the auscultatory method is less than 5 mmHg and its SD is less than 8 mmHg (*17*). Thus, in each subject a maximal 13 mmHg (mean+SD) difference from the auscultatory method is approved on the basis of this standard, suggesting that devices conforming with the AAMI guidelines do not necessarily provide a proper BP value in individuals. It should be emphasized again that there are different purposes for validation: applicability to the general population and suitability of the device for an individual. In this guideline, we recommend a device for practical use when the difference in BP from the auscultatory method is less than 5 mmHg in a particular subject. It is a matter of course that the device should be adapted to the AAMI standards and BHS guidelines.

Home measurement devices should be validated before use, and at regular intervals during use.

Recommendation 3

Devices for home BP measurement should be adapted to the AAMI standards and the BHS guidelines. Furthermore, the difference between the auscultatory method and the device should be within 5 mmHg in each individual. The home measurement device should be validated before use, and at regular intervals during use.

4. Procedure

ABPM provides BP values measured every 15 to 30 min as a function of time and of daily activity on a particular day, and thus control of measurement conditions is not appropriate for ABPM. Conversely, home BP measurement characteristically provides BP values under controlled conditions that should remain as stable as possible for a long period. The JNC-VI and -7, the 1999 WHO-ISH Guidelines, the ESH-ESC Guidelines, and JSH Guidelines 2000 emphasized the clinical significance of self-measured BP at home. However, these guidelines do not refer to standardization of the measurement procedure for home BP. The most authorized guideline for self-BP monitoring, from the International Consensus Conference 2000, only stated very briefly that self-BP should be measured at the heart level after 5 min of rest (*22*). The clinician's manual on the self-monitoring of BP by Pickering, the only manual for home BP measurement, emphasizes that home BP values change markedly with alterations in measurement circumstances, but does not specify how, when, and where home BP should be measured (*23*). Other guidelines, including JNC-VI (*8*), JNC-7 (*9*), the WHO-ISH (*10*), the ESH-ESC (*11*), the American Heart Association (*24*), the American College of Physicians (*25*), the Canadian Coalition for High Blood Pressure Prevention and Control (*26*), the First International Consensus Conference on Self-Blood Pressure Measurement (*27*), and the European Society of Hypertension Recommendations for Conventional, Ambulatory and Home Blood Pressure Measurement (*20*), do not specify standards for the measurement procedure. All guidelines recommend measurement of home BP in the morning and in the evening. In the American Society of Hypertension *Ad Hoc* Panel, Pickering recommended measurement of BP at home on holidays as well as on working days, but he did not refer to the timing of the daily measurements (*28*).

This is an appropriate time to review the characteristics and the purpose of home BP measurement. All the guidelines and recommendations emphasize the good reproducibility and reliability of home BP. These characteristics arise from the ability to make multiple measurements over a long period: Home BP measurements are suitable for an assessment of the effect and duration of action of antihypertensive drugs and for the diagnosis of intractable hypertension and white coat hypertension. Furthermore, morning hypertension has recently been attracting attention as a risk factor for cardiovascular morbidity and mortality. Home BP measurement is the only practical method to obtain BP in the morning. Recently, white coat normotension (reversed white coat hypertension or masked hypertension) has also been attracting attention in relation to morning hypertension. This concept is defined as a normal clinic BP ($<$140/90 mmHg) with a home BP indicating hypertension ($\geq$135/85 mmHg). This white coat normotension, determined by the home BP in the morning, is mediated at least in part by an insufficient duration of action of antihypertensive drugs.

From this viewpoint, if the reproducibility and reliability of home BP measurements could be increased, the clinical significance of these measurements would improve extensively. However, at present no standard exists for the measurement procedure of home BP.

As mentioned in the previous chapter, the most important feature of home BP measurement is long-term and repetitive measurement using arm-cuff devices under controlled conditions. In this respect, compliance or adherence with home BP measurement is a very important issue. Thus, the measurement of BP *per se* should be paramount. However, to increase the clinical significance and comparability of home BP measurement as a component of clinical decision-making, establishment of a standardized procedure for home BP measurement is essential.

The home BP should be measured at least twice daily, in the morning and in the evening. This is a requirement of almost all existing guidelines.

4-1. Morning-Measurement Procedure

In this guideline, the morning is defined as the time within a few hours after waking, *i.e.*, the time between waking and 10:00 AM. The Working Group, first of all, recommends that measurements should be performed within 1 h after waking. This condition is not necessarily strict enough. However, the most important point in home BP measurement is that subjects measure their own BP at home for a long period. Consequently, strict regulation of the timing of

measurements may disturb compliance or adherence with home BP measurements. The period within 1 h after waking includes several potential factors modifying BP, and thus the several conditions mentioned below must be considered. (In shift workers, 1 h after waking is not necessarily the morning. In this case, the timing of 1 h after waking may be kept as a condition, but the measurement time must be recorded.)

1) After Micturition

In general one urinates soon after waking. Before micturition, extension of the urinary bladder elevates BP, and after micturition BP decreases (*29*). The measurement condition of micturition in the morning after waking ensures a consistent physiological background.

2) Sitting Position with 1–2 min of Rest

A sitting position is the common position for BP measurement in all existing guidelines. In Japanese people, a sitting position includes cross-legged sitting or upright sitting, and in this guideline the sitting position depends on one's usual custom. When a sitting position is not available, measurement in a recumbent position is also permitted.

In general, many guidelines recommend 5 min of rest before measurement (*19*, *20*). However, this guideline proposes a more practical and generous condition to maintain compliance with home BP measurements, that is, that measurement be made after 1–2 min of rest.

3) Before Taking Antihypertensive Drugs

One of the most important purposes of home BP measurement is evaluation of the duration of the antihypertensive effect of drugs. Morning BP measurement before taking the next dose of an antihypertensive drug represents a "trough" measurement. Evaluation of the trough effect allows definition of the duration of action of drugs (*30*).

Recently, morning hypertension has been attracting attention, and some antihypertensive drugs are administered just after waking to control morning hypertension. In such cases, BP measurement before drug ingestion is recommended, although measurement 5–10 min after drug ingestion is also permitted.

