The incidence of cardiovascular and cerebrovascular diseases in women is low before the menopause but after the age of 50 years they become the leading cause of mortality and morbidity for women living in most developed countries. This increased incidence is only partially explained by ageing, since the state of oestrogen deficiency developing after the menopause plays a key role in favouring the increased cardiovascular risk. Indeed, cessation of ovarian function and the consequent reduction of sex steroid hormones levels have important metabolic and pathophysiological implications that negatively influence the cardiovascular system.

It has been long known that blood pressure is typically lower in pre-menopausal women than in age-matched men, that arterial blood pressure increases after the cessation of menses and that after the menopause women develop arterial hypertension often together with changes in lipid and glucose metabolism.

However, in postmenopausal women, the prevalence of hypertension and cardiovascular disease risk increases regardless of ethnic origin. The National Health and Nutrition Examination Survey (NHANES III) showed that in Hispanic women and non-Hispanic black women, the prevalence of hypertension was similar to, or higher than, that in men by age 60 years and that in non-Hispanic white populations the prevalence of hypertension was higher in women than in men by age 70 years.

The increase in blood pressure in postmenopausal women does not occur soon after the cessation of menses, but it becomes evident over a number of years. Although the mechanisms responsible for the increased blood pressure in women after menopause are not known, it is reasonable to believe that the underlying mechanisms may be similar in the two sexes and that, in women, after the menopause the lack of oestrogens highlights the underlying defects. However, other mechanisms related to the state of oestrogen deficiency may become important. Furthermore, more recently it has become clear that hypertension and metabolic risk factors are interrelated, influencing each other and often having similar underlying causes. The clustering of metabolic risk factors overweight and hypertension is of particular importance in women after the menopause because of the negative effect of menopause on the development of hypertension and on cardiovascular risk factors.

To this end, menopause, or more correctly oestrogen deficiency, has been considered a risk factor for coronary artery disease because of the negative impact of ovarian hormone deficiency on the development of cardiovascular disease. Menopause acts directly as a risk factor by reducing the direct beneficial effect of ovarian hormones upon cardiovascular functions and indirectly by negatively influencing other traditional risk factors for coronary artery disease (i.e. hyperinsulinaemia, blood cholesterol, blood pressure, coagulation, etc.).

Therefore, in menopausal women, there occur correlated disturbances that have their common etiological factor in the decline in ovarian function that occurs with the menopause. These disturbances will then themselves have negative effects that may augment the effect of menopause. Adverse changes in one factor may induce adverse changes in a variety of other risk factors leading to the concept that, in evaluating cardiovascular risk, it is important to consider co-ordinated changes in risk factors more than attempt to isolate single, independent factors.

The recognition of risk factor interrelationships developed in the 1980s was depicted by Reaven with the term of Metabolic Syndrome X and is now widely accepted as Metabolic Syndrome. This syndrome identifies a cardiovascular risk profile that includes insulin resistance, central obesity, increased triglyceride levels, low high-density lipoprotein (HDL) cholesterol levels and arterial hypertension. In post-menopausal women, the state of ovarian hormones deficiency induces physiological changes leading to a greater prevalence of hypertension and metabolic syndrome compared with the pre-menopausal period. However, all changes occurring
after the menopause must be regarded under a
unifying mechanism that induces changes in body
weight, salt sensitivity, insulin tolerance, plasma
lipids, sympathetic tone and vascular function, and
these changes then interact each other, amplifying
the effect of ovarian hormone deficiency and ageing.

**Menopause, Obesity and Body Fat Distribution**

Increase in body mass index (BMI) and an increased
proportion of visceral fat are strongly correlated with
the development of arterial hypertension and, a range
of metabolic risk factors for cardiovascular disease.
The relationship between obesity and hypertension is
well documented, the Framingham study showing
that the prevalence of hypertension as a function of
age in both sexes increases substantially with increase
in relative weight. It is important to underline that
recent weight gain is a very important factor in the
development of hypertension, as suggested by the
fact that, in the Framingham study, obesity or recent
weight gain accounted for 70% of new onset
hypertension. Apart from body weight, body fat
distribution is an important risk factor of
hypertension. An increase in abdominal circumference or in waist-to-hip ratio, both surrogate markers for android fat distribution, is an
independent factor for the development of high
blood pressure values and is independently associated
with other risk factors for the development of
cardiovascular disease.

The relationship between obesity and blood pressure
cannot be explained adequately by haemodynamics
since, if it is true that obese subjects have increased
blood volumes and cardiac output, these variable are
within the normal range when corrected for body
mass. Also, the greater intake of sodium of
overweight subjects is not sufficient to explain the
development of hypertension, since weight loss in
overweight individuals decreases blood pressure
even if the intake of sodium is not diminished.
Therefore, the shift in the pressure-natriuresis curve
in obese subjects may be secondary to an
increased sympathetic drive, hyperinsulinism and
insulin resistance, factors that are inter-related and
that, in women, are worsened by menopause like
body weight.

