

LETTER TO THE EDITOR

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2018 Korean society of hypertension guidelines for the management of hypertension: part III-hypertension in special situations

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Abstract

Treatment of hypertension improves cardiovascular, renal, and cerebrovascular outcomes. However, the benefit of treatment may be different according to the patients' characteristics. Additionally, the target blood pressure or initial drug choice should be customized according to the special conditions of the hypertensive patients. In this part III, we reviewed previous data and presented recommendations for some special populations such as diabetes mellitus, chronic kidney disease, elderly people, and cardio-cerebrovascular disease.

Keywords: Antihypertensive treatment, Blood pressure, Cardiovascular complications, Cardiovascular risk, Guidelines, Hypertension

Hypertension in special situations

White coat hypertension and masked hypertension

Recommendations	Class	Level	References
It is reasonable to exclude the presence of white coat hypertension (HTN) by using either ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM) before initiation of antihypertensive medication.	I	C	[1]
It is reasonable to check ABPM or HBPM before change of antihypertensive drug treatment intensification.	Ila	C	[2]
It is reasonable to check ABPM or HBPM for the adults with prehypertension or suspected of masked HTN	Ila	B	[3]
For the patients with masked HTN, lifestyle modifications and antihypertensive drug therapy may be reasonable.	Ila	C	[4]

It is important to detect white coat HTN [high office blood pressure (BP) but normal out-of-office BP] and masked HTN (normal office BP but high out-of-office BP)

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using out-of-office BP measurement. White coat effect is more frequently observed in women and older adults. If the diagnosis is not made correctly, it may result in side effects associated with unnecessary medication. Therefore, it is recommended to exclude white coat HTN as much as possible before initiating antihypertensive medication. In patients who are already on medication, it is important to check the effectiveness before adding medication for more aggressive treatment.

For the patients with white coat HTN, lifestyle modifications and regular BP monitoring are recommended. Although there is little evidence, pharmacological treatment as well as lifestyle modifications could be considered when metabolic disturbances and/or subclinical organ damage occurs with white coat HTN [5]. Pharmacological treatment for masked HTN may be beneficial because it has shown a similar cardiovascular (CV) risk profile as sustained HTN [4, 6, 7]. Masked HTN has a higher risk of cardiovascular disease (CVD), thus thorough treatment is considered. There are no clear criteria for the diagnosis of masked HTN and the threshold or reproducibility [8, 9]. However, masked HTN is more common in smokers or in patients with work-related stress and it is observed in about 30% among patients with prehypertension. Special attention should be paid to the



patients with metabolic syndrome with high cardiovascular risk, target organ damage, diabetes mellitus (DM), chronic kidney disease (CKD), smokers, heavy drinking, exercise induced hypertension, and occupational stress for the diagnosis and treatment of masked HTN.

Metabolic syndrome

Recommendations	Class	Level	References
Lifestyle modifications such as diet, weight reduction, and exercise are recommended for the hypertensive patients with metabolic syndrome.	I	B	[10, 11]
Angiotensin converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs) or calcium channel blockers can be considered as the antihypertensive agents for patients with metabolic syndrome.	IIa	C	
Antihypertensive medication is not recommended for prehypertensive patients with metabolic syndrome.	III	A	[12–14]

Many hypertensive patients have obesity and metabolic abnormalities with alterations of lipid and glucose metabolism. Furthermore, subclinical organ damage is common in these patients. Metabolic syndrome consists of abdominal obesity, dyslipidemia, dysglycemia, and raised BP. The criteria for clinical diagnosis of metabolic syndrome are: 1) abdominal obesity; 2) fasting glucose ≥ 100 mg/dL (diabetes included); 3) triglycerides ≥ 150 mg/dL; 4) high-density lipoprotein (HDL)-cholesterol < 40 mg/dL in men and < 50 mg/dL in women; and 5) BP $\geq 130/85$ mmHg [15]. Presence of three or more of these criteria confirms the diagnosis of metabolic syndrome. Abdominal obesity is usually estimated by the measurement of waist circumference. However, cut-off points of waist circumference for abdominal obesity in Korean adults are not established. Cut-off points of waist circumference, which are commonly used, are 1) ≥ 90 cm in men; ≥ 80 cm in women (International Obesity Task Force criteria for Asian-Pacific population); and 2) ≥ 90 cm in men; ≥ 85 cm in women (Korean adult specific values) [15, 16].

The prevalence of metabolic syndrome has been increased over the last 10 years, as reported in the Korean National Health and Nutritional Survey. The prevalence of metabolic syndrome in Korean aged over 30 years is 30.5% [17]. However, the prevalence of metabolic syndrome is twice as high among the hypertensive patients [18].