4) Before Breakfast

Dietary routine affects BP most extensively among the daily habitual behaviors. BP generally increases during a meal and decreases after the meal. To exclude such variability, BP measurements before breakfast are recommended.

4-2. Evening-Measurement Procedure

Controlling the timing of the evening measurement is rather difficult when compared with that in the morning. Although clinical pharmacology studies to determine the effect or duration of the action of a drug often require that measurements take place before supper, before drinking alcohol, before taking a bath, or before taking a drug, in normal daily life in Japan it is practically impossible to request that such conditions be followed.

To improve compliance with measurement of home BP, only a single condition, that of measurement just before bedtime, is proposed. In general, Japanese men take an alcoholic beverage and a bath at about this time. These factors usually decrease BP. In the Ohasama study, where evening BP was measured under the above-mentioned condition, BP in the morning was a few mmHg higher than that in the evening. This was especially true in the hypertensive population of Ohasama, for whom the difference in SBP was 10–20 mmHg (*31*). When a long-acting antihypertensive drug is administered once in the morning, the BP in the evening corresponds to near the peak effect. Recently, the ratio of the morning effect to the evening effect has been used as an indicator of the duration of action of the antihypertensive effect, the morning *vs.* evening (*M/E*) ratio. This concept is derived from the trough *vs.* peak (*T/P*) ratio obtained from ABPM (*30*).

4-3. Measurement at Midnight

Recently, a new home BP device incorporating an integrated circuit memory and timer has been developed (HEM 747 IC-N, Omron, Kyoto, Japan) (*7*). This device is being used in a large-scale interventional study in Japan using home BP measurements and the Internet, known as the Hypertension Objective Treatment Based on Measurement by Electrical Device of Blood Pressure (HOMED-BP) study (*32*). In this study, the devices are preset to work automatically at 2:00 AM, since the nadir of the nocturnal BP was observed at around 2:00 AM in the population of the Ohasama study. Using this device set to work once at 2:00 AM, the subject can recall after waking the quality of sleep during the measurement. On the other hand, it is impossible to evaluate the quality of sleep during ABPM, since one cannot define the quality of sleep during measurements every 30 min. Although determination of nocturnal BP by home measurement devices is not yet widespread, this procedure is significant for determination of the circadian BP variation and the nocturnal BP level.

4-4. Measurement in the Workplace or during Daily Activities

Although portable devices allow self-measurement of BP in the workplace or during daily activities, in practice such measurements are difficult. In the future, development of accurate and reliable wrist-cuff devices may permit BP measurement under stressful circumstances. The importance of measurements in the workplace or under stressful circumstances was emphasized by Pickering (*13*). Elevation of BP in the workplace or under stressful conditions mediates white coat normotension or masked hypertension.

Recommendation 4

Home BP should be monitored under the following conditions:

a: In the morning within 1 h after waking, after micturition, sitting after 1–2 min of rest, before drug ingestion, and before breakfast.

b: In the evening just before going to bed, sitting after 1–2 min rest.

5. Frequency and Duration of Measurements

There is much difference of opinion concerning how many times home BP should be measured on each occasion and for how long home BP should be measured. The answers to these questions depend on the purpose of the home BP measurement. Thus, in this guideline, the most generalized method taking into account the convenience of subjects and the need to obtain useful information for clinical decision-making is proposed.

The guidelines of the International Consensus Conference for Self-Blood Pressure Monitoring (2000) recommended measurements of self-BP in the morning and in the evening, twice on each occasion, for 3 working days a week (a total of 12 measurements a week), but stated that the measurement frequency can vary depending on the indication and the objective for which the measurement is used (*22*). In practice, the measurement frequency can be modified depending on the severity of hypertension and the treatment situation—for example, treatment before prescription, during prescription, or during a change of medication. Pickering stated that a lower measurement frequency is permitted when the BP is stable and well-controlled (*23*). He preferred that in a newly diagnosed patient 3 consecutive readings should be obtained both in the morning and in the evening on 3 days a week for at least 2 weeks (36 measurements over 2 weeks) (*23*). He also stated that frequent readings are needed when a new medication is being prescribed or when the dosage is being changed.

As a tool for clinical pharmacology studies, Mengden *et al.* recommended that at the commencement of the home measurements there should be an initial 7-day measurement period with 2 measurements in the morning and 2 measurements in the evening, respectively, at pre-stipulated times (*27*). The measurements from the first day should be excluded from the statistical analysis. The average of these values (24 measurements over 6 days) is taken as the reference parameter in the dose-titration phase (*27*). Home BP measurements may be performed 1 day a week if hypertension is controlled. If the treatment is changed, the average of the home BP measured over 2 weeks should be used to assess the treatment effect.

Almost all guidelines or manuals recommend two consecutive measurements on each occasion. This recommendation is based on the evidence that regression to the mean during consecutive measurements on each occasion is frequently observed after long-term monitoring (*33*). de Gaudemaris *et al.* reported that even in normal subjects the first measurement was the highest and the third measurement was the lowest among consecutive measurements on a single occasion; the difference was 3/2 mmHg (*34*). In contrast, both the Ohasama study (*14*, *31*) and the HOMED-BP study of Japan (*35*) recommend at least one measurement in the morning and in the evening, respectively. The reasons for this recommendation are as follows.

1. Since home BP must be measured over a long period, a minimal demand on subjects, *i.e.*, at least once on each occasion, may improve compliance with measurement. A permanent requirement for multiple (2 or more) measurements of home BP on each occasion for a long period creates too large a burden for subjects, which lowers compliance.

2. Regression to the mean also appears during long-term measurement of the home BP. In the Ohasama study, it has been confirmed that the home BP level reaches the subject's inherent home BP level after 2 days of measurement in normotensive subjects, whereas it takes 5–7 days to reach the subject's inherent home BP level in hypertensive subjects (*36*).