Menopause in associated with important changes in
weight and in body fat distribution, postmenopausal
women tending to gain weight starting within the
first year from the menopause and redistribute body
fat from a gynoid to an android pattern. The
increase and the change in body fat distribution
occurring after the menopause are strictly related to
the state of ovarian hormone deficiency, as women
taking hormone replacement therapy gain weight by
a lesser extent than women not on hormone
replacement therapy. The exact mechanism through
which ovarian hormone deficiency may cause
weight gain and android body fat distribution is not
clear, although an activation of the renin-
angiotensin-aldosterone system linked with an
increase in salt sensitivity and a negative effect on
the incretion of Leptin and the relative increase in
androgens together with changes in thyroid function
seem to play a key role. In men and women the
increase in body fat is often coupled with negative
changes on insulin resistance, plasma lipids, blood
pressure and increased sympathetic drive, however,
these changes are enhanced in women by ovarian
hormone deficiency.

**Menopause and Glucose Metabolism**

The inter-relationship between insulin sensitivity and
blood pressure has been long known. Patients with
increased insulin resistance have a greater incidence
of hypertension and hypertensive patients frequently
develop alterations of glucose metabolism and
diabetes. Menopause per se does not seem to affect
fasting glucose but is associated with a progressive
decline in glucose-stimulated insulin secretion. This
decline in insulin secretion seems to be compensated,
at least in the initial stages, by a reduction in
peripheral insulin elimination. Several studies have
reported an increased incidence of insulin resistance
and a decrease in insulin sensitivity with menopause
and have related these changes with both an effect of
oestrogen deprivation and with the changes in body
weight and sympathetic activity accompanying the
menopause. Insulin resistance is a multisystem
disorder that induces multiple metabolic alterations
and, in women, is facilitated by the state of ovarian
hormone deficiency.

Insulin resistance is an important risk factor for the
development of type II diabetes mellitus and
cardiovascular disease and occurs at multiple organ
sites including the liver, the skeletal muscle cells
and the adipocytes. As mentioned above, insulin
resistance occurs in combination with a cluster of
other metabolic abnormalities and arterial
hypertension in the metabolic syndrome.
Prospective studies have shown that hypertension
develops more often in subjects with insulin
resistance than in patients with normal insulin
sensitivity suggesting that insulin resistance is a key
factor in the development of hypertension.
Furthermore, Ferrannini et al. showed that
decreased insulin sensitivity (by euglycaemic
clamp) is inversely associated with blood pressure.
The link between hyperinsulinaemia, insulin
resistance and hypertension is supported by the
The exact mechanism through which hyperinsulinaemia predisposes to hypertension is unclear, as insulin administration in healthy subjects induce vasodilation and may even cause a small decrease in blood pressure and attenuates the pressor effect of several hormones such as norepinephrine and angiotensin II. The vasodilator effect of insulin is mediated by the release of nitric oxide. It is probable that, in the development of hypertension, hyperinsulinaemia is consequent to insulin resistance that decreases the release of nitric oxide thereby increasing the effect of pressure hormones on vascular resistances. In hypertensive patients insulin may also affect the vasomotor tone by affecting the Calcium flux into the vascular smooth muscle cells, by increasing the sympathetic nervous system activity and the sodium and volume retention.

It becomes clear that the changes in insulin sensitivity and body weight that occur after the menopause are inter-related and facilitated by the state of ovarian hormone deficiency; these changes, together, with the increase in sympathetic nervous activity may facilitate the development of arterial hypertension. Therefore, in women, hypertension is often the first clinical manifestation of a more complex clinical scenario, which is the metabolic syndrome. This clustering of risk factors includes unfavorable changes in lipid profile.

**Autonomic Nervous Control of the Cardiovascular System**

A close relationship exists between incezation of ovarian and hypothalamic hormones and the autonomic control of the cardiovascular system. Cyclical variations in the secretion of catecholamines occur during the menstrual cycle and after the menopause a clear shift of the autonomic control of the cardiovascular system towards an increased sympathetic tone occurs. This increased sympathetic tone is in part independent from the changes occurring in body weight and glucose metabolism but is, in the long term, heightened by these metabolic changes. Several studies have shown that, after the menopause, there is an increased production of insulin and a decrease in insulin sensitivity, a time when ovarian hormones are no longer present.

