Arterial hypertension is often part of a larger constellation of anthropometric and metabolic abnormalities including abdominal (or visceral) obesity, characteristic dyslipidemia (low high-density lipoprotein cholesterol and high triglycerides), glucose intolerance, insulin resistance (IR) and hyperuricemia, the so-called metabolic syndrome (MS). This cluster of metabolic and cardiovascular risk factors confers an increased risk of cardiovascular events on top of the risk induced by blood pressure (BP) elevation.

Since the description by Reaven, many names and definitions have been given to various clusters of cardiovascular risk factors. Definitions were based on IR or on abdominal obesity, which overlap in a great majority of subjects. The Adult Treatment Panel III definition of the MS is the most clinically oriented and defined threshold values for abdominal (central) obesity, dyslipidemia, and plasma glucose (Table 1). Since the American Diabetes Association has more recently established a cut-off point for fasting glucose ≥100 mg/dl (5.6 mmol/l) above which individuals have either pre-diabetes (impaired fasting glucose) or diabetes, the International Diabetes Federation proposed that the threshold for fasting glycemia should be lowered. Likewise, central (abdominal) obesity, assessed using waist circumference and independently associated with each of the MS components including IR, is a prerequisite risk factor for the diagnosis of the syndrome in the new definition.

Prevalence Among essential hypertensives, prevalence is higher than in the general population and the metabolic syndrome (MS) can be found in as many as one third of patients. In hypertensives with MS, a high prevalence of hypertension-induced target organ damage and a negative prognostic value have been described. Dietary advice and lifestyle changes should be strongly recommended and prompt pharmacologic treatment is required to control high blood pressure and to reduce risk. The effect of particular antihypertensive drugs on other components of the MS is an important clinical issue with consequences for the success of the treatment.
TABLE 1  Criteria for diagnosing the metabolic syndrome according to the Adult Treatment Panel III (ATP III) and the International Diabetes Federation (IDF)

<table>
<thead>
<tr>
<th>Principal criteria</th>
<th>Waist circumference</th>
<th>Fasting glucose mg/dl</th>
<th>HDL mg/dl</th>
<th>Triglycerides mg/dl</th>
<th>Blood pressure mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP III5</td>
<td>M ≥102 cm</td>
<td>≥110&lt;sup&gt;c&lt;/sup&gt;</td>
<td>M ≤40</td>
<td>≥150&lt;sup&gt;c&lt;/sup&gt;</td>
<td>≥130/85&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>W ≥88 cm</td>
<td></td>
<td>W ≤50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDF5</td>
<td>central obesity</td>
<td>M ≥94 cm</td>
<td>≥100&lt;sup&gt;c&lt;/sup&gt;</td>
<td>M ≤40</td>
<td>≥150&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>W ≥80 cm</td>
<td>W ≤50</td>
<td></td>
<td>≥130/85&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Any three or more of the following criteria
<sup>b</sup> Major criterion plus any 2 of the following 4 criteria
<sup>c</sup> Or in treated for

Abbreviations: HDL – high-density lipoproteins, M – men, W – women

of the MS in uncontrolled hypertensives as compared to subjects with BP under control has also been described. It may reflect the more difficult BP control in subjects with a cluster of cardiovascular risk factors and/or higher degrees of end-organ damage.

**Links between hypertension in the metabolic syndrome** Despite close association between the MS components and high BP, the understanding of individual contribution of some of the MS components to the increment in BP levels is complex, since each of them interacts with other MS components and with mechanisms inducing hypertension. The central role of obesity and IR in the rise of BP values has been recognized for many years. These abnormalities lead to overactivity of the sympathetic<sup>15,16</sup> and renin–angiotensin systems<sup>16</sup>, abnormal renal sodium handling<sup>17</sup>, and endothelial dysfunction (figure<sup>18-20</sup>).