In Western countries, people with metabolic syndrome have at 1.5–2-fold higher risk of CV events and death than those without metabolic syndrome and incident diabetes is 5-fold higher in people with metabolic syndrome [19, 20].

In Asian countries, metabolic syndrome had a relative risk of incident diabetes of 3–4, which is a little lower

compared to that in Western countries [21, 22]. The most powerful predictor of incident diabetes is hyperglycemia in people with metabolic syndrome. However, metabolic syndrome, even without hyperglycemia, was associated with an increased risk of incident diabetes; the relative risk is 2.4 in Japanese population [22]. In addition to metabolic syndrome, HTN is associated with twice higher risk of incident diabetes [23, 24].

In hypertensive patients with metabolic syndrome, antihypertensive treatment is used to prevent CV morbidity and mortality, while lowering or preventing incident diabetes. Antihypertensive treatment in non-diabetic patients with metabolic syndrome is discussed below, while that treatment for diabetic/CVD patients with metabolic syndrome is discussed in other respective sections of the special situations chapter. Lifestyle modifications, especially weight reduction and regular exercise, are strongly recommended in all hypertensive patients, as they decrease BP, improve metabolic abnormalities, and delay incident diabetes [10, 11].

Hypertensive patients should be treated with antihypertensive medication as well as lifestyle modification, but there is no evidence available for the drug treatment in prehypertensive patients [12–14].

Antihypertensive drugs should lower BP effectively as well as have favorable or neutral effects on insulin sensitivity and metabolic abnormalities. Thus, ACE inhibitors, ARBs, and calcium channel blockers are preferred. Among beta-blockers, vasodilating beta-blockers such as carvedilol and nebivolol can be used as combination therapy with ACE inhibitors/ARBs.

Thiazides and thiazide-like diuretics are avoided as monotherapy or at high doses, but are used as combination therapy or at low doses. High dose diuretics can induce hypokalemia and new onset diabetes, and have unfavorable effects on lipid metabolism. The preferred approach is combination of ACE inhibitors/ARBs with diuretics to minimize their unfavorable effects on glucose and lipid metabolism.

Diabetes mellitus

Recommendations	Class	Level	References
In patients with DM and HTN, systolic BP should be less than 140 mmHg.	I	A	[25–29]
In patients with DM and HTN, diastolic BP should be less than 85 mmHg.	I	B	[30–32]
In patients with DM and CVD, BP should be less than 130/80 mmHg.	IIa	C	[33]
In hypertensive patients with DM, all hypertensive drugs are recommended as first-line antihypertensive agents.	I	A	[27, 32]
ACE inhibitors or ARBs are recommended for patients with microalbuminuria or proteinuria.	I	B	[34–36]

The prevalence of HTN is two-fold in diabetic patients compared to that in the general population, and the occurrence of diabetes is 2.5-fold higher in hypertensive patients [37, 38]. The coexistence of HTN and diabetes causes the progression of CVD, stroke, and renal disease. The high risk of HTN in diabetic patients is related with weight gain, hyperinsulinemia, sympathetic hyperactivity, and salt retention. Additionally, hyperglycemia itself can further increase the risk of HTN by increasing arterial stiffness and progressing atherosclerosis. The nocturnal dipping disappears in diabetic patients, and it is associated with subclinical organ damage such as left ventricular hypertrophy (LVH) and microalbuminuria. In the UK Prospective Diabetes Study (UKPDS)-36, each 10 mmHg decrease in mean systolic blood pressure (SBP) was associated with risk reductions of 12% for any complication related to diabetes, 15% for deaths related to diabetes, 11% for myocardial infarction, and 13% for microvascular complications [39]. Previous studies have shown that appropriate BP control can reduce the incidence of CVD [34, 40–43].

The recommended target for BP in diabetic patients is < 140/85 mmHg. In previous guidelines, the recommended BP was < 130/80 mmHg or < 140/80 mmHg in diabetic patients [34, 40–43]. However, recent studies have failed to show any beneficial effect on CV outcome with strict BP control [28, 44]. Due to the beneficial effect of strict BP control in Systolic Blood Pressure Interventional Trial (SPRINT)-eligible patients among Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, BP should be lowered less than 130/80 mmHg in patients with diabetes and CVD [33].

According to a recent meta-analysis, all classes of antihypertensive agents, such as ACE inhibitors, ARBs, calcium channel blockers, beta-blockers and diuretics can be used in diabetic patients [31]. However, ACE inhibitors/ARBs are recommended as first-line antihypertensive therapy in patients with microalbuminuria or proteinuria [32, 34–36]. The superiority of one antihypertensive class over others is controversial. The choice of a particular class is less significant in practice because two or more antihypertensives should be combined in order to obtain sufficient decrease in BP in most diabetic patients. However, the combination of beta-blockers and thiazide diuretics is not recommended as it could worsen glucose control by increasing insulin resistance. Sodium-glucose co-transporter-2 (SGLT-2) inhibitor can decreased BP, thus it should be used cautiously with antihypertensive medication [45–47].