3. If the measurement frequency is not regulated, subjects will measure their own BP with a voluntary measurement frequency—for example, 3 consecutive measurements on 1 morning and only 1 measurement on the following morning. Consequently, practitioners would be unsure of which measurements should be evaluated for clinical decision-making.

4. Consecutive and multiple measurements of home BP on each occasion provide different measurement results, which may cause confusion in some subjects. Generally, subjects tend to value the lowest BP obtained from multiple measurements. As a result, the lowest BP value may be reported to the practitioner, introducing selection bias.

5. Ideally, home BP in the morning or in the evening would be evaluated as a mean value averaged for a certain period. However, averaging procedures are very time-consuming, and neither subjects nor practitioners tend to work constructively at this procedure, such that there is often a selection bias in the values chosen for evaluation such that not all values can be evaluated.

6. Use of the first measurement on each occasion is a common procedure in many patients/subjects of many institutes or clinics, and thus averages of the first measurement of the home BP obtained in the morning and/or in the evening for a certain period are comparable among patients/subjects from many institutes or clinics. Furthermore, it has been confirmed that a single measurement of home BP in the morning has a higher predictive value for the prognosis of cardiovascular disease than the average of two clinic BPs, and that averaging the first measurement of home BP in the morning for 21 days has a much higher predictive value than clinic BP (*37*), suggesting that the clinical significance of home BP, even if obtained from one measurement on each occasion,

can be increased by averaging multiple measurements over a long period.

However, this guideline does not deny that multiple measurements on each occasion may be of value. The difference among home BPs measured consecutively on a single occasion includes information on BP variability or on the defense reaction to self-measurement (a kind of white coat effect). Such variability is also a characteristic of BP in individuals. Therefore, as mentioned in the next section, multiple home BPs measured on each occasion should all be recorded without selection. In the present situation, each practitioner instructs subjects differently as to the number of measurements on each occasion, and as a result the method of evaluating home BP may differ among practitioners. If we wish to record population levels of home BP, as well as individual levels for the purpose of clinical decision-making, the first measurement on each occasion might provide the most generalizable information. As a matter of fact, most epidemiological surveys based on self-measurement, including the Pressioni Arteriose Monitorate e Loro Associagiani (PAMELA) study (*38*), the Tecumseh study (*39*), and the Ohasama study (*37*), used one measurement on each occasion. However, as Stergiou *et al.* emphasized, regression to the mean on each occasion persists after long-term measurement (*33*). Therefore, the first measurement on each occasion may be higher than the average of multiple measurements on each occasion, even after long-term monitoring. Although it is important to recognize this fact, the Working Group recommends use of the first measurement on each occasion as a standard for evaluation of home BP, since it is convenient for subjects and results in good compliance and good equivalence for comparison (*13*). In addition, every measurement on each occasion, as well as the long-term average of the first measurement on each occasion, should also be evaluated as a matter of course.

It is not necessary to specify the duration of home BP measurements. Since home BP measurements characteristically provide long-term BP information, it is recommended that hypertensive subjects measure their BP once in the morning and once in the evening for a lifelong period, which may bring about improvements in drug compliance and self-management of health. In healthy normotensive subjects or in prehypertensive subjects, periodic measurements—for example, once a week or once every several weeks—are recommended. However, there is a concern that insisting on frequent self-measurement may sometimes disturb compliance with measurement.

On the other hand, regulation of the number and duration of measurements is indispensable for clinical pharmacology studies. The following recommendations for the number of measurements and the period of measurement needed for clinical pharmacology are based on data obtained from a total of 214 subjects from the general population of the town of Ohasama and in a hypertensive clinic in Japan (*36*). In that study, the reproducibility of home BP was examined. The difference between the home BP averaged over 5 days of an 8-day run-in period without placebo (the initial 3 days of measurement were excluded), and that averaged over 5 days between the 17th and 21st days of the placebo period, was $-1.9\pm7.0/-1.4\pm4.8$ mmHg (SBP/DBP), suggesting that there was good reproducibility and no placebo effect in the measurement of home BP.

Recommendation 5

1. Home BP should be measured at least once in the morning and once in the evening.
2. Home BP should be measured for as long as possible.
3. In clinical pharmacology studies, home BP should be measured over at least 5 days during a 7-day run-in period in subjects with mild-to-moderate hypertension (SBP≦179 and DBP≦109 mmHg in casual-clinic measurement). The run-in period may be 1 to 2 weeks depending on the patient's condition. In subjects with severe hypertension, treatment should generally be started without home BP measurements, although 1 to 3 days of measurement of home BP may be performed according to the judgment of the practitioner.
4. Home BP should be measured at least 3 days a week during periods when hypertension is well controlled.
5. Home BP should be measured at least 5 days a week when a medication is changed.

6. Documentation

All measurements of home BP should be documented without selection. This should help to prevent overestimation or underestimation of the home BP values. Mengden *et al.* reported that, among subjects who measured home BP, excess reports, insufficient reports, and even reports of phantom records were frequently observed (*40*). Therefore, the best way to rule out biases is to use equipment incorporating an integrated circuit memory. However, a personal computer is currently needed to read out the memory, and thus this function does not necessarily work efficiently in general practitioner. Furthermore, discrimination among the data from multiple users is not possible with the present form of the device, and thus a separate device is required for each user, and each user must be informed that the device is only for their personal use.

Among other methods to exclude selection bias, devices with a printer are sometimes useful, although selection bias cannot really by excluded using a printer, since subjects cannot be relied upon to consistently print all results. Therefore, subjects' documentation on worksheets still remains the most popular method to record home BP values. In this case, subjects must be instructed that all measurements, together with the pulse rate and the date and time of the measurement, should be documented.

Recently, many pharmaceutical companies have begun to distribute worksheets for the recording of home BP, although

the formats of these worksheets are inconsistent. For example, some of these forms ask subjects to record the trend of BP, and others ask for numerical information. Both types of information are useful for clinical practice, but recording of numerical information is more important. The worksheet should include spaces for the year, month, day, clock time, BP, and pulse rate. Spaces for morning values, daytime values, and evening values should also be included. A reference column is useful to record episodes of daily life. A duplication function is required on the worksheets so that the information can be available both at clinics/institutions and for subjects.

