding potassium, its supplementation not only attenuated salt-induced elevation of blood pressure, but also improved salt-induced insulin resistance in salt-sensitive hypertensive patients (Fujita & Ando, 1984) and animals (Fujita & Sato, 1983). Consistent with this, in the DASH study, the "dietary approaches to stop hypertension" eating plan (DASH diet), consisting of low-fat dairy products, vegetables and fruits rich in potassium, which could lower lipid-induced oxidative stress in obesity, decreased not only blood pressure, but also the fasting blood sugar in hypertensive patients (Lopes et al., 2003; Azadbakht et al., 2005). In the subsequent DASH-sodium trial, three different dietary sodium intakes were compared, 150, 100, and 50 mmol/24 h, corresponding to approximately 8.8, 5.8, and 2.9 g. of salt per day respectively, with and without DASH diet. Blood pressure was significantly lower when going to a lower group of dietary salt intake in both the control diet or the DASH diet groups. The results of low sodium-DASH diet trial further strengthen the conclusion that reduction of dietary sodium intake through low-salt diet lowers blood pressure effectively and adds to the benefits conferred by the DASH diet (Sacks et al., 2001). Therefore, salt restriction and dietary intake of potassium should be prescribed as a first-line lifestyle therapy for hypertensive patients, especially in coexisting type 2 diabetes; dietary sodium should be reduced to no more than 100 mmol per day, corresponding to 2.4 g of sodium (Sacks et al., 2001; Vollmer et al., 2001).

The therapeutic lifestyle change should be instituted with adequate behavioural and expert support, and reinforced periodically; nevertheless it often is inadequate to achieve blood pressure target. In this case drug therapy is necessary; moreover, most patients can require two or more antihypertensive drugs (Cushman et al., 2002; Black et al., 2001).

A large number of drugs are currently available for reducing blood pressure; five major classes of commonly used antihypertensive agents – diuretics, calcium antagonists, angiotensin converting enzyme Inhibitors (ACE inhibitors), angiotensin receptor blockers (ARBs) and beta blockers – are suitable for the initiation and maintenance of antihypertensive treatment, alone or in combination (JNC-7, 2004; Mancia et al., 2007).

There are a number of intervention trials demonstrating benefits in the treatment of hypertension in type 2 diabetics in reducing outcomes including cardiovascular events and microvascular complications of retinopathy and progression of nephropathy. These studies used different drug classes, including ACE inhibitors, ARBs, diuretics, and beta blockers, as the initial step in therapy; all of these agents were superior to placebo.

In the Systolic Hypertension in the Elderly Program (SHEP) low-dose, chlorthalidone-based treatment was found to be effective compared with placebo in preventing cardiovascular complications in elderly patients with type 2 diabetes mellitus and isolated systolic hypertension (Curb et al., 1996). Later, the Hypertension Optimal Treatment Study (HOT)

investigated the efficacy of antihypertensive treatment using a dihydropyridine calcium antagonist, felodipine, as baseline therapy in hypertensive patients averaging 62 years of age and 170/105 mm Hg in baseline blood pressure, including 1501 patients with type 2 diabetes. In this study the incidence of major cardiovascular events was lowered ($p = 0.005$) from 24.4 to 18.6 and 11.9 events/100 patient-years, respectively, in the randomised tertiles of diabetes patients who had achieved 85, 83, and 81 mm Hg, respectively, in diastolic blood pressure. Approximately twenty patients needed to be treated for 5 years to prevent one major cardiovascular event when blood pressure was further lowered from 84 to 81 mm Hg (Hansson et al., 1998). Similarly, the Systolic Hypertension in Europe Trial (Syst-Eur) compared another dihydropyridine calcium antagonist, nitrendipine, with placebo in elderly patients with isolated systolic hypertension and in a subgroup with type 2 diabetes; the treatment for five years prevented 178 major cardiovascular events in every 1000 diabetic patients treated; approximately six patients had to be treated for five years to prevent one major cardiovascular event (Tuomilehto et al., 1999).