Beside the contribution to the BP rise, cross-sectional and follow-up studies have demonstrated that MS increases the risk for hypertension-induced kidney disease. Increased prevalence of left ventricular hypertrophy, diastolic dysfunction, early carotid atherosclerosis, impaired aortic distensibility, hypertensive retinopathy and microalbuminuria in hypertensive patients with MS have been described when compared to those without it.<sup>21</sup>

The importance of MS diagnosis and of its individual components in the prognostic value of hypertensives has been analyzed in a limited number of studies, supporting the added risk of the metabolic components beyond the high BP values. The Copenhagen Male Study<sup>22</sup> with 2,906 participants demonstrated that men with high BP and dyslipidemia had higher risk as compared to those high BP without dyslipidemia. In the 1,742 hypertensives of the Progetto Ipertensione Umbria Monitoraggio (PIUMA) cohort, those with MS had an almost doubled cardiovascular event rate compared to those without risk.<sup>23</sup> Likewise, among 2,225 men and women followed up for a mean of 4.1 years, subjects defined as dyslipemic hypertensives had a higher cardiovascular risk compared to those without dyslipidemia. In the Hoorn study<sup>24</sup>, 615 men and 749 women, aged 50 to 75, followed up to 10 years and without diabetes or a history of cardiovascular disease at baseline MS were associated with a higher cardiovascular disease risk.

The Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study has recently provided further data on the association of MS with cardiovascular risk.<sup>25</sup> Over 148 months of follow-up, the risk of cardiovascular and all-cause death was significantly higher in MS individuals, the difference vs. those without this condition remaining significant (about 70% and 40%, respectively) after adjustment for differences in age, gender, and other cardiovascular risk factors.<sup>26</sup>

**Treatment of hypertension in the metabolic syndrome** The objective of MS treatment is both to reduce high cardiovascular and renal risk associated with individual components of the MS and to reduce the risk of developing type-2 diabetes. Specific pharmacological agents which interfere at the core of the MS are not yet available. Partial approaches have been developed and insulin-sensitizing drugs and endocannabinoid receptor C1 blockers exert a beneficial effect on the main components of the syndrome but their overall effect...
on cardiovascular risk, quality of life and mood has raised concerns about their use. Consequently, it is currently necessary to treat individual components of the syndrome in order to reduce risk level associated with each component, thereby reducing their overall effect on cardiovascular, renal, and diabetes risks (TABLE 2).

**Targeting metabolic syndrome mechanisms** All current guidelines on the management of individual components of the MS emphasize that a change in lifestyle, particularly weight loss and physical activity, is first-line therapy. Extreme diets are seldom effective in inducing long-term weight reduction. A modest calorie reduction (500–1000 cal/day) is usually more effective and beneficial for long-term weight loss. A realistic goal is to reduce body weight by 7–10% over a period of 6–12 months. Long-term maintenance of weight loss is then best achieved when regular exercise is part of weight reduction management. Current guidelines recommend a daily minimum of 30 minutes of moderate-intensity physical activity. Smoking cessation is mandatory. Lifestyle intervention is unfortunately often neglected in routine practice despite its potential to reduce the severity of all metabolic risk factors and to slow their progress.

Beside the positive effect of physical exercise and weight loss on the mechanisms leading to the MS, there has been, to date, one type of drugs interfering with one of the key MS mechanisms—the insulin-sensitizers. They increase peripheral glucose uptake by acting through the peroxisome proliferator-activated receptor-γ (PPARγ). The effect of this drug class on BP values is not well established yet, although some evidence points to a beneficial effect in terms of BP reduction, at least in type-2 diabetes individuals and those with refractory hypertension. However, systematic literature reviews have shown no notable benefits of thiazolidinediones with regard to BP. The shift in fat storage, moving from visceral to subcutaneous fat and increasing weight, and fluid retention are the main side effects of the drugs, which limit their use. Even more important is the potential increment of cardiovascular risk in subjects treated with rosiglitazone that seems to be absent when pioglitazone is used. Whichever the case, there has been no approval for the MS so far.

**Targeting elevated blood pressure/hypertension** The threshold for intervention in BP values is based on the recognition that underlying risk factors raise BP to ranges that increase the risk of cardiovascular disease. Furthermore, subjects with the MS seem to be at risk of developing hypertension. Consequently, 130/85 mmHg should be the threshold for intervention in the absence of diabetes, although when BP is <140/90 mmHg and no organ damage is present, non-pharmacological treatment needs to be introduced first. Hypertension should be managed according to the individual risk assessment of the European Society of Hypertension (ESH)/European Society of Cardiology guidelines. If diabetes is present, antihypertensive drugs should be introduced at even lower levels, 130/80 mmHg. The goal is to maintain BP <130/80 mmHg.

