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GUIDELINES (JSH 2014)

Chapter 10. Hypertension in women

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POINT 10

Pregnancy-associated hypertension

1. **Drug therapy for pregnancy-induced hypertension (PIH) should be started at a blood pressure of ⩾160/110 mm Hg. However, if systolic blood pressure is ⩾180 mm Hg or diastolic blood pressure is ⩾120 mm Hg in pregnant or post-partum women, antihypertensive treatment should be started under a diagnosis of hypertensive emergency. If an urgent decrease in blood pressure is necessary, drugs for intravenous injection should be used (Recommendation grade: C1, Evidence level: III).**
2. **When selecting antihypertensive drugs for hypertension during pregnancy, methyldopa, hydralazine or labetalol should be selected as a first-choice drug before week 20 of pregnancy (Recommendation grade: B, Evidence level: II).**
3. **After week 20 of pregnancy, nifedipine may be used as a first-choice drug in addition to the three above drugs (Recommendation grade: B, Evidence level: II).**
4. **It is recommended that nifedipine should be administered regardless of the dosage form only when the advantage of treatment exceeds its risk (for pregnant women after week 20 of pregnancy). Basically, a long-acting preparation should be used. The sublingual administration of capsule preparations should not be performed (Recommendation grade: D, Evidence level: II).**
5. **If a sufficient decrease in blood pressure is not achieved using a single drug, combination therapy with two drugs should be considered. Methyldopa and labetalol are classified as sympatholytic drugs, and hydralazine and long-acting nifedipine are classified as vasodilators. Therefore, if two drugs are concomitantly used, drugs with different mechanisms of antihypertensive action should be combined. Before week 20 of pregnancy, a combination of methyldopa and hydralazine or that of labetalol and hydralazine is recommended. After week 20 of pregnancy, combination therapy with a sympatholytic drug (either methyldopa or labetalol) and a vasodilator (either hydralazine or sustained-release nifedipine) is recommended (Recommendation grade: C1, Evidence level: IV).**
6. **If a decrease in blood pressure is insufficient, combination therapy with two or three drugs should be considered. However, it should be switched to drugs for intravenous injection (nicardipine, nitroglycerin or hydralazine), if necessary, based on blood pressure and maternal/fetal conditions. For blood pressure control with drugs for intravenous injection, attention must be paid to the fetal condition, and fetal heart rate monitoring should be conducted (Recommendation grade: C1, Evidence level: IV).**
7. **Concerning the use of other β-blockers and Ca channel blockers, informed consent must be obtained from patients after explaining the contents of treatment, and these drugs should be used under the physician's responsibility.**
8. **If eclampsia is suspected or present, magnesium sulfate ($MgSO_4$) should be intravenously administered (Recommendation grade: A, Evidence level: I).**
9. **In women who may be pregnant and in those who are pregnant, ACE inhibitors and ARBs should not be used as a rule (Recommendation grade: D, Consensus, Evidence level: II).**

Postmenopausal hypertension

1. **Oral contraceptives increase blood pressure in some cases; caution is needed.**
2. **Changes in blood pressure during pregnancy and the presence or absence of proteinuria should be confirmed with reference to a mother-and-baby notebook.**

Hypertension in women is classified into three types: pregnancy-associated hypertension, an estrogen regression (menopause)-related increase in blood pressure and primary/secondary hypertension (similar to that in males). In this section, pregnancy-associated hypertension and postmenopausal hypertension are primarily introduced.

1. PREGNANCY-ASSOCIATED HYPERTENSION (PIH)

Classification of pregnancy-associated hypertension is summarized in Table 10-1. Briefly, PIH refers to a condition in which systolic blood pressure is ⩾140 mm Hg or diastolic blood pressure is ⩾90 mm Hg after week 20 of pregnancy, and it returns to a normal value before 12 weeks after delivery. Concerning normal pregnancy-related changes in blood pressure, these begin to decrease in the initial phase of pregnancy, returning to the pre-pregnancy value before weeks 20–32 of pregnancy, and slightly increases from week 32 of pregnancy until delivery (Figure 10-1).[888] In normal pregnant women, such changes in blood pressure are observed, but blood pressure increases from week 20 of pregnancy in many patients with PIH.