Recommendation 6
All home BP measurements should be documented without selection, together with the date, time, and pulse rate. Use of devices with a printer or an integrated circuit memory is sometimes useful to rule out selection bias.

7. Totaling

Before evaluation of home BP values, totaling of measured and documented values is necessary. As recommended in section 5, the home BP should be measured at least once in the morning and once in the evening for a long period. The home BP should be evaluated on the basis of the mean value and its SD, averaged for a certain period. The home BP in the morning and that in the evening may have different clinical significance because of the different measurement conditions, such as physical activity and environmental factors. Therefore, the home BP in the morning and that in the evening should be totaled and evaluated separately. In the process of totaling, the issue of how many times the home BP should be measured on each occasion arises again. The measurement frequency on each occasion may differ among clinics/institutes and individuals. The information common to all circumstances or individuals is the first measurement on each occasion. Thus, as a tool for clinical decision-making, clinical study, or clinical epidemiology, the mean of the first measurement on each occasion averaged over a certain period would be the most common value and the best for comparison among institutes or individuals. However, each BP value among multiple measurements on each occasion may also have clinical significance. Therefore, all of these measurements must be documented and evaluated by the practitioner. A regression to the mean during multiple measurements of home BP is generally observed in the usual measurement setting. From this viewpoint, the evaluation of all measurements is necessary, whereas for the evaluation of home BP level as a tool for clinical decision-making, a totaling of home BP under standardized measurement conditions is necessary—in other words, the mean of the first measurement on each occasion averaged over a certain period. Such totaling is applicable to clinical epidemiology as well as to daily practice, and as a result, data obtained in daily practice is comparable with data obtained in clinical epidemiology. The period over which the home BP should be averaged depends on the purpose of the measurement. Averaging measurements over 2 to 4 weeks is the most common and convenient method as a unit for evaluation of home BP, since patients usually visit the clinic every 2 to 4 weeks. In clinical pharmacology studies, averaging over at least 5 days is necessary (*36*). Day-by-day variability of home BP is believed to have a predictive value for cardiovascular disease risk, and thus SD should be calculated simultaneously. The home BP in the morning and in the evening must be evaluated separately.

Recommendation 7
The home BP in the morning and that in the evening should be averaged separately for a certain period. The first measurement on each occasion should be used for totaling. Day-by-day variability should be presented as SD.

8. Evaluation

The JNC-VI (*8*) and -7 (*9*), the WHO-ISH Guidelines (*10*), the ESH-ESC 2003 Guidelines (*11*), and the JSH 2000 Guidelines (*12*) all provide reference values for home BP. These reference values were introduced on the basis of the Ohasama study (*41*), the PAMELA study (*38*), and the International database (*42*). The Ohasama study is the only one to provide reference values based on a longitudinal prospective cohort study (*14*, *37*). On the basis of such studies or analyses, most guidelines propose that hypertension be defined as 135/85 mmHg and over, and normotension as less than 125/80 mmHg (*8–11*). The JSH 2000 guidelines define hypertension as 135/80 mmHg and over, and normotension as less than 125/75 (*12*). These values may be revised according to the results of future large-scale observational studies, although the values accepted at present are not expected to differ greatly from such future revised values. Therefore, the reference values of home BP are now considered to have reached a consensus.

Recommendation 8
Home BP values averaged for a certain period indicate hypertension when 135/80 mmHg and over (JSH 2000) and definite hypertension when 135/85 mmHg and over (JNC-VI and -7). Normotension is defined as less than 125/80 mmHg (WHO-ISH 1999) and definite normotension is defined as less than 125/75 mmHg (JSH 2000).

9. Conclusion

Home BP measurements are indispensable for the improvement of management of hypertension in medical practice as well as for the recognition of hypertension in the population. Therefore, establishment of self-measurement of BP is the first priority, and for this purpose it is not necessarily expect-

ed that strict measurement conditions will be set. However, the presence of a standard for home BP measurement may be convenient and useful for practitioners as well as for subjects. This guideline for home BP measurement is intended to instruct patients and subjects in the general population on how to measure BP at home. As a result, home BP measurements based on this guideline may provide a shared basis of information for clinical decision-making.

Fortunately, international reference values are now established. However, the treatment goal for home BP level has not yet been established. At present, the normotensive value of home BP is set at the level of 125/75–80 mmHg. This value is approximately equivalent to a casual-clinic BP level of 140/90 mmHg. Therefore, it seems that a value of less than 125/75–80 mmHg should be the goal for home BP. However, the setting of the goal for home BP must be based on the results of large-scale intervention studies. Among such studies, the Treatment of Hypertension according to Home or Office Blood Pressure (THOP) study (*43*) and the HOMED-BP study (*35*) are ongoing. Although such reference values have been proposed in several guidelines, standardization of measurement conditions has not yet been achieved. For example, in the Tecumseh study the measurement frequency was once in the morning and once in the evening, and the measurement duration was 7 days (14 measurements in total) (*39*). In the PAMELA study (*38*), the home BP was measured once in the morning and once in the evening on only 1 day (2 measurements in total). In the Ohasama study (*37*), the home BP was measured once in the morning and once in the evening for 21 days (42 measurements in total). In the THOP study, home BP was measured 3 times in the morning and 3 times in the evening for 7 days (*43*), while in the HOMED-BP study home BP was measured once in the morning and once in the evening for at least 5 days during the run-in period, and an average of these measurements was used as a reference value (*35*). In all studies except the HOMED-BP study, the measurement procedure was not controlled. In the HOMED-BP study, the home BP in the morning was measured within 1 h after waking, after urination, in the sitting position after a 1–2 min rest, before drug ingestion, and before breakfast, and in the evening before going to bed in the sitting position after a 1–2 min rest. Because of the great variety of measurement procedures among studies, it seems impossible to compare the results among them. In the future, internationally standardized measurement procedures will be established by consensus, and reference values on the basis of such standardized procedures will be proposed. However, common to all these measurements of home BP values, including those in past databases, is the use of the first measurement on each occasion. Therefore, the common information on home BP, which is available for retrospective analysis, prospective analysis, and even meta-analysis, is the mean of the first measurement on each occasion averaged over a certain period. For this reason, this Working Group recommends that home BP should be evaluated by the mean of the first measurement in the morning and in the evening, respectively, averaged for at least 5 days.