The results of the Heart Outcomes Prevention Evaluation (HOPE) Study and the MIcroalbuminuria, Cardiovascular, and Renal Outcomes (MICRO-HOPE) substudy showed that treatment with the ACE inhibitor ramipril, compared with placebo, significantly lowered the risk of cardiovascular events and overt nephropathy in type 2 diabetic patients with a previous cardiovascular event or at least one other risk factor. Although 56% of the HOPE diabetics (n=3577) had a history of hypertension, uncontrolled diabetic hypertensives (blood pressure >160/90 mmHg) were not randomized; thus, the cardiovascular benefit of ramipril was greater than that attributable to the decrease in blood pressure (Heart Outcomes Prevention Evaluation (HOPE) Study Investigators, 2000).

The Reduction of Endpoints in NIDDM with the Angiotensin II Receptor Antagonist Losartan (RENAAL) study is a randomized, double-blind clinical trial that studied 1513 patients with type 2 diabetes and nephropathy for a mean of 3.4 years. Patients were administered either losartan or placebo, each in addition to conventional antihypertensive therapy, with dosage adjustments as necessary to achieve a target blood pressure of less than 140/90 mm Hg. The study showed a significant benefit of losartan, beyond the effects of lowering blood pressure, on the primary composite end point of doubling serum creatinine level and end-stage renal disease; however, losartan had no effect on rate of death. In addition, losartan was associated with a 21% risk reduction for the composite cardio-renal outcome (Brenner et al., 2001).

In 2007, in the ADVANCE trial it was shown that addition of the combination of ACE inhibitor perindopril and diuretic indapamide to type 2 diabetic patients, irrespective of initial blood pressure levels or the use of other blood pressure lowering drugs, was associated with substantial clinical benefits versus placebo treatment. Routine administration of a fixed combination of perindopril and indapamide was well tolerated and reduced the risks of major vascular events, including death. Although the confidence limits were wide, the results suggest that over 5 years, one death due to any cause would be averted among every 79 patients assigned active therapy (Patel et al., 2007).

Other several trials found an improvement in renal outcomes in patients with type 2 diabetes and overt nephropathy through antihypertensive treatment with other ARBs such as irbesartan (Lewis et al., 2001) and telmisartan (Barnett et al., 2004; Mann et al., 2008). Moreover, recent results of the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial showed that the addition of valsartan to lifestyle

modification reduced the risk of diabetes but did not improve cardiovascular outcomes. (McMurray et al., 2010). Finally, in the recent Aliskiren in the Evaluation of Proteinuria inDiabetes (AVOID) study, it has been shown that aliskiren, a new antihypertensive drug, added to losartan reduced albuminuria and renal dysfunction and it was well tolerated. The AVOID study was the first double-blind, randomized controlled trial to demonstrate the antiproteinuric ability of aliskiren, an oral direct renin inhibitor, as add-on to standard treatment including an ARB, in patients with type 2 diabetes, hypertension and nephropathy (Persson et al., 2010).

Regarding the selection of medications, the most suitable antihypertensive drug to reduce the risk of cardiovascular disease in patients with hypertension and diabetes is unclear, also because the majority of patients requires two or more drugs to achieve blood pressure target (Sowers & Reed, 2000; Sowers & Haffner, 2002). In order to this purpose numerous comparative studies have been carried out to define the question of which class of antihypertensive agents is superior for lowering blood pressure in diabetic patients.

After more than 8 years of follow-up of 1148 hypertensive patients in the United Kingdom Prospective Diabetes Study (UKPDS), a tight blood pressure control was successful to prevent macro- and micro-vascular complications, especially for prevention of stroke and retinopathy (UK Prospective Diabetes Study Group, 1998). However, no significant effect difference was found between captopril and atenolol, but the patients on atenolol needed significantly more oral anti-glycaemic drugs due to weight increase and dysmetabolic effects of beta blocker agent (UK Prospective Diabetes Study Group, 1998).

Subsequently, in the Swedish Trial in Old Patients with Hypertension-2 (STOP-2) study all patients were above the age of 70 years, and as many as 719 of them had type-2 diabetes at baseline; the prevention of cardiovascular mortality was similar on conventional standard therapy (diuretics, beta-blockers, or both), ACE inhibitor, or calcium-antagonist treatment and the reduction in blood pressure was also the same in the three treatment groups of diabetics. There were, however, significantly fewer ($P = 0.025$) myocardial infarctions during ACE inhibitor treatment than during calcium antagonist treatment (Lindholm et al., 2000).