Recently, the pathogenesis of PIH has been rapidly clarified. Although various theories have been proposed, it is assumed that vascular dysplasia may occur on placentation due to some etiological factor, increasing blood pressure through the release of cytokines and tyrosine kinase into maternal blood.[889] Among these, soluble fms-like tyrosine kinase 1 has been emphasized, and a high soluble fms-like tyrosine kinase 1/placental growth factor ratio is useful for the diagnosis of PIH.[890]

Table 10-1 Classification of pregnancy-associated hypertension

1. Gestational hypertension
   Hypertension (systolic blood pressure ⩾140 mm Hg or diastolic blood pressure ⩾90 mm Hg) occurring after week 20 of pregnancy but resolving within 12 weeks after delivery.

2. Pre-eclampsia
   Hypertension (systolic blood pressure ⩾140 mm Hg or diastolic blood pressure ⩾90 mm Hg) with proteinuria (basically ⩾300 mg per day) occurring after week 20 of pregnancy but resolving within 12 weeks after delivery.

3. Eclampsia
   Convulsive seizure occurring after week 20 of pregnancy. Exclusion of epilepsy and secondary convulsion is essential. Eclampsia is classified into three types: eclampsia gravidarum, intrapartum eclampsia and puerperal eclampsia based on the timing of convulsive seizure.

4. Superimposed pre-eclampsia
   (a) Chronic hypertension diagnosed before pregnancy or before week 20 of pregnancy, along with proteinuria emerging after week 20 of pregnancy.
   (b) Aggravation of pre-existing (before pregnancy or before week 20 of pregnancy) hypertension and proteinuria after week 20 of pregnancy. Either one or both aggravations are acceptable.
   (c) Hypertension emerging after week 20 of pregnancy in patients with pre-existing renal diseases that manifest solely as proteinuria.

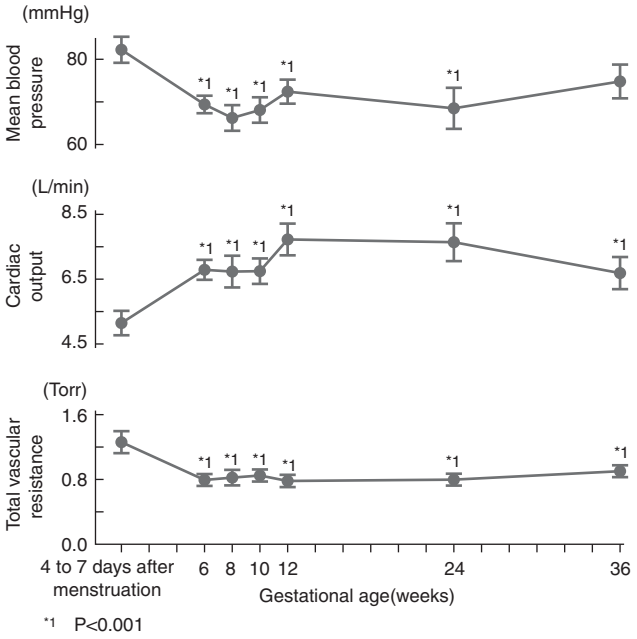

Figure 10-1 Normal pregnancy-related changes in blood pressure. In normal pregnant women, blood pressure begins to decrease immediately after the onset of pregnancy. At this point, the cardiac output slightly increases, but peripheral vascular resistance markedly reduces. Simultaneously, the renal blood flow volume and glomerular filtration rate increase. This tendency reaches a peak in week 12 of pregnancy. Peripheral vascular resistance gradually increases and blood pressure also slightly increases. These parameters return to the pre-pregnancy values in week 36 of pregnancy. A full color version of this figure is available at the Hypertension Research journal online.

In Japan, the rapid aging of society is well advanced, and older pregnant women are not exceptional. Currently, the mean age of pregnant women on delivery is ~30 years. The number of pregnant women with hypertension or diabetes mellitus (complication pregnancy) is also gradually increasing. In such cases, various risks for maternal and fetal conditions must also be adequately explained. In the management of hypertension, renin–angiotensin (RA) system inhibitors have recently been used in many patients, but it is also important to repeatedly explain that pregnancy should always be avoided while taking these drugs.

