

## A comprehensive management of hypertension among patients with metabolic syndrome: an evidence-based update

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### Abstrak

Individu dengan hipertensi dan sindrom metabolik memiliki risiko yang lebih besar untuk menderita berbagai komplikasi di masa depan. Oleh karena itu, tatalaksana komprehensif yang berdasarkan bukti sangat diperlukan. Perubahan pola hidup merupakan langkah awal yang disarankan dan jika tidak berhasil dapat dilanjutkan dengan pemberian obat anti-hipertensi. Penurunan berat badan melalui penurunan konsumsi kalori dan peningkatan olahraga terbukti memberikan efek yang baik pada kontrol diabetes, tekanan darah, dan profil lipid. Penghambat renin-angiotensin merupakan pilihan pertama untuk populasi ini, sementara penghambat reseptor- $\beta$  dan diuretik lebih baik disimpan untuk pilihan kedua karena peningkatan risiko terjadinya diabetes dengan penggunaan obat ini. Sasaran tekanan darah pada populasi ini adalah  $<130/80$  mmHg. Tatalaksana komprehensif dengan kontrol baik terhadap tekanan darah, berat badan, gula darah, dan profil lipid, diharapkan dapat menurunkan morbiditas pada penyandang hipertensi yang juga menyandang sindrom metabolik. (*Med J Indones.* 2013;22:189-94. doi: 10.13181/mji.v22i3.590)

### Abstract

Individuals with hypertension and metabolic syndrome are at increased risk of developing future morbidities. Therefore, an evidence-based comprehensive approach is required. It is recommended to start with lifestyle modification as the first step, then followed by antihypertensive drugs. Weight loss through decreased caloric intake and increased exercise have been proven to yield a better control over diabetes, blood pressure, and lipid profile. Inhibitor of renin-angiotensin is the recommended first-line drugs for this population, while  $\beta$ -blocker and diuretic should remain as the second line drugs due to increased risk of developing new onset diabetes with these drugs. A more rigorous blood pressure control is reasonable with a target of  $<130/80$  mmHg. A comprehensive management which include good control over blood pressure, weight, blood glucose, and lipid profile, may reduce future morbidities among hypertensive individuals with metabolic syndrome. (*Med J Indones.* 2013;22:189-94. doi: 10.13181/mji.v22i3.590)

**Keywords:** Cardiovascular; diabetes; hypertension; metabolic syndrome

Metabolic syndrome (MetS) refers to the clustering of cardiovascular (CV) risk factors that include fasting hyperglycemia, obesity, dyslipidemia, and hypertension. Each of these risk factors when considered individually has a borderline significance, but when taken together pose an increased risk of developing future complications like diabetes and CV disease.<sup>1</sup> The rate of MetS is increasing worldwide. As MetS cases increase, the complications would eventually rise as well. According to non-communicable disease risk factor the surveillance in 2006 performed in Jakarta, the prevalence of MetS among 1591 subjects was 28.4%. The increasing number of MetS cases is very much associated with obesity cases.<sup>2</sup> Judging by today's obesogenic environment, it seems the MetS cases will continue to rise.

Hypertension, one component of MetS, is a common diagnosis in daily clinical practice yet the control rate is poor. Hypertension is the number one cardiovascular risk factor, contributing to one half of coronary heart disease and two thirds of cerebrovascular disease cases worldwide. As evidence showed, there is a

trend towards increased prevalence of hypertension. This alarming number of hypertensive cases are expected to be higher in the future.<sup>3</sup>

It is postulated that there is a substantial interconnection between metabolic factors and hypertension, beyond what we comprehend at the moment.<sup>4</sup> The underlying pathophysiology of this interplay is yet to be understood, however increasing evidence regarding this topic is emerging. Among non-diabetic hypertensive patients, poor blood pressure (BP) control is associated with two fold increased risk of diabetes.<sup>5</sup> The incident of type 2 diabetes mellitus is more frequent in hypertensive than in normotensive subjects. BP progression are associated with an increased risk of incident type 2 diabetes.<sup>6</sup> Therefore, it is mandatory to have a more comprehensive knowledge regarding hypertension and MetS. Doctors should be aware of the "hypertension-metabolic syndrome" relationship to optimize the management of their patients. This review would elaborate crucial evidence-based information that are new to us, that still stand, and that are out dated.