Hypertension in older adults

Recommendations	Class	Level	References
SBP goal of less than 140 mmHg is recommended for noninstitutionalized, ambulatory community-dwelling adults (≥65 years of age).	Ila	B	[48, 49]

The treatment of HTN in older adults reduces the risk of CVD and mortality. The benefit of treatment is also observed with regard to isolated systolic HTN. Accordingly, HTN needs to be actively diagnosed and treated in older adults.

However, the benefit of pharmacological treatment for grade I hypertensive patients older than 80 years remains controversial. Thus, the characteristics of the patient should be considered. The characteristic findings of elderly hypertensive patients are increased SBP and widened pulse pressure due to increased central arterial stiffness. Moreover, atherosclerotic renovascular HTN is commonly observed. Non-dipper, increased daytime BP variability, and orthostatic or postprandial hypotension are also characteristic findings in elderly patients with HTN.

The non-pharmacological treatment in elderly HTN patients is effective; however, the impact on the patient’s quality of life should be considered [50]. Target SBP for older patients is < 140 mmHg, but orthostatic hypotension should be avoided [51]. Additional studies are required to confirm the target SBP among the frail older patients. The initial dose of the pharmacological treatment is reduced by half in younger patients, and gradually increased. Elderly hypertensive patients without co-morbidities should be treated with ACE inhibitors, ARBs, calcium channel blockers, and diuretics [52–55]. Beta-blockers do not improve prognosis as much as other drug classes in elderly hypertensive patients. However, beta-blockers would be effective in patients with angina, heart failure, or tachycardia. Combination therapy with two or more drugs should be considered if the BP is not controlled with monotherapy. Patients with co-morbidities require special consideration. It is safe to slowly lower the BP in elderly patients. Complications caused by medication should be monitored when increasing the drug dose. Orthostatic hypotension should be periodically checked by positional BP measurement.

Cardiac diseases

Coronary artery disease

Recommendations	Class	Level	References
In adults with coronary artery disease (CAD) and HTN, a BP target of 130/80 mmHg is recommended.	Ila	B	[56–60]

HTN is a major risk factor of CAD and is associated with the occurrence of myocardial infarction. The incidence of ischemic heart disease increases when SBP is > 140 mmHg and mortality increases when SBP is > 120 mmHg [61, 62]. Considering J-curve phenomenon, it is important not to decrease DBP < 70 mmHg, especially in older patients, multivessel disease without revascularization, and diabetic patients. The preferred drugs within 1 month after acute myocardial infarction are beta-blockers and ACE inhibitors [63, 64]. Any first line antihypertensive drugs are

available in patients with ischemic heart disease, but beta-blockers and calcium channel blockers are initially considered for the symptomatic CAD.

Chronic heart failure

Recommendations	Class	Level	References
In adults with HTN and increased risk of heart failure, a BP target of 130/80 mmHg is recommended.	I	B	[65]
Adults with heart failure with reduced ejection fraction (HFrEF) and hypertension should be prescribed to attain a BP of 130/80 mmHg.	I	B	[66]

HTN is the most important risk factor in heart failure [67–69]. Strict BP control in hypertensive patients with HFrEF is helpful for the prevention of heart failure aggravation and CV events as well as mortality reduction [70]. Most BP-lowering drugs such as diuretics, beta-blockers, ACE inhibitors, and ARBs are effective in the prevention of heart failure. In decompensated heart failure patients, a 25% reduction of BP can be achieved with vasodilator and loop diuretics within few hours. For the HFrEF and hypertensive patients, beta-blockers, ACE inhibitors, ARBs, and aldosterone antagonists are recommended considering the beneficial effects on mortality reduction and re-hospitalization. Thiazides can be used for the additional BP lowering. A dihydropyridine calcium channel blocker can be used, but in contrast, a non-dihydropyridine calcium channel blocker such as verapamil or diltiazem should not be used because of negative inotropic effects [71]. HTN is also a risk factor for heart failure with preserved ejection fraction (HFpEF) and it is likely that strict BP control is helpful for the CV events and mortality reduction in HFpEF patients.