Standardization of the measurement procedure may elevate the position of home BP measurements in the practice of diagnosing and treating hypertension, and as a result, home BP measurements may bring an improvement of the accuracy of screening for hypertension, an improvement in drug compliance, and more accurate assessment of BP control during treatment. Home BP measurements under such controlled conditions are expected to have a beneficial effect on the economics of the diagnosis and management of hypertension.

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特集：早朝高血圧――重要性とその管理――

Q&A 早朝高血圧の臨床的意義とその具体的治療法

（回答）国立循環器病センター 高血圧腎臓内科部長 河野雄平（かわのゆうへい）

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Q&A 早朝高血圧の臨床的意義とその具体的治療法

（回答）国立循環器病センター 高血圧腎臓内科部長 河野雄平（かわの ゆうへい）

――早朝高血圧は，なぜ悪いのでしょうか？

血圧が覚醒，起床とともに急に上昇することはよく知られています．朝の血圧上昇はモーニング・サージと呼ばれますが，これが著しい高血圧の患者さんは少なくありません．また，そのような例の多くは，朝が他の時間帯より明らかに高い早朝高血圧を呈します．

早朝高血圧が臨床的に問題となるのは，起床後の数時間は脳卒中や心筋梗塞が最も多い時間帯であり（図1），朝の血圧上昇がこれらの心血管事故の発症に重要な役割をもつと考えられるからです[1,2]．また，早朝高血圧を呈する患者さんの外来血圧は比較的低いことが多く，診察室での測定では日常の血圧を過小評価することになります．病院での血圧は正常で家庭血圧や24時間血圧は高い病態は，逆白衣高血圧や仮面高血圧と呼ばれますが，臓器障害が進行すると考えられます．

――早朝高血圧は，どのようにして診断すればよいでしょうか？

血圧のモーニング・サージの評価には，24時間血圧モニタリング（ABPM）が最も適しています．しかし，朝と夜の家庭血圧の測定によっても可能で，実用上はこちらが勧められます．家庭血圧は朝が夜より少し高い場合が多く，我々の検討では，降圧薬を服用していない高血圧患者の朝の家庭血圧は夜より平均で5/3 mmHgほど高値でした[3]．

早朝高血圧の診断には，朝の血圧が高いことと，またそれが他の時間帯より高いことを

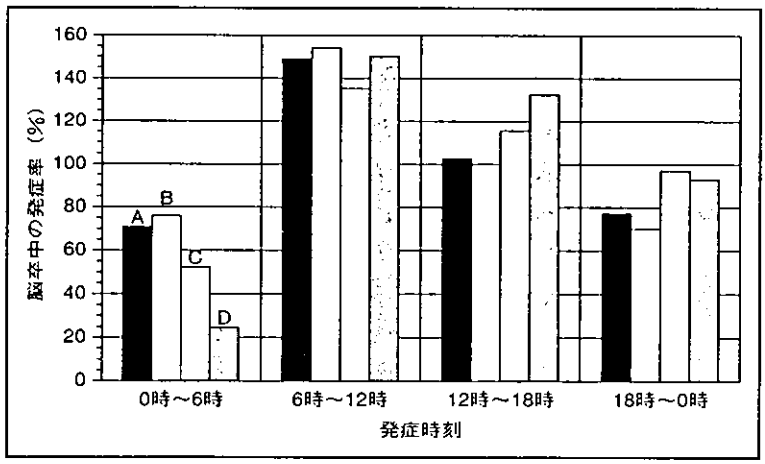

図1 脳卒中の時間帯による発症頻度のメタアナリシス（文献2：Elliott WJ, 1998による）
A：全脳卒中，B：虚血性脳卒中，C：出血性脳卒中，D：一過性脳虚血発作．

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確認することが重要と思います．まだ統一された診断基準はありませんが，家庭血圧による高血圧の基準が 135/80 mmHg ですので，朝の血圧がこれ以上で，しかも夜より高いことが目安になるでしょう．朝の家庭血圧が 140/90 mmHg 以上で夜より 10 mmHg 以上高ければ，明らかな早朝高血圧と考えられます．

――― 早朝高血圧の原因は，何でしょうか？

血圧の日内変動は種々の因子の影響を受けますが，交感神経系が最も重要と考えられます．覚醒，起床に伴う交感神経の活性化は生理的現象でもありますが，血圧上昇や心拍数増加，血液凝固能亢進をもたらします[4]．これらはプラーク剥離や動脈瘤破裂，心筋虚血や不整脈，血栓形成に働き，心血管事故発症の誘因になると考えられます．また，朝の急な血圧上昇には，夜間からの α 受容体の感受性亢進も関与しています．

生活習慣や環境因子によって早朝高血圧が生じることがあります．アルコールやストレス，寒冷などです．また，しばしば見られるのが，降圧治療の結果としての早朝高血圧です．すなわち，昼や夜は降圧薬により下がっているが朝のコントロールが不充分な場合です．しかし，早朝高血圧の原因を特定できない患者さんも少なくありません．

――― 早朝高血圧に対する生活上の注意は，何かありますか？

種々の生活習慣が血圧の値や変動に影響しますが，アルコールが早朝高血圧の原因となることがあります．アルコールは血圧を上げて高血圧の原因になると考えられていますが，実際には夜の血圧下降と朝の血圧上昇をもたらし，朝と夜の血圧差を増大させます[5,6]（図 2）．したがって，早朝高血圧を示す患者さんが飲酒者であれば，飲酒制限の指導が望まれます．ただし，アルコールによるモーニング・サージは朝の血圧上昇より飲酒後の血圧低下による部分が大きいので，アルコール制限だけで朝の血圧を正常化させるのは困難かもしれません．