## Metabolic syndrome

Currently, there is no internationally-agreed criteria for diagnosing MetS. The most common criteria used in clinical setting is the criteria by National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III). An increased waistline is the first criteria of MetS in addition to BP elevation, fasting hyperglycemia, increased triglycerides, and decreased high density lipoprotein cholesterol (HDL-C). Three of this components are required for the diagnosis of MetS. The complete ATP III criteria is summarized in Table 1.<sup>7</sup>

Three potential etiological factor of MetS are obesity and disorders of adipose tissue, insulin resistance, and constellation of independent factors (eg, molecules of hepatic, vascular, and immunologic origin) that mediate specific components of the MetS.<sup>7</sup> Evidence accumulating that insulin resistance may be the initial culprit for MetS.<sup>7,8</sup>

## Hypertension and metabolic syndrome

It is common to find a person with abnormal glucose tolerance that also has other CV disease risk component, such as hypertension. Hypertension is more common in individuals with diabetes mellitus than the general population, with the prevalence of hypertension in diabetic populations ranging from 40% to 80%. In a recent analysis by Chen G<sup>9</sup> from the Framingham original and offspring cohorts, the risk of CV complications has a linear pattern with blood pressure. Moreover, the combination of hypertension and other

risk factors in the MetS would eventually increase the likelihood of future CV complications.<sup>9</sup>

Sattar, et al<sup>10</sup> analyze the association of the amount of risk factors with CV outcome. The risk of developing future CV events is proportional to the amount of MetS features. Individuals with 4 or 5 features of MetS had a 3.7 fold increase risk of coronary heart disease and a 24.5 fold increase risk for diabetes compared with those with none.<sup>10</sup> The risk of future CV events among hypertensive patients with MetS is obvious, so a rigorous hypertensive management among this population is strongly advised (Table 2).

## Treating hypertension, when to start?

According to The Seventh Joint National Committee Report (JNC 7), pre-hypertension is defined as systolic blood pressure of 120-139 mmHg or a diastolic blood pressure of 80-89 mmHg. Patients with pre-hypertension were considered at increased risk for progression to hypertension.<sup>12</sup> Is it necessary to start early and treat pre-hypertensive patients who also have MetS?

Individuals with high CV risk, such as MetS, but with blood pressure still fall into pre-hypertensive stage, should be first advised to adopt an intense lifestyle measure. A close BP monitoring and detailed assessment of subclinical organ damage is recommended. Since this particular group of people has an increased risk of developing overt hypertension, measuring ambulatory and home blood pressure is also desirable, when available. Current guidelines consider a reduction in

Table 1. ATP III criteria for metabolic syndrome

Component	Description
Elevated waist circumference	≥ 102 cm in men, ≥ 88 cm in women*
Elevated triglycerides	≥ 150 mg/dL or On drug treatment for elevated triglycerides
Reduced HDL-C	< 40 mg/dL in men, < 50 mg/dL women or On drug treatment for elevated HDL-C
Elevated blood pressure	≥ 130 mmHg systolic blood pressure or ≥ 85 mmHg diastolic blood pressure or On anti-hypertensive drug treatment in a patient with a history of hypertension
Elevated fasting glucose	≥ 110 mg/dL or On drug treatment for elevated glucose

\*Lower waist circumference cutpoint (≥ 90 cm in men and ≥ 80 cm in women) appears to be appropriate for Asian Americans.

Source: Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American heart Association/ National heart, Lung and Blood Institute Scientific statement. *Circulation* 2002; 112:2735-52.

Table 2. Risk stratification of blood pressure related to the amount of other risk factors

Other risk factors or disease	Blood pressure (mmHg)				
	Normal SBP 120-129 or DBP 80-84	High normal SBP 130-139 or DBP 85-89	Grade 1 HT SBP 140-159 or DBP 90-99	Grade 2 HT SBP 160-179 or DBP 100-109	Grade 3 HT SBP $\geq 180$ or DBP $\geq 110$
No other risk factor	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1-2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
3 or more risk factors, subclinical organ damage, metabolic syndrome or diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
Established cardiovascular or renal disease	Very high added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

HT: Hypertension; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

Adapted from: Mancia G, De Backer G, Dominiczak A, et al. Management of Arterial Hypertension of the European Society of Hypertension; European Society of Cardiology: 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)<sup>11</sup>

body weight by low caloric diet and physical exercise as the first and main treatment strategy in subjects with the MetS.<sup>11</sup> Intense lifestyle intervention has been proven to decrease the onset of diabetes and reduce systolic BP in the range of 8 mmHg.<sup>13-15</sup>