Atrial fibrillation

Hypertension is one of the risk factor for atrial fibrillation and atrial fibrillation is frequently observed in hypertensive patients, but it can be prevented with BP control [72, 73]. Patients with HTN and atrial fibrillation have a high risk of thromboembolism and need chronic antithrombotic treatment if no contraindications are present [74]. Recently, antithrombotics such as direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) have been shown to be effective and relatively safe compared with the classic antithrombotic therapy using warfarin [75, 76]. In patients with atrial fibrillation and HTN, lowering the BP can decrease the incidence of fatal bleeding during antithrombotic treatment. However, BP should be maintained above 120/70 mmHg [77, 78].

Vascular diseases

Carotid atherosclerosis

The progression of carotid atherosclerosis can be prevented by lowering BP. For this purpose, calcium channel blockers and ACE inhibitors are superior to beta-blockers and diuretics [79, 80].

Arterial stiffness

Most antihypertensive drugs decrease vascular stiffness because BP reduction can decrease vascular wall stress and pulse wave velocity. However, it is not clear whether there is any difference in the reduction of arterial stiffness according to drug class [81–83]. Renin-angiotensin-aldosterone inhibitors can decrease the pulse wave velocity, independent of BP reduction [84–86]. Vasodilating beta-blockers are better for central aortic SBP reduction compared to atenolol. Although an improvement in vascular stiffness with antihypertensive drugs has been reported in numerous studies, it is still uncertain whether the improvement in vascular stiffness is closely related to the CV benefits, except for CKD patients [87]. Further studies are needed to determine the relationship between vascular stiffness and CV outcomes.

Peripheral arterial disease

It is important to control the CVD risk factors because patients with peripheral arterial disease (PAD) have a higher risk of CV mortality (10-year mortality of 40%) [88]. Lowering the SBP decreases the leg amputation rate and mortality in hypertensive patients with diabetes and PAD [39]. The target BP is around 130/80 mmHg in patients with PAD according to a recent meta-analysis and the SPRINT trial [89–91].

Lifestyle modifications such as salt restriction, weight control, moderation of alcohol intake, and regular aerobic exercise are very important. Pharmacological treatment consists of ACE inhibitors, ARBs, and aspirin [92, 93]. ACE inhibitors decrease long-term CV events from either BP lowering effects or indirect BP lowering effects [41, 94]. However, other drugs are also effective in the reduction of CV events associated with BP lowering [90, 94–97]. Furthermore, it is important to evaluate and manage CV risk factors other than HTN, such as lipid and blood glucose. The appropriate drugs are determined according to the presence of heart failure or coronary artery disease. In general, beta-blockers are relatively contraindicated to avoid worsening of PAD symptoms. However, some reports have revealed that beta-blockers do not aggravate the symptoms in patients with mild to moderate PAD. Therefore, beta-blockers are effective in PAD patients with co-existing ischemic heart disease or tachycardia [98, 99]. Renal artery stenosis is frequently observed in patients with HTN and PAD. Overall, ongoing evaluation of the disease and monitoring are needed during HTN treatment [100].

Aortic disease

In patients with aortic aneurysm, it is strongly recommended to lower the BP to the lowest levels tolerated by the patient [101]. Beta-blockers are preferred owing to their ability to reduce the maximum ventricular ejection of the left ventricle, as well as the BP and heart rate. In acute aortic syndrome, including aortic dissection, the BP and heart rate should be controlled aggressively with antihypertensive medication including beta-blockers. BP should be lower less than 140 mmHg within 1 h and maintained less than 120 mmHg thereafter. It is recommended to reduce BP around 130/80 mmHg in patients with atherosclerosis [60, 91].

Chronic kidney disease

Recommendations	Class	Level	References
In adults with HTN and CKD (with albuminuria ≥ 30 mg/day, or albumin-to-creatinine ratio ≥ 30 mg/g), treatment with ACE inhibitor or ARB may be reasonable.	Ila	B	[30, 102–104]

CKD is defined as the presence of kidney injury for > 3 months, with markers of kidney injury being a decrease in estimated glomerular filtration rate (eGFR) (< 60 mL/min/1.73 m²), urinary abnormalities including albuminuria (≥ 30 mg/day or albumin-to-creatinine ratio ≥ 30 mg/g), hematuria and pyuria, electrolyte disturbances caused by tubular dysfunction, renal structural abnormalities detected by imaging or biopsy procedures, and renal transplants. CKD patients frequently suffer from HTN; hence, the rate of decline in renal function and the incidence of CV complications can be reduced with HTN control [105, 106]. However, we still need to determine the target BP levels, optimal tools to be used in HTN control, and the real benefits and risks associated with treatment [107].