In 2001, the Collaborative Study Group randomly assigned 1715 hypertensive patients with nephropathy, due to type 2 diabetes, to treatment with irbesartan 300 mg daily, amlodipine - a dihydropyridine calcium antagonist - 10 mg daily, or placebo. The target blood pressure was 135/85 mm Hg or less in all groups. It was compared the groups with regard to the time to the primary composite end point of a doubling of the base-line serum creatinine concentration, the development of end-stage renal disease, or death from any cause. Treatment with irbesartan was associated with a risk of the primary composite end point that was 20% lower than that in the placebo group ($P=0.02$) and 23% lower than that in the amlodipine group ($P=0.006$). The risk of a doubling of the serum creatinine concentration was 33% lower in the irbesartan group than in the placebo group ($P=0.003$) and 37% lower in the irbesartan group than in the amlodipine group ($P<0.001$). Treatment with irbesartan was associated with a relative risk of end-stage renal disease that was 23% lower than that in both other groups ($P=0.07$ for both comparisons). These differences were not explained by differences in the blood pressure that were achieved. The serum creatinine concentration increased 24% more slowly in the irbesartan group than in the placebo group ($P=0.008$) and 21% more slowly than in the amlodipine group ($P=0.02$). There were no significant differences in the rates of death from any cause or in the secondary cardiovascular

composite end point (Lewis et al., 2001). Another comparative study between an ARB and other antihypertensive drugs was the Losartan Intervention For Endpoint reduction (LIFE) trial; in this study a subgroup of 1195 patients with diabetes, hypertension, and left-ventricular hypertrophy on electrocardiograms were randomised to either losartan-based or atenolol-based treatment; losartan was more effective than beta blocker atenolol in reducing cardiovascular morbidity and mortality, as well as mortality from all causes. Losartan seemed to have benefits beyond blood pressure reduction. (Lindholm et al., 2002).

In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) a subgroup of patients (36%) with diabetes were randomised to treatment with thiazide-type diuretic chlorothalidone, calcium channel blocker amlodipine, or ACE inhibitor lisinopril; the primary composite cardiovascular outcome was combined fatal coronary heart disease or nonfatal myocardial infarction. There were no differences between these three drugs, used in a very heterogeneous study population; likewise, all-cause mortality did not differ between groups (The ALLHAT Collaborative Research Group, 2002). A similar result of equity between treatment arms for the primary composite cardiovascular end-point was found in the International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT), based on a sub-analysis of 1302 patients with hypertension and diabetes randomised to either dihydropyridine calcium antagonist nifedipine slow-release or hydrochlorothiazide plus amiloride (Mancia et al., 2003).

In 2004, the groundbreaking Diabetics Exposed to Telmisartan And enalaprIL (DETAIL) study revealed that telmisartan, an ARBs, conferred comparable renoprotection to enalapril, an ACE inhibitor; moreover, telmisartan was associated with a low incidence of mortality. The DETAIL study was designed to compare the long-term renal outcome of treatment with telmisartan versus enalapril in patients with type 2 diabetes, mild-to-moderate hypertension and albuminuria. The primary endpoint was the change in glomerular filtration rate after 5 years. The secondary endpoints are annual changes in glomerular filtration rate, serum creatinine and urinary albumin excretion, as well as incidences of end-stage renal disease, cardiovascular events, all-cause mortality and adverse events (Barnett et al., 2004). Similar results were obtained recently in the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) study. In this multicentre, randomised, double-blind, controlled trial it was investigated the renal effects of ramipril, telmisartan, and their combination in patients aged 55 years or older with established atherosclerotic vascular disease or with diabetes with end-organ damage. The primary renal outcome was a composite of dialysis, doubling of serum creatinine, and death. The number of events for the composite primary outcome was similar for telmisartan and ramipril; and also the secondary renal outcome, dialysis or doubling of serum creatinine, was similar between two drugs (Mann et al., 2008).

The Anglo-Scandinavian Cardiac Outcome Trial (ASCOT) has shown substantial benefits for the reduction of stroke and total mortality in patients randomised to a treatment based on amlodipine, adding perindopril as required, versus atenolol-based treatment, with thiazide as add-on therapy if needed; moreover, in this study the incidence of developing diabetes was significantly ($p<0.0001$) less on the amlodipine-based regimen (Dahlöf et al., 2005).