The high-normal BP is a further stratification of pre-hypertensive stage, defined as systolic BP of 130-139 mmHg or a diastolic BP of 85-89 mmHg. The increased chance of developing overt hypertension among this high risk population, made it rationale to start pharmacological agent for those who have high-normal BP. The recommendation to start pharmacological treatment in high risk individuals when BP is still in the high-normal stage is supported by European Guidelines. Nevertheless, lifestyle modification should always be implemented first and concomitantly. Doctors may consider anti-hypertensive agents particularly those drugs more effective in protecting against organ damage, new-onset hypertension, and new-onset diabetes among high risk population, like inhibitors of renin-angiotensin system.<sup>11</sup>

#### The best anti-hypertensive agent, any class effect?

The fact that more and more anti-hypertensive agents available in the market will lead to the question, as to which one is the best for patients with MetS. Is there any class effect? Or is it solely the achieved blood pressure that determine any future morbidities? The best answer to that question is by looking at existing studies on that particular topic.

The first class to be considered is ACE inhibitors or angiotensin receptor blocker (ARB). Angiotensin II is playing a deleterious role in the atherosclerotic process. Therefore, the blockade of the renin-angiotensin system is effective in preventing renal and CV events in high risk patients.<sup>16</sup> The ultimate goal of hypertensive medication is to prevent any future morbidities and put as little side effects as possible to the patients. So a drug with good efficacy, good safety profile, and less side effects would be the best choice.

A meta analysis of 50 studies by Matchar, et al<sup>17</sup> conclude that ACE inhibitor and ARB have a similar blood pressure control and outcome (including mortality and CV events). Both of these drugs have similar good control over risk factors, such as lipid control and diabetes progression. The population in this analysis is mainly the so called "relatively low-risk" individual, unfortunately detailed patient's characteristic elaboration was lacking. Furthermore, it is also noteworthy that there were fewer withdrawals due to adverse events and greater persistence with therapy for ARBs than for ACE inhibitors.<sup>17</sup> Additional information was provided by ONTARGET study, in which study the conclusion justified equal benefit of ACE-inhibitor and ARB which extends into high risk population (diabetes, CV disease) as well.<sup>18</sup> So, what are the lessons we can take from these studies? ARB has the ability to reduce blood pressure as effective as ACE-inhibitor, with similar benefit in hard end points such as CV related death, yet with minimal side effects (cough in particular) in a wide range of patients.

In Indonesia, with its current “out of pocket” healthcare system and the low economic background of some patients, cost condiseration is inevitable. ARBs are usually more expensive than ACE-inhibitor since these drugs generally are not available as generic drugs. So the choice on which drug is the best, should always be decided upon patient’s characteristics, some of which are patients’ health profile, side effects or response to previous therapy and socio-economic condition.

Current guideline advise againts initial use of  $\beta$ -blocker and high dose diuretic in individuals with MetS.<sup>11</sup> Some studies linked  $\beta$ -blocker and diuretic with increased risk of developing new-onset diabetes, while calcium channel blocker remain a neutral choice.<sup>19,20</sup> Nebivolol and carvedilol might be an exception, however lack of studies warrant a cautious use of this agents.<sup>11</sup> So, unless required by specific indications,  $\beta$  blockers and diuretic should remained a second line drugs for individuals with MetS. Based on existing studies, it is prudent to give preference on ACE inhibitor and ARB as the first line agents for hypertensive individuals with MetS.

### **Blood pressure target, the lower the better?**

Current international guidelines on hypertension recommend to obtain a blood pressure target below 140 mmHg systolic and 90 mmHg diastolic in the general hypertensive population.<sup>11</sup> High risk individuals like diabetic patients, would receive additional benefit with a more aggressive blood pressure goal. Since the presence of MetS is related to high CV risk, it is logical to pursue a more rigorous blood pressure control, similar to that of diabetic patients. A study by Schrier, et al<sup>21</sup> demonstrated a slowed progression of diabetes nephropathy, diabetes retinopathy, and lowered incidence of stroke among diabetic patients with intensive hypertension treatment with BP target of 128/75 mmHg. However, a different result was reported by ACCORD study. According to this study there was no further benefit by lowering systolic blood pressure down to 120 mmHg as compared to 140 mmHg among diabetic individuals. Nevertheless, this conflicting result should be intepreted with caution. Since in the ACCORD study, the populations’ other risk factors (lipid profile and blood glucose) were well controlled with other treatment that could mask the statistical analysis of BP lowering beneficial effect. Other explanation would be that it requires longer period of follow up to prove any beneficial effect in this population, as CV complications happen over a long period of time.<sup>22</sup>