The recent 2017 American College of Cardiology/American Heart Association/American Society of Hypertension guideline recommended a BP target of < 130/80 mmHg in all CKD patients [108]. However, previous major clinical trials failed to show any beneficial effect of strict BP control in non-proteinuric CKD patients. Accordingly, CKD patients without albuminuria are recommended to maintain BP < 140/90 mmHg [109–111]. On the other hand, randomized controlled trials have suggested that a lower target may be beneficial in proteinuric CKD patients. Thus, we recommend that CKD patients with albuminuria should be treated to maintain SBP < 130 mmHg [30, 112–114]. BP target levels do not depend on the presence of DM.

Lifestyle modifications should be used as a basic tool for BP control in all hypertensive CKD patients. Although no large scale randomized controlled trials have reported the effects of lifestyle modification on clinical outcomes in CKD patients, the beneficial effects can be inferred from

the results reported in previous studies in general populations [115–121]. The 2011–2014 Korea National Health and Nutrition Examination Survey showed that body mass index (BMI) associated with the risk of CKD [122]. We recommend achieving or maintaining a healthy weight (BMI 20 to 25), lowering salt intake to < 90 mmol (< 2 g) per day of sodium unless contraindicated, undertaking regular exercise compatible with CV health and tolerance, limiting alcohol intake to < 2 standard drinks per day for men and < 1 standard drink per day for women.

Pharmacological treatment in CKD patients includes single or multiple antihypertensive therapies to achieve the target BP. Although any antihypertensive can be used in CKD patients, ACE inhibitors or ARBs have been reported to be renoprotective owing to the reduction in albuminuria and improvement in the rate of decline of the glomerular filtration rate [30, 102–104]. Thus, we recommend that ACE inhibitors or ARBs should be used in CKD patients with albuminuria. ACE inhibitors or ARBs are preferred in both diabetic and non-diabetic CKD patients with either microalbuminuria (30–300 mg/day) or macroalbuminuria (> 300 mg/day). However, the combination of ACEIs and ARBs in CKD patients are not recommended.

It should be noted that there are occasions when the BP target and the preferred agent mentioned above may be inappropriate. Treatment should be individualized based on the patient's age, presence of albuminuria and comorbidities. Diabetic or elderly patients need to be questioned about orthostatic dizziness because of the possibility of postural hypotension [123–125]. ACE inhibitors and ARBs are contraindicated in bilateral renal artery stenosis, and should be used with caution in patients with diffuse atherosclerosis.

Cerebrovascular diseases

The risk of ischemic and hemorrhagic stroke increases proportionally as the BP increases, with HTN being the most common modifiable risk factor in stroke prevention and having the highest attributable risk for stroke in the population. HTN treatment, particularly SBP control, will remarkably reduce the incidence of stroke. For the management of high BP, lifestyle modifications (weight loss, low-fat diet, reduced salt intake, exercise or physical activity, moderation of alcohol intake, and smoking cessation) must routinely precede drug therapy. According to an epidemiologic study, with each increase of 20/10 mmHg from BP level of 115/75 mmHg or higher, deaths from stroke increased at least two-fold. Conversely, a 10/5 mmHg decrease in BP resulted in a 40% decrease in deaths from stroke [61]. In addition, a meta-analysis of clinical studies showed that stroke risk was expected to decrease by about 30–40% by lowering the BP by 10/5 mmHg with drug therapy, regardless of the past history of

the patient [63, 126, 127]. For the primary prevention of stroke, it is recommended to maintain the BP < 140/90 mmHg. Although it remains unknown whether a specific drug or class is superior to other antihypertensive drugs in the prevention of stroke, a limited number of reports have shown that calcium channel blockers, ACE inhibitors, or ARBs are superior to beta-blockers [128]. However, for the primary prevention of stroke, it is most important to lower the BP based on an individualized approach for each patient rather than the choice of a specific drug or drug class [129].

Acute ischemic stroke

Recommendations	Class	Level	References
If blood pressure is high in patients with acute ischemic stroke suitable for intravenous thrombolytic therapy, we recommend lowering the BP to less than 185/110 mmHg before initiating intravenous thrombolytic therapy.	I	B	[130, 131]
BP in patients with acute ischemic stroke should be reduced to 185/110 mmHg or lower before intravenous thrombolytic therapy and maintained below 180/105 mmHg for 24 h.	I	B	[132]
Starting or resuming anti-hypertensive medication during hospitalization in ischemic stroke patients with BP greater than 140/90 mmHg who are neurologically stable is safe and reasonable to improve long-term BP control, unless contraindicated.	IIa	B	[133, 134]
In patients with BP of 220/120 mmHg or higher who did not receive intravenous thrombolysis or thrombectomy, and have no comorbid conditions requiring acute antihypertensive treatment, the benefit of initiating or reinitiating treatment of HTN within the first 48 to 72 h is uncertain. It might be reasonable to lower BP by 15% during the first 24 h after onset of stroke	IIb	C	[135]
In patients with BP less than 220/120 mmHg who did not receive intravenous thrombolysis or endovascular treatment and do not have a comorbid condition requiring acute antihypertensive treatment, treatment of HTN within the first 48 to 72 h after an acute ischemic stroke is not effective to prevent death or dependency.	III	A	[133, 134, 136]