In the Shiga Microalbuminuria Reduction Trial (SMART) the objective of the study was to assess the effect of an angiotensin receptor blocker, valsartan, on microalbuminuria in

comparison with that of a calcium channel blocker, amlodipine, in patients with the targeting blood pressure level < 130/80 mmHg. The reductions in blood pressure were similar between the valsartan group and the amlodipine group. However, valsartan was more effective than amlodipine for reducing microalbuminuria. In addition, the reduction of the urinary albumin creatinine ratio was significantly greater in the valsartan group with uncontrolled systolic blood pressure than that in the amlodipine group with controlled systolic blood pressure. These findings showed that the antiproteinuric effect of valsartan may be independent of its effect on blood pressure (Uzu et al., 2007). Moreover, data from the recent VALUE trial revealed that the angiotensin receptor blocker valsartan, compared with calcium-channel antagonist amlodipine, reduces the risk of developing diabetes mellitus, particularly in hypertensive patients with the highest susceptibility for development of diabetes (Kjeldsen et al. 2008). However, in 2004 a subanalysis of the Captopril Prevention Project (CAPPP) revealed a similar result assessing the effects of an ACE inhibitor, captopril, with a conventional antihypertensive treatment, including diuretic and/or beta blockers, in middle-aged hypertensive patients; for each tertile of risk, captopril therapy was associated with a reduced risk of diabetes development compared with conventional treatment. (Niklason et al., 2004).

Finally, in the ACCOMPLISH (Avoiding Cardiovascular Events Through COMbination Therapy in Patients Living With Systolic Hypertension) trial a total of 6946 diabetic patients were randomized to treatment with fixed combination of a renin-angiotensin system blocker, benazepril, and amlodipine, or fixed combination of benazepril and hydrochlorothiazide; it was shown that combining benazepril with amlodipine, compared with hydrochlorothiazide, was superior in reducing relative risk of cardiovascular events (Weber et al., 2010).

There are no significant long-term studies regarding the effect of other classes of antihypertensive agents, such as αlpha-1 antagonists, for instance doxazosin, or centrally alpha-2 agonist drugs, like clonidine, on long-term cardiovascular complications of diabetes. The αlpha-1 antagonists arm of the ALLHAT study was stopped by the safety monitoring committee because of an increase in cases of new-onset heart failure in patients assigned to the doxazosin (Davis et al., 2002). While this could merely represent unmasking of heart failure in patients previously treated with an ACE inhibitor or a diuretic, it seems reasonable to use these antihypertensives as second-line agents.

In summary, the benefits of treating hypertension in type 2 diabetic patients, in terms of reductions in cardiovascular morbidity and mortality, have been documented in several trials, but the optimal first-step therapy remains unknown. It has been shown that most of commonly used antihypertensive agents have nearly similar efficacy; however is well established that renin-angiotensin system blockade lowers significantly the frequency of various diabetic complications, including diabetic nephropathy. Furthermore, in the high risk group of diabetic patients, blockade of the renin-angiotensin system reduces cardiovascular mortality and morbidity. ACE inhibitors and ARBs have also been shown to lower cardiovascular events in diabetic patients and to delay or avoid the onset of type 2 diabetes. Both drug classes are believed to improve endothelial function by increasing nitric oxide bioavailability, and rennin-angiotensin system blockade has demonstrated protective effects on pancreatic beta-cells attributed, in part, to a reduction in oxidative stress (Lupi et al., 2006; Nakayama et al., 2005). Strong evidences indicate that oxidative stress plays a key role in the pathogenesis of diabetic microvascular and macrovascular complications; thus,

abrogation of oxidative stress through inhibition of angiotensin II production and enhancement of antioxidant activity with rennin-angiotensin blockers would be expected to reduce this risk. Recently, it has been shown that aliskiren, a new oral antihypertensive drug, by direct renin inhibition reduces albuminuria and renal dysfunction in hypertensive type 2 diabetic patients; however, as for aliskiren, further research are warranted to build on the favourable effects that have been observed with ACE inhibitors and ARBs in high-risk diabetic patients, with the goal of achieving cardiovascular outcomes benefits.

Finally, regarding the selection of medications, the therapeutic choices must also consider the potential adverse metabolic effects of some antihypertensive drugs (Black, 1991).