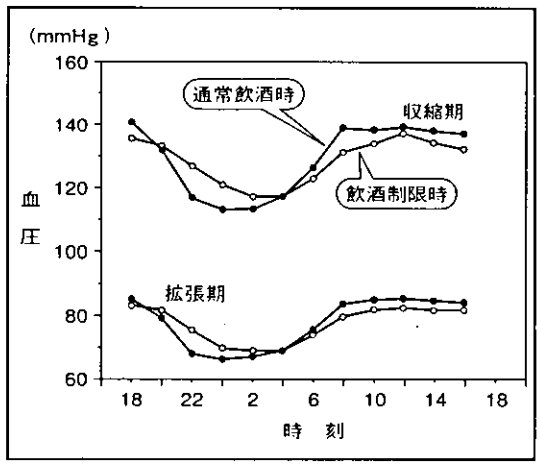

図 2　高血圧患者におけるアルコールの血圧日内変動への影響（文献 6：河野雄平，1998による）

ストレスや行動様式も血圧変動に関係します．患者さんが起床後の時間を慌ただしく過ごしていないか尋ねて，そうであれば余裕のある行動を勧めるのがよいでしょう．朝の血圧は，勤務日より休日のほうが低いことがしばしば観察されます．

また，早朝高血圧を呈する例では，朝の家庭血圧の測定状況にも注意を払うべきでしょう．例えば，寒い部屋での薄着や腕まくりしての測定や，排尿前で膀胱が充満した状態では，血圧が高くなります．家庭血圧では早朝高血圧なのに，ABPM ではモーニング・サージは明らかでないことがあります．朝の家庭血圧は，起床後なるべく早く，食事や服薬の前に測ることが勧められますが，排尿を済ませて少しゆっくりして測定するほうがよいでしょう．

――― 早朝高血圧に対する降圧薬の使い方を教えて下さい．

早朝高血圧に対する薬物治療においては，

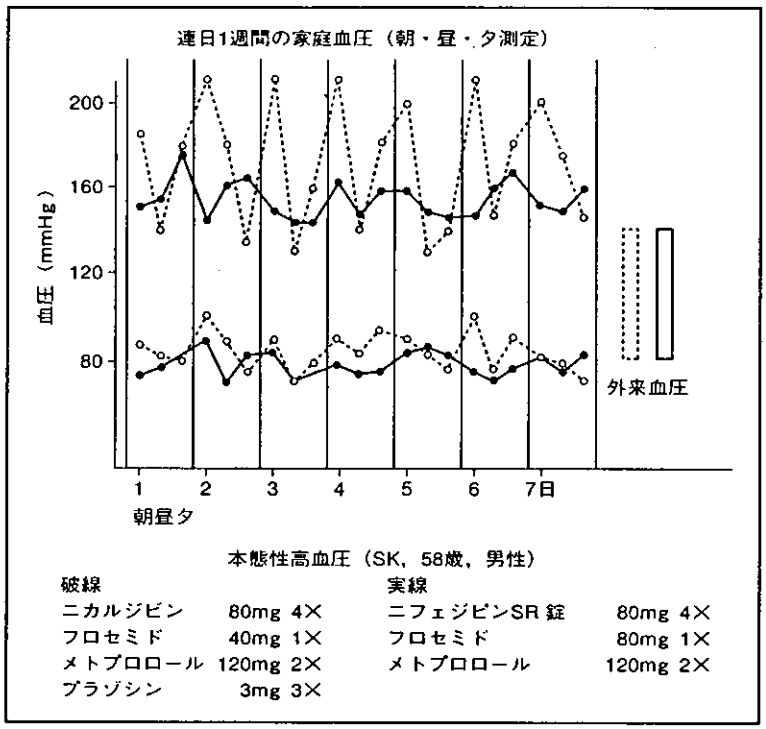

図3　短時間作用性降圧薬より長時間作用性薬剤への変更により早朝高血圧が改善した1例
（文献7：阿部　仁 他，1987による）

降圧薬の薬効持続時間と作用機序に注意する必要があります．日常診療においてしばしばみられるのが，使用した薬剤の持続時間が充分でないため，昼や夜は低いが朝は高い場合です．短時間作用性の降圧薬，とくにカルシウム拮抗薬は，1日3回食後に服用しても起床時には薬効が消失し，著しいモーニング・サージの原因になることがあります[7,8]（図3）．このような例では長時間作用性の薬剤に変更すべきであり，それによって朝の血圧はかなりコントロールできるでしょう．

しかし，長時間作用性の降圧薬でも，持続時間は薬剤によって異なります．1日1回朝の服薬では，翌朝には薬効が減弱してモーニング・サージの原因となることがあります．この可能性があれば，より長時間作用性の薬剤に変更する，現在の薬剤を朝と夜に分割投与する，現在の薬剤を夜に服用してもらう，などによって朝の血圧低下が期待できます．

夜の降圧薬投与が予後を改善し，また危険性は少ないことは，ニトレンジピンを用いた大規模臨床試験で示されています[9]．

血圧のモーニング・サージには，交感神経系の活動亢進とα受容体の感受性亢進が関与しています．α遮断薬やαβ遮断薬，中枢性交感神経抑制薬は，モーニング・サージを抑制することが示されており，早朝高血圧の治療に有用です[10]．作用時間や副作用の面からは，夜の服薬，あるいは朝と夜の分割投与が効果的でしょう．図4に示す例では，α遮断薬ドキサゾシンを夜に追加することにより，早朝高血圧を効果的にコントロールできました．

これらの方法により，モーニング・サージや早朝高血圧の改善が得られると考えられます（表1）．しかし，降圧薬の変更や追加によっても早朝血圧のコントロールが困難な場合もあり，そのような例では早朝血圧を厳格