In general, the BP rises in acute ischemic stroke [137]. It is assumed that BP increases owing to the acute stress, previous HTN, and the automatic compensation in an attempt to maintain perfusion of the brain tissue in the ischemic state. Thus, continuous BP monitoring is important, as a sudden drop in BP should be avoided to maintain the appropriate perfusion to the brain. Although a previous study has shown that ARB administration for 1 week in stroke patients within a week of the attack reduced the mortality after a 12-month period, large-scale studies are needed [41, 138]. Conversely, because active

treatment against rising BP would reduce the perfusion to the ischemic area and expand the area of the infarction, it is undesirable to lower the BP actively within the period of 1 week of the acute ischemic stroke [7, 139].

When thrombolytic therapy is used in the hyperacute period of an ischemic stroke, the incidence of bleeding is closely related to the BP before and after thrombolysis; hence, the target BP should be < 185/110 mmHg. For thrombolytic therapy using tissue-plasminogen activator (t-PA), the drug could only be administered after the BP was < 185/110 mmHg. The antihypertensive regimens consisting of intravenous drugs such as labetalol, nicardipine, diltiazem, nitroglycerin, and nitroprusside are recommended [140–143]. In the acute phase of the ischemic stroke, it is recommended to use antihypertensive drugs only when BP is > 220/120 mmHg, to avoid a decrease in the cerebral perfusion around the infarct area [144]. Target BP levels should be 85–90% of the baseline BP. However, in cases of hypertensive encephalopathy, aortic dissection, acute renal failure, acute pulmonary edema, and acute myocardial infarction, it is recommended to lower the BP sufficiently in order to prevent complications associated with the elevated BP itself [140, 141].

Acute parenchymal hemorrhage

Recommendations	Class	Level	References
If the SBP of a patient with acute parenchymal hemorrhage within 6 h of the onset is 150–220 mmHg, immediate lowering of SBP may be considered with a target SBP above 140 mmHg.	IIb	A	[145, 146]
In adults with intracerebral hemorrhage who present with SBP greater than 220 mmHg, it is reasonable to use continuous intravenous drug infusion and close BP monitoring to lower SBP.	IIa	C	[147–149]

From a theoretical viewpoint, the optimal BP treatment in the acute phase of a parenchymal hemorrhage could prevent re-bleeding and subsequent expansion of a hematoma and edema; hence, it is recommended to lower the BP during the acute phase of the hemorrhage. If the SBP is ≥200 mmHg or if the mean BP is ≥150 mmHg, the BP should be lowered by monitoring BP every 5 min. In patients with increased intracranial pressure, BP should be lowered by maintaining the cerebral perfusion pressure between 60 and 80 mmHg using an intracranial pressure monitoring device only when the SBP is > 180 mmHg or the mean BP is > 30 mmHg. Because a sudden drop of BP during the acute phase is associated with higher mortality rates, it is recommended to maintain a cerebral perfusion pressure of ≥60 mmHg. When the SBP is 180 mmHg or the mean BP is 130 mmHg—as long as there is no evidence of increased intracranial pressure, with the assessment of BP

every 15 min—the BP should be lowered below the level of 80% of baseline BP, <160/90 mmHg, or mean BP <110 mmHg. Antihypertensive regimens including intravenous drugs such as labetalol, nicardipine, diltiazem, nitroglycerin, and nitroprusside are recommended [150]. Despite recent studies showing benefits associated with lowering BP to less than 140 mmHg during the acute phase, the supportive evidence is insufficient; hence, the BP should not be reduced to below 140 mmHg [145, 146, 151].

Secondary prevention of stroke

Recommendations	Class	Level	References
Patients with previously treated HTN who experience stroke or transient ischemic attack should be advised to resume HTN medication a few days after stroke for the prevention of recurrent stroke or vascular disease.	I	A	[76, 152, 153]
We recommend thiazide diuretic, ACE inhibitor/ARB or combination treatment consisting of a thiazide diuretic plus ACE inhibitor/ARB for the treatment of HTN in stroke or transient ischemic stroke patients.	I	A	[76, 152, 154]
It is reasonable to consider calcium channel blockers to control HTN in stroke or transient ischemic stroke patients.	Ila	C	[155, 156]
Patients without HTN treatment are advised to start HTN treatment several days after stroke or transient ischemic attack to prevent stroke and vascular disease recurrence if BP is above 140/90 mmHg.	I	B	[152–154]
The usefulness of antihypertensive treatment has not been established when blood pressure is below 140/90 mmHg after stroke or transient ischemic attack.	IIb	C	[157]
Patients with lacunar infarction, a BP goal of less than 130/80 mmHg may be reasonable.	IIb	B	[158]