Treatment of high BP in the MS should be based on lifestyle changes, diet and physical exercise, which reduce weight and improve muscular blood flow. As far as antihypertensive drugs are concerned, whether or not a particular antihypertensive agent is superior to others, they have not been tested in trials including subjects specifically with the MS. However, a large body of information is available from both long-term

### TABLE 2 European Society of Hypertension management recommendations for hypertension and metabolic syndrome

<table>
<thead>
<tr>
<th>MS component</th>
<th>Threshold</th>
<th>Goal</th>
<th>Recommended</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>high blood pressure</td>
<td>130/85 mmHg</td>
<td>&lt;130/80 mmHg</td>
<td>non-pharmacological treatment</td>
<td>thiazide-like diuretics should be avoided in monotherapy or in high-dose β-blockers should be avoided if not compelling indication exists</td>
</tr>
<tr>
<td>dyslipidemia</td>
<td>triglyceride &gt;150 mg/dl (1.7 mmol/l)</td>
<td>LDL &lt;75 mg/dl</td>
<td>non-pharmacological treatment</td>
<td>OGTT should be performed in subjects with fasting glucose &gt;100 mg/dl</td>
</tr>
<tr>
<td></td>
<td>HDL &lt;40 mg/dl (1.03 mmol/l) in men or &lt;50 mg/dl (1.29 mmol/l) in women</td>
<td></td>
<td>statins alone or with ezetimibe</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>fibrates other than gemfibrozil are recommended to combine with statins</td>
<td></td>
</tr>
<tr>
<td>impaired fasting glucose</td>
<td>&gt;110 mg/dl</td>
<td>&lt;100 mg/dl</td>
<td>non-pharmacological treatment:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>– first choice: thiazolidinediones</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>– second choice: metformin</td>
<td></td>
</tr>
<tr>
<td>hypercoagulability</td>
<td>in subjects at high risk or creatinine &gt;1.4 mg/dl</td>
<td>reduce platelet aggregability</td>
<td>acetylsalicylic acid</td>
<td>avoid until BP is under control</td>
</tr>
</tbody>
</table>

Abbreviations: ACEI—angiotensin-converting enzyme inhibitors, ARB—angiotensin II-AT1 receptor blockers, CCB—calcium channel blockers, CHD—coronary heart disease, LDL—low-density lipoprotein, MS—metabolic syndrome, OGTT—oral glucose tolerance test, other—see TABLE 1.
anthypertensive trials with major outcomes and a myriad of shorter studies.

After changes to lifestyle have been introduced, the drugs to be used should be the ones which may induce reduction of IR and subsequent changes in lipid profile and glucose levels. Therefore, angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB) or even calcium channel blockers are preferable over diuretics and β-blockers in monotherapy, if no compelling indications are present for its use. If a combination of drugs is required, low-range doses of diuretics can be used.

The effect of particular antihypertensive drugs on other components of the MS is an important clinical issue with consequences for the success of the treatment. Changes in lipid profile and IR during antihypertensive treatment with diuretics and β-blockers have been reported to be responsible for lower reductions in coronary heart disease morbidity and mortality than expected. On the contrary, the reduction in new-onset diabetes rate has been observed during treatment with ACEI, ARB or even calcium channel blockers (CCB) as compared to diuretics and β-blockers.

The most recognized metabolic change associated with antihypertensive drug classes is IR. It is induced by a combination of different mechanisms including reduction of the microcirculatory flow in the muscles and impaired in intracellular glucose disposal rate. The former is a consequence of the use of β-blockers, since β-blockade activity goes unopposed by the α-receptors. The latter is not as well understood. β-blocker agents with additional properties can reduce the impact of the pure β-blockade and even exert a partially beneficial effect. The simultaneous α-blockade of carvedilol or the increase in the nitric oxide bioavailability of nebivolol have shown a neutral effect on glucose metabolism indexes and a trend towards a favorable lipid profile.