1) Diagnosis

Many studies have also reported clinic, home and 24-h blood pressure measurement in pregnant women. Some studies have suggested that home blood pressure measurement and ABPM are useful for the early detection of PIH,[891–897] as indicated for hypertension in the general population. These parameters should be adopted in addition to the blood pressure measurement in the clinic; however, currently, a diagnosis should be usually made, according to the criteria for in-clinic blood pressure measurement shown in Table 10-1.

2) Treatment

The basic treatment for PIH is the interruption of pregnancy, and maternal protection must be predominantly considered with respect to antihypertensive therapy for this disease. Considering the two points, the contents of treatment should be explained to patients, and the treatment of PIH should be performed. Simultaneously, it is important to establish a close cooperative relationship with an obstetrician.

As shown in Table 10-2, PIH is classified into mild and severe conditions. This classification is based on the necessity for antihypertensive drugs. In the clinical practice of the obstetrics, 'mild/severe' concept-based diagnosis and treatment are performed, which differ from the classification of hypertension in the general population.

(1) Mild PIH. In pregnant women with PIH, an increase in vascular resistance, a decrease in the cardiac output and a decrease in the circulating plasma volume are observed.[898] This may be because the blood perfusion volume in the uteroplacental circulation is maintained by increasing blood pressure. Therefore, an inappropriate decrease in blood pressure may lead to a decrease in the blood perfusion volume, causing fetal dysgenesis.

In standard treatment of hypertension, guidance is given on salt restriction, but excessive salt restriction may reduce placental blood flow, and a rapid decrease in salt intake should be avoided in pregnant women. However, in those who have been instructed to reduce salt intake before pregnancy, there are no problems regarding the continuation of this strategy.

Some studies have reported that antihypertensive therapy is useful for preventing the progression of this disease to a severe status[899] and fetal dysfunction[900] even when the severity of hypertension is mild. As the number of women who deliver a child at an advanced age or pregnant women with hypertension has been increasing, criteria for the start of antihypertensive drug therapy should be established in the future.

(2) Severe PIH. In patients with severe hypertension, prompt antihypertensive treatment to prevent maternal organ damage (cerebrovascular, heart or kidney damage) is necessary.[901] Antihypertensive drug therapy for PIH should be indicated for patients with a blood pressure exceeding criteria for severe hypertension. Some studies have indicated that, if the pregnancy period is prolonged with continued

Table 10-2 Disease-type classification of pregnancy-induced hypertension

Mild	
blood pressure	Corresponding to either of the following: Systolic blood pressure: ⩾140 mm Hg, but not exceeding 160 mm Hg Diastolic blood pressure: ⩾90 mm Hg, but not exceeding 110 mm Hg
Proteinuria	⩾300 mg per day, <2 g per day
Severe	
blood pressure	Corresponding to either of the following: Systolic blood pressure: ⩾160 mm Hg Diastolic blood pressure: ⩾110 mm Hg
Proteinuria	Patients with a urinary protein level of 2 g per day or more are regarded as having severe proteinuria. As there is no correlation between the semi-quantification of urinary protein using the test paper method with randomly sampled urine and 24-h urine quantification, the severity of proteinuria should be evaluated using a 24-h urine sample as a rule. When only the results of the test paper method with randomly sampled urine are available, patients in whom several fresh urine samples consecutively show positive reactions (3+ or higher: 300 mg dl^{-1} or more) are regarded as having severe proteinuria.

antihypertensive treatment in the immature fetal phase, the fetal prognosis may be improved while avoiding the maternal risk. However, the data are not always sufficient as evidence.[902]

With respect to concrete criteria for the start of drug therapy, there are slight differences among investigators: systolic blood pressure, 160–170 mm Hg and diastolic blood pressure, 105–110 mm Hg.[903,904] In the Guidelines, a criterion for the start of drug therapy is established as ⩾160/110 mm Hg. However, if precursor symptoms for the onset of eclampsia are present, drug therapy must be promptly initiated.[905]

(3) Emergency. If systolic blood pressure is ⩾180 mm Hg or diastolic blood pressure is ⩾120 mm Hg in pregnant or post-partum women, antihypertensive treatment should be started under a diagnosis of hypertensive emergency.

In particular, after week 30 of pregnancy, obstetricians are responsible for hypertension management, including delivery, and should consult specialists in hypertension if necessary.