HTN treatment as a measure of secondary prevention after stroke significantly reduces mortality and the recurrence of stroke or vascular diseases [126, 154, 159, 160]. Regardless of the history of HTN, treatment of HTN after stroke significantly reduces the mortality and complications associated with HTN. Lifestyle modifications should be maintained in addition to the pharmacological treatment. For the selection of the optimal antihypertensive drugs, the individual characteristics of the patient such as the presence of extracranial cerebrovascular disease, kidney disease, heart disease, and diabetes should be considered. In a recent meta-analysis, a combination therapy using ACE inhibitors and diuretics is preferred [154].

Erectile dysfunction

Erectile dysfunction is considered to be one of the a CV risk factors associated with poor prognosis [161]. Therefore, risk factors such as DM, dyslipidemia, and smoking should be controlled aggressively, and lifestyle modifications should be recommended to the patients

with erectile dysfunction to reduce the CV risk. However, most cases of the erectile dysfunction are not properly diagnosed by doctors and only a minority of patients seeks medical advice. Therefore, more cautious history taking and comprehensive management are required for the improvement of CV prognosis among hypertensive patients with erectile dysfunction [162].

In general, the prevalence of erectile dysfunction associated with antihypertensive medication is reported to be 0–25%, but the prevalence may be affected by underlying conditions such as endothelial dysfunction, and oxidative stress [163]. Erectile dysfunction related to antihypertensive medication is usually observed within 4 weeks. Beta-blockers and diuretics are known to cause erectile dysfunction, and ACE inhibitors and calcium channel blockers are neutral, whereas ARBs are reported to be beneficial [164]. A vasodilating beta-blocker such as carvedilol, nebivolol, and labetalol may be an alternative for hypertensive patients with erectile dysfunction. A phosphodiesterase-5 (PDE5) inhibitor is relatively safe and effective in patients with erectile dysfunction caused by antihypertensive medications, and the additional BP lowering effect is negligible. However, the BP after administration of PDE5 inhibitors should be closely monitored and PDE5 inhibitors must not be co-administered with nitrates [165, 166].

Pregnancy

High BP occurring during pregnancy can be divided into four categories: 1) chronic HTN in pregnancy: existing HTN or taking antihypertensive medication before the 20th week of pregnancy; 2) gestational HTN: newly diagnosed HTN after the 20th week of pregnancy in the absence of proteinuria; 3) pre-eclampsia: HTN diagnosed after 20 weeks of pregnancy accompanied by proteinuria (albumin more than 300 mg in 24 h urine or urine albumin/creatinine ratio of 300 mg/g or greater); and 4) pre-eclampsia superimposed on chronic HTN: pre-eclampsia diagnosed in the chronic HTN pregnant women. Based on the BP level, it is classified as mild: 140–149/90–99 mmHg, moderate: 150–159/100–109 mmHg, and severe: 160/110 mmHg or higher.

Generally, there are few controversies regarding drug treatment for BP of >160/110 mmHg or higher. Previous studies have reported that patients with BP >150/95 mmHg are more likely to be hospitalized due to incident stroke during the peripartum period [167, 168]. In pregnancy, BP should be controlled below 150/100 mmHg, but it is not recommended to lower DBP below 80 mmHg [169, 170].

Antihypertensive drugs used during pregnancy are methyldopa, labetalol, and nifedipine. Specific drugs are selected in consideration of the drug class previously used, their side effects, and the risk of teratogenicity.

Beta-blockers can cause fetal growth retardation, thus they can be used later in the pregnancy. Diuretics should be prescribed cautiously because they can induce volume depletion. ACE inhibitors or ARBs may increase the risk of congenital malformations in pregnancy, it is recommended to replace these drugs before pregnancy or when planning a pregnancy. If a pregnancy is detected during the administration of ACE inhibitors or ARBs, they should be discontinued and replaced promptly. In emergency situations, such as pre-eclampsia, intravenous labetalol is recommended but intravenous nitroprusside or nitroglycerin could be alternatives. After delivery, BP should be controlled below 140/90 mmHg.