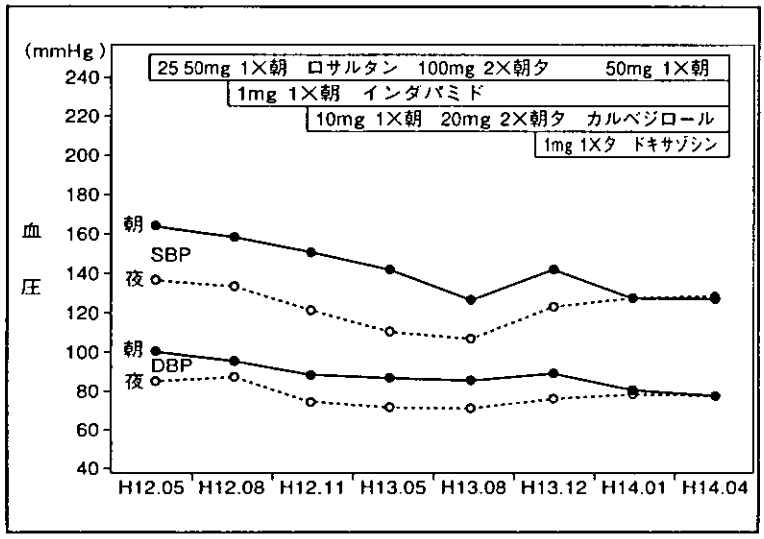

図4　夕食後のα遮断薬により早朝高血圧が改善した1例(文献10：河野雄平，2002による)

表1　早朝高血圧の治療

生活習慣に注意する（飲酒，ストレス）
長時間作用性の降圧薬を用いる
降圧薬を夜に服薬させる
交感神経系の抑制薬を用いる（α遮断薬，αβ遮断薬，中枢性交感神経抑制薬）

にコントロールすると昼や夜の血圧が下がり過ぎることがあります．患者さんの症状や朝と夜の家庭血圧，外来血圧などをみながら，早朝血圧を含めての適正な血圧コントロールができればよいと思います．

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特集　日本人のための降圧療法

総論

2．降圧療法における日本人のエビデンス

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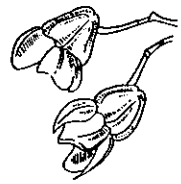
特集 日本人のための降圧療法



総論
2．降圧療法における日本人のエビデンス

又吉哲太郎*1)・河野雄平*2)

降圧療法が高血圧患者の予後を改善することは，大規模な臨床研究により確かめられているが，降圧治療のエビデンスのほとんどは欧米における研究によるものである。わが国では高血圧治療の臨床試験は少なく，エビデンスは乏しいが，NICS-EH(National Intervention Cooperative Study in Elderly Hypertensives)，GLANT (The evaluation Group of Long-term Antihypertensive Treatment)，JATE (Japanese Trial on the Efficacy of Antihypertensive Treatment in the Elderly)，PATE-Hypertension (Practitioner's Trial on the Efficacy of Antihypertensive Treatment in the Elderly Hypertension) などの研究が行われてきた。これらの研究は規模や方法にいくらか弱点があるが，高血圧患者の予後への効果は，Ca (カルシウム) 拮抗薬と利尿薬，ACE (アンジオテンシン変換酵素) 阻害薬の間にあまり差はないことが示唆されている。現在，JATOS (Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients)，CASE-J (Candesartan Antihypertensive Survival Evaluation in Japan)，HOMED-BP (Hypertension Objective Treatment based on Measurement by Electrical Devices of Blood Pressure Study)，HOSP (Hypertension Control Based on Home Systolic Pressure Study) などの無作為の大規模臨床試験が進行中であり，その成果が期待される。

1．はじめに

高血圧が種々の循環器病の主要な危険因子であり，降圧治療がそれらを予防し，予後を改善することはよく知られている。欧米では，1960年代後半から大規模な臨床試験が次々と実施され，多くの知見が得られてきた。一方，本邦では大規模な臨床試験はほとんど行われず，わが国の高血圧治療は欧米の，人種や生活習慣の異なるデータによるエビデンスに基づいてきた部分が大きい。循環器疾患の病態が異なるわが国において，欧米の成績がそのまま適用されるか否かは明らかではなく，日本人におけるエビデンスが求められている。

しかし，規模や方法などにやや弱点はあるものの，わが国でも降圧治療の臨床試験がいくつか行われてきた。また現在，いくつかの無作為の大規模臨床試験が進行中である。ここでは降圧療法における日本人のエビデンスとして，それらの臨床研究について解説する。

2．NICS-EH

NICS-EH (National Intervention Cooperative Study in Elderly Hypertensives)は，1989年に開

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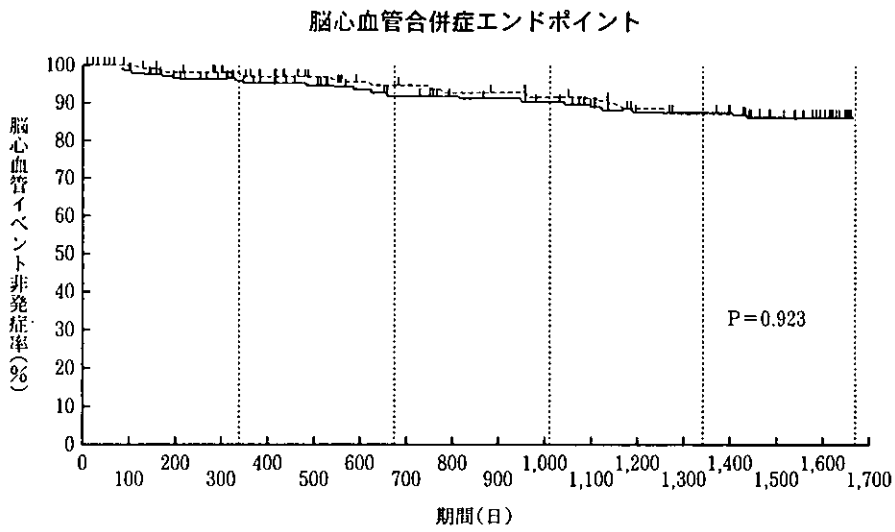

