

## The Meaning of Cardiometabolic Risk in Hypertensive Patients

a report by

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Cardiometabolic risk is a condition in which the possibilities of developing atherosclerotic cardiovascular (CV) disease and diabetes mellitus are significantly enhanced as a consequence of the presence of insulin resistance and atherogenic dyslipidemia, the latter being characterized by the presence of low high-density lipoprotein (HDL)-cholesterol and high triglyceride levels.<sup>1,2</sup> Cardiometabolic risk is diagnosed by the identification of an enhanced waist circumference (above 102cm in males and 88cm in females) accompanied by the alterations in lipid profile quoted above (HDL-cholesterol below 40mg/dl in males and 50mg/dl in females, and serum triglycerides above 150mg/dl).

Cardiometabolic risk is particularly prevalent in patients diagnosed as having metabolic syndrome. Correct diagnosis of metabolic syndrome requires—besides an increased waist circumference—low HDL-cholesterol and elevated triglycerides, the potential presence of blood pressure (BP) values above 130/85mmHg, and a fasting serum glucose above 100mg/dl according to a recently revisited Adult Treatment Panel (ATP)-III definition.<sup>3,4</sup> The International Diabetes Federation (IDF) has similarly defined metabolic syndrome in Europids by the presence of a waist circumference above 94cm in males and 80cm in females, accompanied by the finding of two out of the other four criteria defined by ATP-III.<sup>5</sup>

### How Frequent and Relevant is Cardiometabolic Risk in the Hypertensive Population?

Figure 1 details the prevalence of metabolic syndrome according to ATP-III<sup>3</sup> and IDF<sup>5</sup> definitions in a population of more than 1,800 hypertensive patients attending the Hypertension Unit located at the 12 de Octubre Hospital in Madrid, Spain. As can be seen, around 50–70% of patients were diagnosed as having metabolic syndrome according to the two aforementioned definitions. This figure is not significantly different when a hypertensive population attending primary care settings is considered.<sup>6</sup>



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Cardiometabolic risk is, therefore, prevalent in the hypertensive population and, as depicted in Figure 2, needs to be structured into a correct stratification of risk that has to be considered in every hypertensive patient. In fact, the new guidelines of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC)<sup>7</sup> consider the concomitant finding of arterial hypertension and metabolic syndrome as a situation of high added CV risk. The reason for this is based on two facts. First, metabolic syndrome and the accompanying cardiometabolic risk result in a significant increase in CV morbidity and mortality in several population-based studies, as recently reviewed,<sup>9</sup> as well as in hypertensive patients.<sup>10</sup> Second, the presence of metabolic syndrome is accompanied by a 3–6-fold increase in the risk of developing type 2 diabetes.<sup>11</sup>

Furthermore, the presence of cardiometabolic risk is accompanied by a significant enhancement in the risk of developing chronic kidney disease, albuminuria, and/or a diminished estimated glomerular filtration rate (GFR). The higher the number of criteria satisfied in the diagnosis of metabolic syndrome, the higher will be the prevalence of either microalbuminuria and/or an estimated GFR value <60ml/min/1.73m<sup>2</sup>.<sup>12</sup>

### How Relevant is the Development of Diabetes Mellitus in a Hypertensive Population?

The development of new-onset diabetes and its relevance in hypertensives has been widely considered recently.<sup>13,14</sup> The type of antihypertensive therapy used, alone or in combination, affects the acceleration of the appearance of diabetes. A recent network meta-analysis<sup>15</sup> has shown that the best protection is obtained when angiotensin receptor blockers (ARBs) and converting enzyme inhibitors (CEIs) are used, while diuretics and beta-blockers offer the least protection, especially when used in combination.

Although some authors have denied that the development of new-onset diabetes contributes to worsening the short-term (3–5-year) prognosis of hypertensive patients according to the data of studies such as the Systolic Hypertension in the Elderly Program (SHEP)<sup>16</sup> and the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack trial (ALLHAT),<sup>17</sup> it seems clear that becoming a diabetic must be relevant to the patient's long-term prognosis. In fact, it has been shown that after two and a half years of follow-up beyond that in ALLHAT, the risk of new diabetics was equal to that of patients entering the study as declared diabetics.<sup>18</sup>

### How Should a Patient with Hypertension and Cardiometabolic Risk be Treated?

The aim of intervention in patients with cardiometabolic risk is to achieve an optimal reduction of such risk. Lifestyle modifications counteract the effect

of the underlying risk factors (abdominal obesity, physical inactivity, and atherogenic diet). Moreover, hypertensives also require a tight BP control, a choice of antihypertensive treatment not producing other metabolic disturbances, and, quite often, parallel drug treatment for associated metabolic risk factors (dyslipidemia, insulin resistance, and prothrombotic and proinflammatory states).