There is a large evidence that both ARBs and ACE inhibitors could be considered first-line antihypertensive drugs in type 2 diabetic patients. Calcium channel blockers, peripheral alpha-1 antagonists and central alpha-2 agonist drugs are metabolically neutral, while diuretics, except for indapamide and anti-aldosterone drugs, can reduce insulin sensitivity (Ramsay et al., 1992; McCarty, 2004**;** Bousquet at al., 2000) thus they are not first-line therapy, yet they are recommended in selected cases only. Beta blockers, especially non-selective and without intrinsic sympathomimetic activity, also reduce insulin sensitivity and they have adverse effects on carbohydrate and lipid metabolism; moreover an higher incidence of new onset diabetes was observed in patients with hypertension taking beta-blocking drugs (Lithell, 1991; Lind et al., 1994). For these reasons, beta blockers are not considered first-line therapy in hypertensive diabetic patients and are recommended only in selected cases as heart failure, acute or previous myocardial infarction and ischemic heart disease (Black, 1991). However, two large studies have revealed that third generation beta blockers with vasodilating properties, such as nebivolol and especially carvedilol, have not shown negative effects on blood lipids, carbohydrate metabolism and insulin sensitivity in hypertensive patients with type 2 diabetes mellitus (Bakris et al., 2004; Schmidt et al., 2007). The vasodilating and antioxidant properties of these beta blockers could play a key-role in mediating their favourable metabolic profile (Agabiti Rosei & Rizzoni, 2007; Feuerstein & Ruffolo; 1995). It can be supposed that the vasodilation, improving the blood flow in the skeletal muscle, allows more adequate, opportune and efficacious release of insulin and glucose to myocytes. Moreover, the antioxidant action, reducing oxidative stress, could improve both the insulin sensitivity of peripheral tissue and the pancreatic beta cell dysfunction (Jacob et al., 1999). The metabolic advantages of vasodilating third-generation beta blockers highlight the importance of dissociating older conventional agents from newer agents. These are a class of antihypertensive drugs that could be a valuable aid for hypertensive patients with type 2 diabetes because of increased cardiovascular risk of these patients and the high proportion of concomitant cardiac diseases, such as congestive heart failure and coronary heart disease. Thus, Carvedilol and Nebivolol could be a valuable tool for hypertension treatment in patients with metabolic syndrome too.

3. Conclusion

The association of hypertension and type 2 diabetes is increased in the population and there is a strong epidemiological link between hypertension and cardiovascular outcomes of diabetes. Clinical trials have demonstrated the efficacy of the antihypertensive treatment in reducing these outcomes. The general consensus for treatment of hypertension in type 2 diabetes is to aim for a well controlled blood pressure of 130/80 mm Hg. In order to this purpose, lifestyle measures should be instituted in all patients, including those who require

drug treatment; where applicable, intense non-pharmacological measures should be encouraged, with particular attention to weight loss and reduction of salt intake. Drug therapy is necessary if lifestyle change is inadequate, and it is very clear that many patients need two or more drugs to achieve the recommended blood pressure target. Regarding the selection of medications, clinical trials with major classes of antihypertensives have demonstrated the efficacy of drug therapy versus placebo in reducing cardiovascular outcomes. The question of which class of agents is superior for lowering blood pressure in diabetic patients is somewhat moot, thus to reduce blood pressure values, all effective and well tolerated antihypertensive drugs can be used. However, ACE inhibitors and ARBs, because of their considerable cardiovascular and nephroprotective properties could be considered first-line antihypertensive drugs in type 2 diabetic patients with high blood pressure.

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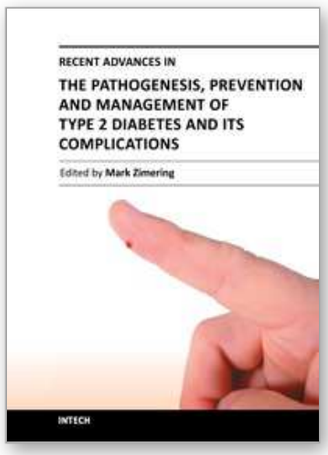

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Type 2 diabetes â€œmellitusâ€ affects nearly 120 million persons worldwide- and according to the World Health Organization this number is expected to double by the year 2030. Owing to a rapidly increasing disease prevalence, the medical, social and economic burdens associated with the microvascular and macrovascular complications of type 2 diabetes are likely to increase dramatically in the coming decades. In this volume, leading contributors to the field review the pathogenesis, treatment and management of type 2 diabetes and its complications. They provide invaluable insight and share their discoveries about potentially important new techniques for the diagnosis, treatment and prevention of diabetic complications.

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