3) Target of blood pressure control in antihypertensive drug therapy

In patients with PIH, it is necessary to reduce the risk of maternal organ damage without affecting placental blood flow; however, there is no evidence regarding the target for blood pressure control. Generally, a target systolic blood pressure is <160 mm Hg, and a target diastolic blood pressure is <110 mm Hg, or the rate of decrease in the mean blood pressure should be 15–20%. In the Guidelines, target systolic and diastolic blood pressures are established as <160/110 mm Hg. In pregnant women undergoing antihypertensive drug therapy, it is necessary to confirm the absence of abnormalities by maternal physiological function and fetal heart rate monitoring at appropriate points.

4) Selection of antihypertensive drugs

In 2011, the attached inserts for long-acting nifedipine and labetalol were revised as follows: long-acting nifedipine can be administered after week 20 of pregnancy and labetalol may be used in pregnant women or in those who may be pregnant only when the advantage of treatment is considered to exceed its risk. As a result, these drugs became available when the advantage of treatment was considered to exceed its risk, as described for the use of methyldopa and hydralazine, which have commonly been used.

Concerning the use of nifedipine, the contents have been revised as follows: all nifedipine preparations are available, but a long-acting preparation should be primarily used according to recent guidelines. In the JSH 2014 Guidelines, it is recommended that, for the use of nifedipine, long-acting preparations (Adalat CR, Adalat L and Sepamit R) should be used as a rule.[906,907] On the other hand, the sublingual administration of capsule preparations is not recommended.

Based on the new information, the selection of antihypertensive drugs for PIH is described below:

As first-choice antihypertensive drugs, methyldopa, hydralazine (oral) and labetalol should be used. For combination therapy, a combination of two drugs with different antihypertensive action mechanisms is desirable, as methyldopa and labetalol are classified as sympatholytic drugs, and hydralazine and sustained-release nifedipine as vasodilators. Before week 20 of pregnancy, a combination of methyldopa and hydralazine or that of labetalol and hydralazine is recommended. After week 20 of pregnancy, combination therapy with a sympatholytic drug (either methyldopa or labetalol) and a vasodilator (either hydralazine or sustained-release nifedipine) should be performed.

If the decrease in blood pressure is insufficient, combination therapy with 2–3 drugs should also be considered. However, treatment must be switched to intravenous injection therapy (nicardipine, nitroglycerin or hydralazine), if necessary, based on the blood pressure level and maternal/fetal conditions even in the phase of two or three drug combination. For blood pressure control by intravenous injection, much attention should be paid to the fetal condition, and fetal heart rate monitoring should be performed.

For intravenous injection, nicardipine,[908] nitroglycerin[909] or hydralazine should be used. These drugs should be used to reduce blood pressure in the case of hypertensive emergency on delivery if blood pressure control with oral drugs is inappropriate. In such cases, particular attention should be paid to the fetal condition of the fetus, and fetal heart rate monitoring should be performed.

5) Various antihypertensive drugs

(1) Methyldopa. This is a centrally acting sympatholytic drug, and is still the most commonly used to treat PIH.[910–912] Although there is no evidence, this drug has been in use for 40 years or more. No serious adverse effect on maternal or fetal conditions has been reported. Side effects such as sleepiness, dry mouth, general malaise, hemolytic anemia, and hepatopathy are observed.

(2) Hydralazine. This is a vasodilator and frequently causes side effects. Usually, this drug is not normally used for hypertension treatment, but the Guidelines recommend it as a first-choice drug, considering the fact that it is still selected by a large number of obstetricians. According to a recently reported meta-analysis, this drug was less effective than labetalol for PIH from all aspects.[913]

(3) Ca channel blockers. Ca channel blockers other than nifedipine are contraindicated for pregnant women or those who may be pregnant. When administering Ca channel blockers other than long-acting nifedipine, they should be used in accordance with the physician's evaluation and responsibility after explaining their necessity for treating the condition and obtaining informed consent,

although this approach is not recommended in guidelines because of insufficient supporting evidence.

(4) Beta-blockers. The α1β-blocker, labetalol, has become available. This drug has been relatively commonly used in Europe and the United States, and there may be no sufficient problems regarding its safety.[914,915] In addition, a meta-analysis has shown that labetalol was more useful than hydralazine with respect to adverse effects on the maternal condition.[913]

Most β-blockers are contraindicated for pregnant women (attached inserts). Therefore, if the administration of other β-blockers is necessary, informed consent must be obtained after explaining the contents of treatment, as described for Ca channel blockers other than sustained-release nifedipine.