**Lifestyle Interventions**

Lifestyle interventions are the first step in achieving cardiometabolic risk reduction. The key lifestyle interventions are the promotion of exercise and energy expenditure and the reduction of overweight by caloric restriction.<sup>19</sup> The minimal requirements for long-term effectiveness include caloric restriction in the range of 500–1,000kcal with 7–10% weight loss in 12 months and regular aerobic exercise of 30–45 minutes daily. Whereas extreme caloric-restricted or element-dissociated diets have no long-term advantages, more intensive exercise programs have additional CV benefits and help to maintain weight loss. Lifestyle interventions have beneficial effects on BP and the lipid profile and reduce the incidence of new-onset diabetes.<sup>20</sup> Moreover, recent data suggest a long-term effect on the reduction in CV morbidity.<sup>21</sup>

Other lifestyle changes also have a beneficial effect on specific CV risk factors and must be encouraged in specific patients. Lowering salt intake and alcohol consumption have moderate BP-lowering effects, which are enhanced in conjunction with weight loss and increased exercise.<sup>7</sup> In addition, a diet rich in fruit, vegetables, and low-fat dairy products—dietary approaches to stop hypertension (DASH) diet—substantially lowers BP in comparison with the standard American diet.<sup>22</sup> Finally, the Mediterranean diet, which is also rich in fruit, vegetables, fish, and olive oil, has a favorable impact on atherogenic dyslipidemia in metabolic syndrome patients.<sup>23</sup>

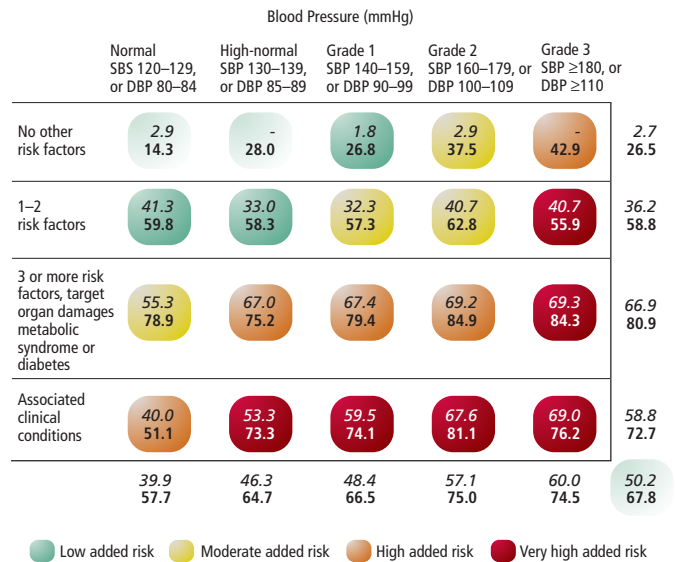
Maintenance of lifestyle changes requires counseling and may prove difficult in the long term. For this reason, pharmacological treatment of BP, dyslipidemia, insulin resistance, and obesity will be required for most patients to reduce cardiometabolic risk.

**Antihypertensive Therapy**

As mentioned above, the new ESH/ESC guidelines<sup>7</sup> emphasize the importance of metabolic syndrome as an indicator of high added CV risk in hypertensives, thus indicating early antihypertensive treatment if lifestyle measures are not enough to reach BP targets.

No comparative studies of the different antihypertensive drug classes in hypertensives with metabolic syndrome are available. However, the choice of antihypertensive treatment must take the increased risk of developing new-onset diabetes in these subjects into account. Some international guidelines recommend diuretics as the first-step therapy for hypertensive patients without a compelling indication for other antihypertensive drug classes. However, it has been established that diuretics increase the risk of new-onset diabetes compared with placebo (23% increase for diuretics).<sup>15</sup> Conversely, calcium channel blockers and, especially, renin-angiotensin system (RAS) blockers—angiotensin receptor blockers (ARBs) and angiotensin-converting-enzyme (ACE) inhibitors—decrease this risk (33% decrease with ACE inhibitors and 43% decrease with ARBs). These differences are probably even more pronounced in the specific subset of patients with metabolic syndrome

**Figure 1: Prevalence of Metabolic Syndrome in the Hypertensive Population Followed in Our Hypertension Unit Distributed within the Algorithm of Risk Stratification of ESH/ESC Guidelines**



Figures are percentages: ATP-III (figures in italics) and IDF (figures in bold).