The reduction of glucose disposal is worse when insulin secretion decreases. This can occur as a direct consequence of the β-blockade, reducing the response of the pancreatic β-cell, and by hypokalemia induced by thiazide-like diuretics. Reductions in glucose disposal and in the compensatory insulin secretion lead to metabolic abnormalities of the glucose homeostasis and dyslipidemia, as previously described.

Nevertheless, a beneficial effect on decreasing the risk for the development of diabetes with ACEI or ARB-based treatments has been described. Detailed systematic reviews of the potential beneficial effects have been published recently. In general, treatment with these drug classes reduces the rate of new-onset diabetes as compared with the use of diuretic and/or β-blockers.

Inhibiting the renin–angiotensin system may improve blood flow to muscles, decrease the activity of the sympathetic nervous system, enhance insulin signaling, lower free fatty acids levels, increase plasma adiponectin levels, and improve glucose disposal. Another putative mechanism by which the inhibition of the renin–angiotensin system may improve insulin sensitivity is through effects on PPARγ, which is inhibited by angiotensin II.

The impact of other antihypertensive drug classes demonstrated the neutral metabolic effect of both long-acting CCBs, as well as other sympatholytic drugs with central action such as reserpine, α-methyl-dopa or moxonidine. The pure peripheral α-blocker, doxazosin, improves lipid profile reducing IR and consequently increasing high-density lipoprotein cholesterol and reducing triglycerides. A trend to reduce total cholesterol has also been described. The main mechanism implicated in the positive changes of α-blockers seems to be mediated by increasing microcirculation flow. Additional effects of α-blockade on the activity of the key lipid metabolism enzymes are less known.

A final question is the net effect of the interaction when 2 different kinds of drugs with opposite effects are combined. This is the case of combination treatments with diuretics. Simultaneous administration of thiazide diuretic with ACEI or ARBs reduces the hypokalemia and does not significantly modify lipid and glucose profiles. Whether or not this combination substantially reduces the beneficial effects in cardiovascular risk needs to be assessed. A recent publication points out that valsartan alone reduced the levels of high sensitivity C-reactive protein (hsCRP). In contrast, a combination of valsartan plus hydrochlorothiazide, despite a significantly larger BP reduction, was unable to reduce the level of hsCRP. No interaction with statins was demonstrated.

**CONCLUSIONS** Recently the ESH acknowledged the clinical relevance of the MS in hypertension. The MS is a frequent clinical condition among hypertensive subjects and its prevalence has been on the increase driven by the obesity epidemic. It increases the cardiovascular and renal risk associated with hypertension. Consequently, the thresholds to initiate antihypertensive treatment and the goals to be achieved need to be redefined. Drugs which potentially lead to worsened metabolic profile should be avoided unless compelling indications exist.

**REFERENCES**


ARTYKUŁ POGŁĄDOWY

Nadciśnienie tętnicze w zespole metabolicznym
Podsumowanie nowego stanowiska European Society of Hypertension

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STRESZCZENIE

Nadciśnienie tętnicze jest częstą składową zespołu nieprawidłowości antropometrycznych i zaburzeń metabolicznych obejmującego otyłość brzuszną (trzewną), charakterystyczną dyslipidemię (małe stężenie cholesterolu frakcji lipoprotein o dużej gęstości i duże stężenie triglicerydów w osoczu), nieprawidłową tolerancję glukozy, oporność na insulinę i hiperurycemię. Częstość występowania zespołu metabolicznego (metabolic syndrome – MS) definiowanego na podstawie kryteriów Adult Treatment Panel III jest większa u chorych na nadciśnienie tętnicze niż w populacji ogólnej; zespół ten stwierdza się aż u 1/3 pacjentów. U chorych na nadciśnienie tętnicze z MS opisuje się częstszes występowanie powikłań narządowych nadciśnienia i gorsze rokowanie. Zdecydowanie zaleca się po radnictwo w zakresie właściwego odżywiania się oraz zmiany stylu życia, a w celu kontroli wysokiego ciśnienia krwi i zmniejszenia ryzyka wymagane jest niezwłoczne leczenie farmakologiczne. Wpływ poszczególnych leków przeciwnadciśnieniowych na inne składowe MS jest ważnym zagadnieniem klinicznym i ma znaczenie dla powodzenia leczenia.