**Precautions and special information:**

Contraindications:

- Pregnancy; lactation; undiagnosed genital bleeding; known, past or suspected who cannot use other treatments.

Use:

- Replacement therapy (HRT) for oestrogen deficiency symptoms in women at least 1 year post menopause.

Dosage and administration:

- 1 tablet daily without a break.

Low dose continuous combined HRT:

2 mg Drospirenone, 1 mg Estradiol

Film coated tablets (estradiol/drospirenone)

Uses:

- Provides relief from climacteric symptoms

- Anti-mineralocorticoid activity counters water and sodium retention, reducing the likelihood of fluid retention

- That some women may experience with HRT

**Side effects:**

- Asthenia, pain in extremity, nausea, headache, mood swings, hot flushes, nervousness, enlarged breast, dyspareunia, dysmenorrhea, vaginitis, urinary frequency, hot flushes, insomnia, weight gain.

- Common side effects: abdominal pain or bloating, breakthrough bleeding and spotting, asthenia, pain in extremity, nausea, headache, mood swings, hot flushes, nervousness, enlarged breast, dyspareunia, dysmenorrhea, vaginitis, urinary frequency, weight gain.

- Uncommon side effects: migraine, hypertension, abnormal liver function tests, hyperlipidaemia. See also section 4.8.
of catecholamines and a clear shift of the autonomic control towards an increased sympathetic activity of the cardiovascular system has been shown by our group. This increased sympathetic drive is closely related to the state of oestrogen deficiency as it occurs within few days from surgical oophorectomy and is reversed by oestrogens.

The increased sympathetic drive together with the metabolic changes occurring after the menopause, contribute to cause the metabolic syndrome but is also worsened by the metabolic changes. The increased sympathetic drive causes physiological and structural changes, leading to hypertension or facilitating its development (i.e. vasoconstriction, rarefaction of skeletal muscle arterioles, increase in angiotensin II plasma levels), changes in insulin sensitivity leading to reduced glucose tolerance because of the effect of sympathetic stimulation to the liver, fat tissue and muscle metabolism.

Apart from the structural changes in arterioles and their rarefaction, an important mechanism through which the increased sympathetic tone affects hypertension is related to the mutual changes induced by sympathetic stimulation on insulin sensitivity and renin activity. The adrenergic stimulation leads to both an increase in insulin and angiotensin II, which in turn act centrally and peripherally increasing SNS outflow and catecholamine release. Therefore, the reduction of sympathetic tone in women with metabolic syndrome has beneficial effect on glucose metabolism and on blood pressure. The modulation of sympathetic activity with centrally acting agents has therefore a clear indication in the treatment of hypertensive patients with metabolic syndrome.

**Ovarian Hormones in Postmenopausal Hypertension**

Ovarian hormones have a variety of effects that should be protective for the cardiovascular system. However, the effect of oestrogens and progestins on blood pressure are dependent on the route of administration and chemical structure. In fact, apart from selected hormone replacement therapy (HRT) preparations that have a clear effect on blood pressure, HRT has not always been shown to consistently lower blood pressure in postmenopausal women.

Many of these studies were short-term, i.e. <1 year. In contrast, Scuteri et al. studied healthy postmenopausal women who had been using HRT for at least five years and found that HRT significantly lowers blood pressure in both hypertensive and non hypertensive women. In elderly mostly overweight post-menopausal women, some of whom with not controlled arterial hypertension, the Women’s Health Initiative study found that HRT, using a progestin with mineralocorticoid properties, slightly increased systolic blood pressure. Progesterone and progestins with an anti-mineralocorticoid or anti-aldosterone effect used in HRT schemes have positive effects on blood pressure values in normotensive as well as in hypertensive women.

**Renin-angiotensin-aldosterone System in Postmenopausal Hypertension**

It is commonly thought that the plasma renin activity and the activity of the renin-angiotensin-aldosterone system (RAAS), decreases with age in humans and animals. However, studies that measured plasma renin activity serially for nine years in men and women found that oestrogen status influenced the renin activity as it was higher in postmenopausal than in pre-menopausal women.

It is well known that the RAAS plays a major role in control of blood pressure and body fluid volume (i.e. pressure natriuresis). Apart from its direct effect on vessels and on the release of aldosterone, Angiotensin II can also raise blood pressure in postmenopausal women by stimulating synthesis of preproendothelin or by producing oxidative stress. Therefore, activation of the RAAS may cause direct increases in blood pressure but also may stimulate endothelin and oxidative stress, further increasing blood pressure in postmenopausal women.

In women receiving HRT, oral administration of oestrogens may increase angiotensinogen production from the liver, thus facilitating the development of hypertension. This effect is buffered by the co-administration of progestins with anti-mineralocorticoid or anti-aldosterone properties. Recent studies have shown that the co-administration of Drospirenone in HRT schemes significantly reduces blood pressure in hypertensive women treated with Enalapril.