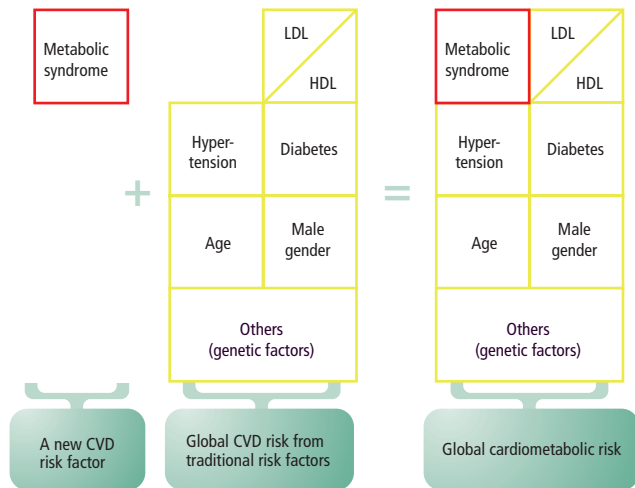
and high cardiometabolic risk. Thus, it seems reasonable that the first consideration in antihypertensive treatment in hypertensives with high cardiometabolic risk should be the inhibition of the RAS with either ACE inhibition or angiotensin blockade.

There is no evidence to support a preference for one or the other of these two forms of RAS blockade. Some of the ARBs seem to have specific metabolic actions, such as partial agonism of the nuclear receptor peroxisome proliferator-activated receptor (PPAR)-gamma, although this has not yet been translated into a proven clinical benefit.

Non-hypertensive patients with metabolic syndrome usually have high-normal BP (systolic 130–139mmHg and/or diastolic 85–89mmHg). Specific dietary interventions, such as sodium restriction or the adoption of the DASH diet, in addition to caloric restriction and increased exercise, could be helpful. For patients also having diabetes or chronic kidney disease, antihypertensive therapy is mandatory.<sup>7</sup> For the remaining subjects, there is no consensus on whether antihypertensive treatment is recommendable when lifestyle measures are not effective.

Various evidence can help to guide this decision. First, the Framingham Study<sup>24</sup> found that subjects with high-normal BP were at increased risk for CV events compared with those with optimal BP (less than 120/80mmHg). Second, the rate of developing hypertension in a short period (three years) for those with BP higher than 120/80mmHg has been reported as very high (40% in subjects older than 64 with BP higher than 130/85mmHg).<sup>25</sup> In the same way, the recent Trial of Preventing Hypertension (TROPHY) found that, over a period of four years, stage 1 hypertension developed in nearly two-thirds of patients with untreated pre-hypertension (values of 120–139 and/or 80–89mmHg), and that antihypertensive treatment reduced the risk of incident hypertension in these patients.<sup>26</sup>

**Figure 2: Global Cardiometabolic Risk Includes the Presence of Metabolic Syndrome and Traditional Cardiovascular Risk Factors**



On the basis of these considerations, it can be hypothesized that antihypertensive treatment could be of benefit for subjects with high-normal BP and high cardiometabolic risk. However, a clear indication needs to be based on a prospective interventional study showing decreased mortality and/or morbidity.

### Lipid-lowering Therapy

For hypertensives with cardiometabolic risk but without diabetes or CV disease, the evidence is scarce. However, the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) demonstrated that treatment with 10mg atorvastatin was effective in reducing CV events when hypertension was accompanied by three or more additional risk factors, including most that are contained in the definition of metabolic syndrome.<sup>29</sup>

The typical dyslipidemia in hypertensives with cardiometabolic risk is characterized by low HDL-cholesterol and increased triglycerides. Two classes of drugs reduce triglycerides and increase HDL-cholesterol: nicotinic acid and fibrates. Although limited evidence is available, some *post-hoc* analyses suggest a beneficial effect of these drugs in patients with metabolic syndrome, insulin resistance, or diabetes.<sup>30-33</sup> Thus, current evidence recommends the use of fibrates or nicotinic acid in hypertensive patients with metabolic syndrome and hypertriglyceridemia, but these agents should be used with caution in those receiving concomitant statin treatment, especially at higher doses, due to the increased risk of myopathy and liver disorders. Finally, other apparently promising alternatives, such as cholesteryl ester transfer protein (CETP) inhibition, have recently been associated with increased mortality.<sup>34</sup>