Is it really necessary to achieve a lower blood pressure target among MetS population? Is there any such principle as “the lower the better”? There is currently

limited data regarding the optimal blood pressure target among individuals with MetS. However, recent evidence rebutted the idea of J-shaped curve of blood pressure control and support the idea of lowering the blood pressure, even below the normal value. A meta analysis study involving almost one million participants by Lewington,<sup>23</sup> showed that a difference as small as 2 mmHg in systolic BP is associated with a 10% reduction of stroke mortality and 7% reduction in risk of ischemic disease mortality. The benefit from BP lowering showed no threshold down to at least 115/75 mmHg. This evidence conclude that there is a linear relationship between BP and CV events and achieving a more aggressive blood pressure target indeed reduce the occurence of future morbidities.<sup>23</sup> So, does the rule of “the lower the better” really applies? Based on latest studies yes it is, but to a certain level. According to the current insight, it is logical to pursue a BP target as low as 130/80 mmHg among individuals with MetS.

### **Healthy lifestyle**

Managing a person with hypertension and other features of the MetS should focus not only on BP control but also on other CV risk factors. One simple way to start is by adopting a healthy lifestyle measures. Tuomilehto, et al<sup>13</sup> study the efficacy of intense lifestyle changes in preventing the progression of impaired glucose intolerance to full blown diabetes. Most of the patients had some characteristics of MetS. The incidence of diabetes was 11% in the intervention group as compared to 23% in the control group.<sup>13</sup>

This positive outcome on healthy lifestyle is also supported by a study performed by Diabetes Prevention Program Research Group among 3234 individuals with impaired glucose tolerance and impaired fasting glucose. Weight reduction (7% from initial weight), low-fat diet and regular excercise (150 minutes per week) are proven to reduce the incidence of diabetes as much as 58% as compared to placebo.<sup>16</sup> Healthy lifestyle which include healthy diet rich in fiber, decreased fat intake, and increased endurance excercise should be adopted by every individuals with MetS.<sup>13,14</sup> We should pay more attention on disease primary prevention than secondary prevention. Healthy lifestyle, are a cost-effective primary prevention to lower future diseases and morbidities.<sup>24</sup> The reduced rate of lifestyle related-diseases would eventually reduce one’s country financial burden over the cost that was spent over disease and its complication management, that could be otherwise prevented by healthy lifestyle measures. The reduction of lifestyle related diseases would eventually reduce one’s country financial burden over

the cost that was spent over lifestyle related disease and its complication management. Please bear in mind that metabolic syndrome would result in many complication that could be otherwise prevented by healthy lifestyle measures.

### **Multifactorial intervention: weight control, lipid control, and glucose control**

Weight control, lipid control, and glucose control are as much important as maintaining a good blood pressure control among individuals with MetS. Weight loss through decreased calory intake and increased physical activity, is proved to have a better control over diabetes, blood pressure, and lipid profile.<sup>25</sup> In selected patients, drug regimens might be needed. Statin therapy is justified if patients have dyslipidemia. Statin administration significantly reduce the occurrence of CV complication, cerebrovascular complication, and mortality among high risk individuals.<sup>26-28</sup> To aim low-density lipoprotein cholesterol (LDL-C) below 100 mg/dL seems appropriate for individuals with MetS. Even further reduction of LDL-C to below 70 mg/dL is reasonable for very high risk individuals (individuals with establish CV disease plus one of the following: diabetes, cigarette smoking, dyslipidemia).<sup>29</sup> Some studies also report a beneficial effect of early metformin administration among glucose intolerance individuals to halt the disease progression into overt diabetes, especially those with other features of metabolic syndrome.<sup>13,14,30</sup>

In conclusion, managing hypertension among individuals with MetS should comprise not only BP control but also other risk factors control. Inhibitor of the renin-angiotensin should be the first-line anti-hypertensive agent used in MetS population in general. The reasonable BP target is < 130/80 mmHg, even lower value is proved to yield further benefit. Lifestyle modification should always be the cornerstone of MetS management. There should never be an exact pattern of MetS management since a comprehensive treatment should always be tailored according to each patients risk factors profile. Finally, a sustained and good control over BP, weight, blood glucose and lipid profile, would hopefully reduce future morbidities among hypertensive individuals with MetS.

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