**Therapeutic Approach of Menopausal Women with Arterial Hypertension and Metabolic Syndrome**

Therefore, menopause is associated with unfavourable changes in a broad range of risk factors for cardiovascular disease. These disturbances may themselves be interrelated and in most case associate in the metabolic syndrome. The frequent presence of metabolic syndrome in postmenopausal hypertensive women has important implications for the therapeutic approach of these patients, as some anti-
hypertensive drugs may worsen the already altered metabolic profile of these patients while few others may have a beneficial effect.

Because of the clustering of hypertension with other metabolic risk factors, the therapeutic approach of the syndrome must include lifestyle modifications as well as pharmacological interventions. Several studies have shown that weight reduction is an effective and well-tolerated long-term treatment for hypertension in overweight patients. Moderate weight loss in overweight patients has been shown to decrease intravascular volume and cardiac output without affecting total peripheral resistances. Weight reduction has a beneficial effect on glucose metabolism and sympathetic nervous activity, as it reduces plasma insulin levels by increasing the number and the affinity of the insulin receptors and reduces sympathetic activity.

Although still under debate, several studies have suggested that weight loss is associated with a reduction in plasma renin activity, plasma aldosterone levels and intracellular sodium. Despite the beneficial effect of weight loss on glucose and lipid metabolism and blood pressure levels, several studies suggest that dropout rates in weight-loss programs range from 50% to 70% within one to two years. In order to enhance long-term maintenance of weight loss programmes, it is important to induce a gradual change in eating habits with increase intake of fruits and vegetables coupled with a gradual increase in physical activity up to 30 minutes/day. However, in patients with moderate or severe hypertension, or in those unable to lose weight, a pharmacological approach is needed.

The therapeutic approach of patients with metabolic syndrome should be twofold: to improve glucose tolerance and thereby delay the onset of type II diabetes, and the other to allow an aggressive control of blood pressure values. The metabolic control of patients with metabolic syndrome and high insulin levels should be focused on drugs that improve insulin sensitivity. Several studies have shown that in patients with metabolic syndrome, therapy with metformin, acarbose and glitazones delay the onset of diabetes mellitus, also ACE-inhibitors and Angiotensin II receptor blockers have been proven effective in reducing the progression of glucose intolerance to type II diabetes.

Our group has shown that metformin improves endothelial function in patients with metabolic syndrome independently from the changes in glucose levels supporting the importance of this drug in the treatment of these patients. These drugs, however, had been tested against beta-blockers and, since beta-blockers have a negative effect upon glucose metabolism, it is likely that the effect on glucose metabolism was the result of a neutral effect compared to a negative effect of beta-blockers.

Nowadays, it is possible to choose amongst several anti-hypertensive drug classes, all effective in the control of blood pressure. However, some drugs, such as beta-blockers and diuretics, may not be indicated in patients with metabolic syndrome because of their unwanted effect on glucose and lipid metabolism. The association of Amlodipine/Perindopril has been recently shown to be effective in reducing cardiovascular events and the new onset diabetes in hypertensive patients. However, it is most likely that the metabolic effect of this association is related to the known effect of Perindopril on glucose metabolism. ACE-Inhibitors and ATII receptor blockers are effective in controlling blood pressure and have been shown to reduce the development of diabetes mellitus. However, among ACE-inhibitors, it seems that the metabolic effect is more pronounced with those drugs that increase bradikinin while the metabolic effect of most of the ATII blockers is neutral on glucose metabolism. We have also shown that Telmisartan, an angiotensin II receptor blocker with a PPARγ activity, improves glucose metabolism while reducing blood pressure in hypertensive patients with metabolic syndrome.

Centrally acting agents and alpha-2 blockers have been proven to effectively reduce blood pressure and to improve the glycemic and lipid profile of hypertensive patients. Therefore, it seems that they should be indicated alone or in combination in the treatment of patients with metabolic syndrome. However, regarding the use of alpha blockers especially after the ALLHAT Study, there is no evidence to support the use of monotherapy with alpha blockers in hypertensive patients.

Studies evaluating the effect of the different classes of anti-hypertensives in patients with metabolic syndrome have always been conducted in relatively small patient populations. Therefore, at the present, as also highlighted by the recent ESH/ESC guidelines, there is no clear evidence for the superiority or inferiority of different drug classes and it appears reasonable to recommend that all effective and well-tolerated antihypertensive can be used, generally in combination.

This article is continued, with references, in the Reference Section on the website supporting this briefing (www.touchbriefings.com).