### Insulin Sensitizers

In addition to lifestyle changes, treatment with metformin,<sup>20</sup> acarbose,<sup>35</sup> and thiazolidindiones<sup>36</sup> decreases the risk of new-onset diabetes in patients with impaired glucose tolerance. However, the long-term benefits of these drugs and the cost-benefit analysis have not been adequately addressed. In fact, a recent meta-analysis suggests a deleterious effect of rosiglitazone on cardiac outcomes.<sup>37</sup>

### Antiobesity Drugs

Abdominal obesity is one of the main components of cardiometabolic risk. In addition to a restricted caloric diet and increased exercise, three different pharmacological approaches are available for weight loss. Sibutramine is the only drug affecting monoaminergic systems currently approved for the long-term control of obesity. Several clinical trials have demonstrated the superiority of sibutramine with respect to placebo in reducing weight and waist circumference (median at one year: 4.5kg). In hypertensives, sibutramine slightly increases BP and heart rate and should be used with caution.<sup>38</sup> However, a recent trial suggests that the effects of sibutramine in hypertensives under antihypertensive treatment largely depend on the type of antihypertensive drug used.<sup>39</sup> Thus, sibutramine—when co-administered with a combination of RAS blockers and calcium channel blockers—does not interfere with the antihypertensive effect of such a combination.

Orlistat is an inhibitor of gastrointestinal lipases, especially pancreatic lipase. Its efficacy in producing a superior weight loss with respect to placebo has also been proven, although the weight loss is usually less than that obtained with sibutramine. Orlistat has a favorable influence on lipids and glycemic control, especially in diabetics, although gastrointestinal tolerance is poor.<sup>40</sup>

Rimonabant is the first antagonist of the endocannabinoid (CB1) receptor. The Rimonabant In Obesity (RIO) program has demonstrated a significant effect of this drug on long-term weight reduction in overweight patients with additional CV risk factors at one year,<sup>41</sup> maintained at two years,<sup>42</sup> in hyperlipidemic overweight subjects,<sup>43</sup> and in type 2 diabetics.<sup>44</sup> In all these trials, the beneficial effects on HDL-cholesterol and triglycerides, and on glycated hemoglobin in diabetics, exceeded those expected due to weight loss.

These facts have led to the consideration that Rimonabant is a drug primarily directed to CV protection through a direct reduction of the components of cardiometabolic risk. Studies of the effect of this CB1 receptor antagonist on CV outcomes in patients at risk are ongoing.

### Antithrombotic Drugs

A key feature of metabolic syndrome that explains the increased cardiometabolic risk is an enhanced pro-thrombotic state, especially in the presence of insulin resistance. Postprandial hyperglycemia, increased free fatty acids, and elevated triglyceride levels may all have adverse effects on platelets, coagulation, and fibrinolysis. Pharmacological interventions targeting these abnormalities have the potential to reduce thrombosis. Antiplatelet drugs such as low-dose aspirin or clopidogrel represent an option in the management of hypertensives with cardiometabolic risk. The benefit is probably higher in type 2 diabetics<sup>45</sup> and conclusive in those with previous CV disease.<sup>46</sup> Efforts to control BP should be reinforced before the introduction of aspirin.

### Anti-inflammatory Drugs

Insulin resistance is now recognized as an inflammatory disease, with levels of inflammatory markers such as C-reactive protein, plasminogen activator inhibitor (PAI)-1, and interleukin (IL)-6 being present in higher concentrations in insulin-resistant individuals than in healthy counterparts.<sup>47</sup> C-reactive protein is increasingly regarded as a useful measure of CV risk.<sup>48</sup> Aspirin, statins, and—to a lesser extent—RAS inhibitors reduce the

inflammatory process and prevent CV disease. Vitamins or other specific anti-inflammatory drugs are not usually recommended.

### Closing Remarks

Although there are several areas of uncertainty with respect to the definition, usefulness, and pathogenesis of metabolic syndrome, simple clinical tools exist that identify subjects at a higher risk of developing both type 2 diabetes and CV disease, and thus having high cardiometabolic risk. The management of these subjects is based principally on lifestyle measures, but various antihypertensive, lipid-

lowering, insulin-sensitizing, antiobesity, and antiplatelet drugs could be helpful in reducing the cardiometabolic risk.

Population-based strategies are necessary to reduce the impact of underlying risk factors for cardiometabolic risk (obesity, physical inactivity, and atherogenic diet). Although evidence is scarce, there is general agreement that more aggressive therapy is required to reduce the risk of new diabetes and CV disease further. Prospective, randomized trials addressing the effect of potentially beneficial treatments on cardiometabolic outcomes should be strongly encouraged. ■

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