(5) Diuretics. Diuretics may deteriorate hemoconcentration/a reduction in the circulating plasma volume related to pre-eclampsia, reducing placental blood flow. Therefore, diuretics should be avoided in patients with pre-eclampsia, as a rule, if pulmonary edema or heart failure signs are absent.[916] In patients who had taken an antihypertensive diuretic before pregnancy, continued treatment may not markedly reduce placental blood flow.

(6) Alpha-blockers. According to the attached of α-blockers inserts, these drugs are not contraindicated for pregnant women or those who may be pregnant. However, generally, they are not used, and should be avoided. Only one study has reported the use of these drugs in pregnant women with pheochromocytoma.[917]

(7) RA system inhibitors. In Japan, RA system inhibitors are classified into three types: ACE inhibitors, ARBs and direct renin inhibitors. Although ACE inhibitors have not been routinely used because of a high incidence of cough as a side effect, the administration of these drugs during pregnancy may induce teratogenicity, renal dysplasia or oligohydramnios; these drugs are therefore contraindicated.[918,919] Some recent studies have indicated that ACE inhibitors do not always induce teratogenicity,[920,921] but these drugs are contraindicated as a rule in the Guidelines, in consideration of the safety. ARBs and direct renin inhibitors are also considered to exhibit similar adverse effects. In women who may become pregnant, these drugs should be avoided. Even in those who may be pregnant, administration should be carefully performed only after confirming their wishes for pregnancy and plans. If women taking RA system inhibitors become pregnant, they should consult the Pregnancy and Drug Information Center (http://www.ncchd.go.jp/kusuri/), which is open as a consultation counter.

6) Drugs for intravenous injection

In the attached inserts of all drugs for intravenous injection that are available, it is described that they can be administered only when the advantage of treatment is considered to exceed its risk, as described for oral drugs.

(1) Nicardipine. This is a Ca channel blocker, and is primarily used in first-aid treatment for abnormal hypertension during surgery, as well as for the treatment of hypertensive emergency and acute heart failure. Side effects of paralytic ileus, hypoxia and liver dysfunction are observed.[908]

(2) Nitroglycerin. This drug is used to maintain a low blood pressure during surgery, as well as for first-aid treatment for abnormal hypertension during surgery and for the treatment of acute heart failure and unstable angina. As severe side effects such as a rapid decrease in blood pressure and a reduction in the cardiac output are observed.[909]

(3) Hydralazine. This is a vasodilator. Side effects such as headache, tachycardia and heart failure are observed.[913]

7) Others

(1) $MgSO_4$. As a drug used to treat eclampsia, $MgSO_4$, exhibits mild hypotensive effects, although it is not an antihypertensive drug. Furthermore, its preventive effects on the onset of eclampsia have also been demonstrated in severe pre-eclampsia patients with impending symptoms of eclampsia.[922] This drug is commonly used under high-risk circumstances regarding the onset of eclampsia, such as the delivery induction and a 24-h period after delivery. However, currently, the use of this drug for the prevention of eclampsia is also approved. When using Magsent R (magnesium sulfate hydrate at 10 g per 100 ml), as an initial dose, 40 ml (4 g as magnesium sulfate hydrate) of this preparation should be intravenously administered over 20 min or more. Subsequently, continuous intravenous administration should be performed from a rate of 10 ml (1 g) per hour. The dose should be increased by 5 ml (0.5 g) per hour in accordance with symptoms, and the maximum dose of this preparation should be 20 ml (2 g) per hour. This preparation should be administered using a pump for continuous infusion, excluding initial-dose administration.

8) Precautions immediately after delivery

PIH is considered to subside after the completion of pregnancy.

However, symptoms of severe/early-onset PIH do not promptly decrease, and eclampsia or hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome (HELLP syndrome is not included in PIH, but is regarded as a relevant disease. H: hemolysis, EL: elevated liver enzyme, LP: low platelet count, the etiology remains to be clarified) are frequently observed immediately to 48 h after delivery. In patients with severe/early-onset PIH, strict blood pressure management is necessary for 3 days after delivery.