Gestational HTN and preeclampsia are associated with an increased risk of developing HTN after delivery and pre-eclampsia is a risk factor for CVD. Patients with a history of pre-eclampsia have about a two-fold risk of ischemic heart disease, stroke, and venous thrombosis and a four-fold risk of developing sustained HTN. Especially in cases of preeclampsia within 32 weeks of gestation, stillbirth, and fetal growth retardation, the risk of HTN increases much more. Thus, active BP control and lifestyle modification even after delivery is strongly recommended for patients with HTN during pregnancy.

Women and hypertension

In younger populations, women have lower prevalence of HTN than men. But after menopause, the prevalence of HTN in women increases rapidly as reaches the prevalence in men in their 60s and prevalence becomes even higher than that in men in their 70s or 80s. As for age, the increase in pulse pressure is the same between men and women, however, the systolic and diastolic BPs are higher in women after menopause. Care should be taken in the diagnosis of HTN in menopausal women, because white coat HTN occurs more frequently in these women.

After menopause, weight gain, hormonal changes, and psychological changes occur [171]. In particular, the deficiency of estrogen induces menopausal symptoms and CV events [172]. In the past, hormone replacement therapy (HRT) was widely recommended after menopause, but clinical studies found no beneficial effects for CVD or it sometimes worsened, and therefore, HRT is no longer recommended. Because HRT can increase BP, women who have a greater chance of developing HTN need to be carefully observed for a few months [173].

There is no difference in HTN treatment between women and men. Additionally, there is no difference in BP reduction and drug effects between women and men [174]. Oral contraceptives can increase BP in some subjects, and the occurrence of accelerated or malignant HTN is rare. Family history of HTN, past history of HTN during pregnancy, kidney disease, obesity, or oral

contraceptive use can increase the risk of BP increase. Therefore, in the early period of oral contraceptive use, BP needs to be carefully monitored, while periodic measurements are recommended thereafter.

Sleep apnea

Recommendations	Class	Level	References
Consider continuous positive pressure ventilation for patients with sleep apnea with HTN.	IIb	B	[175–178]

Continuous positive airway pressure (CPAP) therapy is effective in improving sleep apnea. However, in studies concerning sleep apnea, CPAP was reported cause a 2–3 mmHg decrease of BP, and the effects differed according to adherence, disease severity, and daytime sleepiness [175–177, 179].

Cognitive impairment

Recommendations	Class	Level	References
Consider HTN treatment to prevent cognitive dysfunction and dementia in adult hypertensive patients.	IIa	B	[55, 180–184]

Vascular disease and its related factors are the major risk factors of dementia, including Alzheimer's disease [185, 186]. HTN is a major risk factor for ischemic microvascular disease and cerebral white matter disease, which can lead to cognitive dysfunction by damaging the cerebral nerve circuit [187–189]. It has been reported that Alzheimer's dementia and other dementia were less likely to develop when systolic BP was well controlled. Furthermore, it was more effective in preventing dementia when treatment was started individuals in their 50s rather than in those treated in their 60s [185, 190]. In most randomized clinical trials, HTN treatment did not have a negative impact on cognitive dysfunction and dementia. However, results from studies have been inconsistent due to lack of study power, insufficient follow-up duration, and inadequate tools for cognitive evaluation [55, 180–184].

Abbreviations

ABPM: Ambulatory blood pressure monitoring; ACE: Angiotensin converting enzyme; ARB: Angiotensin II receptor blocker; BMI: Body mass index; BP: Blood pressure; CAD: Coronary artery disease; CKD: Chronic kidney disease; CPAP: Continuous positive airway pressure; CT: Computed tomography; CV: Cardiovascular; CVD: Cardiovascular disease; DBP: Diastolic blood pressure; DM: Diabetes mellitus; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; HBPM: Home blood pressure monitoring; HDL: High-density lipoprotein; HRT: Hormone replacement therapy; HTN: Hypertension; LVH: Left ventricular hypertrophy; PAD: Peripheral arterial disease; PDE5: Phosphodiesterase-5; SBP: Systolic blood pressure; t-PA: Tissue plasminogen activator

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Authors' contributions

K-IK reviewed previous papers and drafted the manuscript. S-HI reviewed previous papers and drafted the manuscript. GHK reviewed previous papers and drafted the manuscript. HCK reviewed previous papers and drafted the manuscript. JHK reviewed previous papers and drafted the manuscript. H-YL reviewed previous papers and drafted the manuscript. JHL reviewed previous papers and drafted the manuscript. J-MP reviewed previous papers and drafted the manuscript. SP reviewed previous papers and drafted the manuscript. WBP reviewed previous papers and drafted the manuscript. JS reviewed previous papers and drafted the manuscript. SCC reviewed previous papers and drafted the manuscript. All authors read and approved the final manuscript. As the corresponding author, SCC had full access to all the data in the study and was responsible for the decision to submit this manuscript for publication.

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