9) Antihypertensive drugs in regard to lactation

In the JSH 2009 Guidelines, lactation during therapy with antihypertensive drugs was prohibited as a rule. However, currently, there are differences in the quality and quantity of safety information among drugs, and antihypertensive drugs that are available during lactation are shown in Table 10-3. In North America, many drugs are not positively discontinued during lactation, and the LactMed Guidelines are presented as reference. In addition, detailed information on lactation and drugs is provided at the Pregnancy and Drug Information Center (http://www.ncchd.go.jp/kusuri/), which is open as a counseling counter. Drug therapy after delivery must be performed in cooperation with pediatricians.

2. POSTMENOPAUSAL BLOOD PRESSURE

In women, various physical and mental changes occur with the menopause.[923] Various changes in the cardiovascular system have also been reported/discussed, suggesting an influence of menopause on blood pressure.[924,925]

1) Mechanisms involved in an increase in blood pressure in postmenopausal women

Factors associated with estrogen regression include vascular endothelial disorder, oxidative stress and inadequate RA system activity. The relationship between the vascular endothelium and estrogen is generally known, and the involvement of NO has also been

Table 10-3 Antihypertensive drug treatment during which lactation may be possible

	Generic name	*Proprietary name*	*Pregnancy and Drug Information Center*	*LactMed (National Institutes of Health)*	*RID (%)*[a]
Ca channel blocker	Nifedipine	Adalat	Possible	Possible	1.9
	Nicardipine hydrochloride	Perdipine	Possible	Possible	0.07
	Amlodipine besilate	Norvasc Amlodin	Possible	As information is absent, other drugs are recommended	1.4
	Diltiazem hydrochloride	Herbesser	Possible	Possible	0.87
Alpha-/beta-blocker	Labetalol	Trandate	Possible	Possible, but other drugs are recommended for premature infants	
Beta-blocker	Propranolol hydrochloride	Inderal		Possible	0.28
Central agonist	Methyldopa	Aldomet	Possible	Possible	0.11
Vasodilator	Hydralazine	Apresoline	Possible	Possible	
ACE inhibitor	Captopril	Captoril	Possible	Possible	0.02
	Enalapril maleate	Renivace	Possible	Possible	0.17

Abbreviations: ACE, angiotensin-converting enzyme; RID, relative breast milk intake.
[a]If the RID is 10% or less, lactation is possible. If it is 1% or less, administration is not problematic. LactMed: Website primarily utilized in North America.

suggested. Briefly, estrogen promotes NO synthesis, but NO synthesis may be reduced with its regression, inhibiting vasodilation and leading to an increase in blood pressure through the inadequate enhancement of RA–aldosterone system activity.[926,927] Such vascular changes are also supported by the following findings: flow rate-dependent vasodilation is affected in postmenopausal women, and the pulse wave velocity, as an index of arteriosclerosis, is accelerated.[928] In addition to these, a recent study reported that active oxygen had an important role in the formation of cardiovascular lesions along with the regression of estrogen. However, in humans, evidence that the activity of active oxygen is enhanced after menopause has not always been obtained.[929]

2) Association with PIH

The association between superimposed pre-eclampsia during pregnancy and cardiovascular lesions after menopause has been reported over many years.[930] In 1986, Sibai *et al.*[931] reported that superimposed pre-eclampsia or eclampsia on first pregnancy was associated with the onset of hypertension in women. In addition, they indicated that, when similar pregnancy was repeated several times, this tendency became more marked.

3) Clinical importance of a mother-and-baby notebook in postmenopausal women

In Japan, the mother's body weight, blood pressure and urinary protein level during pregnancy, as well as growth of the fetus//the baby's growth, are recorded in a mother-and-baby notebook. However, this notebook is not used in the clinical practice of hypertension treatment in the mother. In Northern Europe, all pregnancy/birth episodes have been registered since the World War II. The data have shown that the presence of PIH or superimposed proteinuria causes cardiovascular lesions later.[932] In Japan, hypertension treatment in women should also be performed with reference to a mother-and-baby notebook.[933]

Citation Information

We recommend that any citations to information in the Guidelines are presented in the following format:

The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014). *Hypertens Res* 2014; **37**: 253–392.

Please refer to the title page for the full list of authors.