図1　NICS-EHにおけるNicardipine群（N群）とTrichlormethiazide群（T群）の心血管イベントの非発症率

全追跡期間を通して，両群のイベント発症率には差がない．

実線：N群，破線：T群

NICS-EH：National Intervention Cooperative Study in Elderly Hypertensives

（文献1より）

始された多施設二重盲検比較試験である[1]。この研究は，カルシウム(Ca)拮抗薬のnicardipineと，利尿薬のtrichlormethiazideの，老年者高血圧における脳心血管イベントに対する効果を比較したものである。対象は60歳以上で，収縮期血圧(SBP) 160～220mmHg，拡張期血圧（DBP）115mmHg未満の本態性高血圧患者414例で，無作為割付，二重盲検で5年間の追跡が行われた。Nicardipine群（N群）には，nicardipine徐放錠20mgを朝夕2回，trichlormethiazide群（T群）には，trichlormethiazideを2mg朝1回内服させた。効果不十分の場合は，倍量まで増量し，他剤の併用は禁止した。脳心血管イベントの発症をエンドポイントとした。

N群204例，T群210例が解析対象となった。両群とも25%の収縮期高血圧症例を含んでいる。両薬剤群で，ともに同程度に降圧された。（N群：172/94→152/85mmHg，T群：173/93→153/85mmHg)。脳心血管イベントは，N群が21例，T群が18例で，発症率はそれぞれ27.8/1,000例/年と26.8/1,000例/年であった。（図1）。年齢，性別で調整したN群の相対危険度は0.973であり，有意差はなかった。脳卒中が両群とも8例ずつ，一過性脳虚血発作がN群のみ4例，心筋梗塞・狭心症は両群2例ずつ発症した。副作用では糖尿病の発症と，血清ナトリウムの低下，尿酸，尿素窒素の上昇がT群でN群に比べて有意に多かった。

この研究は，規模はあまり大きくないが，老年者高血圧の日本人において，Ca拮抗薬と利尿薬の心血管予後は同等であり，副作用は前者が少なかったことを示した点で評価される。

3．GLANT

GLANT（The evaluation Group of Long-term Antihypertensive Treatment）研究は，1990年に開始された臨床試験で，軽症から中等症の本態性高血圧患者を対象に，ACE（アンジオテンシン変換酵素）阻害薬であるdelaprilと，Ca拮抗薬の心血管イベントの予防効果を比較した試験である[2][3]。本試験はオープン試験ではあるが，大規模な多施設共同の臨床介入試験である。対象は，収縮期血

表1 GLANT研究におけるDelapril群とCa拮抗薬群の脳心血管系イベント

降圧薬投与前に脳血管障害や心筋梗塞の既往のある例，狭心症を有する例，血清クレアチニンが2.0mg/dL以上の腎障害例を除外した症例（Delapril群988例，Ca拮抗薬群981例）において脳心血管系イベントの発症を検討したところ，脳心血管系イベントはCa拮抗薬群で多い傾向がみられるが，有意差はない．

	Delapril群（n = 988）		Ca拮抗薬群（n = 981）	
	発症例数	死亡例数	発症例数	死亡例数
脳血管障害	5（0.5%）	0	11（1.1%）	3（0.3%）
脳出血	1（0.1%）		2（0.2%）	1（0.1%）
脳梗塞・血栓	3（0.3%）		8（0.8%）	2（0.2%）
TIA	1（0.1%）		1（0.1%）	
心疾患	5（0.5%）	2（0.2%）	7（0.7%）	0
心筋梗塞	1（0.1%）	1（0.1%）		
突然死	1（0.1%）	1（0.1%）		
狭心症	1（0.1%）		3（0.3%）	
心不全			2（0.2%）	
不整脈	2（0.2%）		2（0.2%）	
眼底出血	1（0.1%）		0	

GLANT：The evaluation Group of Long-term Antihypertensive Treatment，TIA：一過性脳虚血発作，Ca：カルシウム

（文献2，3より）

圧160mmHg以上かつ拡張期血圧90～114mmHgで，原則50～80歳の本態性高血圧患者である。最終的にACE阻害薬群988例と，Ca拮抗薬群981例が解析対象となった。薬剤の割り付けは，担当医師が臨床背景の似通った2例を選び，1例にdelapril，他方に市販のCa拮抗薬を投与するオープン試験の形式として，1年間追跡した。単剤で効果不十分の時は，β遮断薬か利尿薬，または両方を併用した。

試験開始時と終了時の血圧は，ACE阻害薬群170/99→147/86mmHg，Ca拮抗薬群171/99→142/83mmHgであり，有意にCa拮抗薬群の降圧度が大きかった。脳心血管イベントの発症率は，脳血管障害がACE阻害薬群5例，Ca拮抗薬群11例，心疾患がACE阻害薬群5例，Ca拮抗薬群7例と，Ca拮抗薬群で高い傾向があったものの，有意差はなかった。（表1）。副作用はACE阻害薬群で19.6%，Ca拮抗薬群で13.0%であった。

この研究は無作為ではなく追跡期間が短いが，Ca拮抗薬群で降圧効果が高かったにもかかわらず，ACE阻害薬群で脳血管障害発症頻度が低い傾向が見られた。ACE阻害薬が，Ca拮抗薬よりも臓器保護に優れている可能性を示唆し，また，Ca拮抗薬が忍容性では優れていることを示している。

4．PATE-Hypertension

PATE-Hypertension（Practitioner's Trial on the Efficacy of Antihypertensive Treatment in the Elderly Hypertension）は，60歳以上の本態性高血圧患者を3年間，ACE阻害薬のdelaprilまたはCa拮抗薬のmanidipineで治療し，脳心血管イベントの発症率と，薬剤の副作用について検討した研究である[4]。薬剤は主治医の選択で，非盲検的に投与された。

総死亡は両群間で有意差はなかった。脳心血管イベントはACE阻害薬群が699例中34例（22.5/1,000例/年），Ca拮抗薬群が1,049例中50例（19.7/1,000例/年）であり，やはり有意差はなかった。治療期間中の血圧と心血管イベントの関係は，過

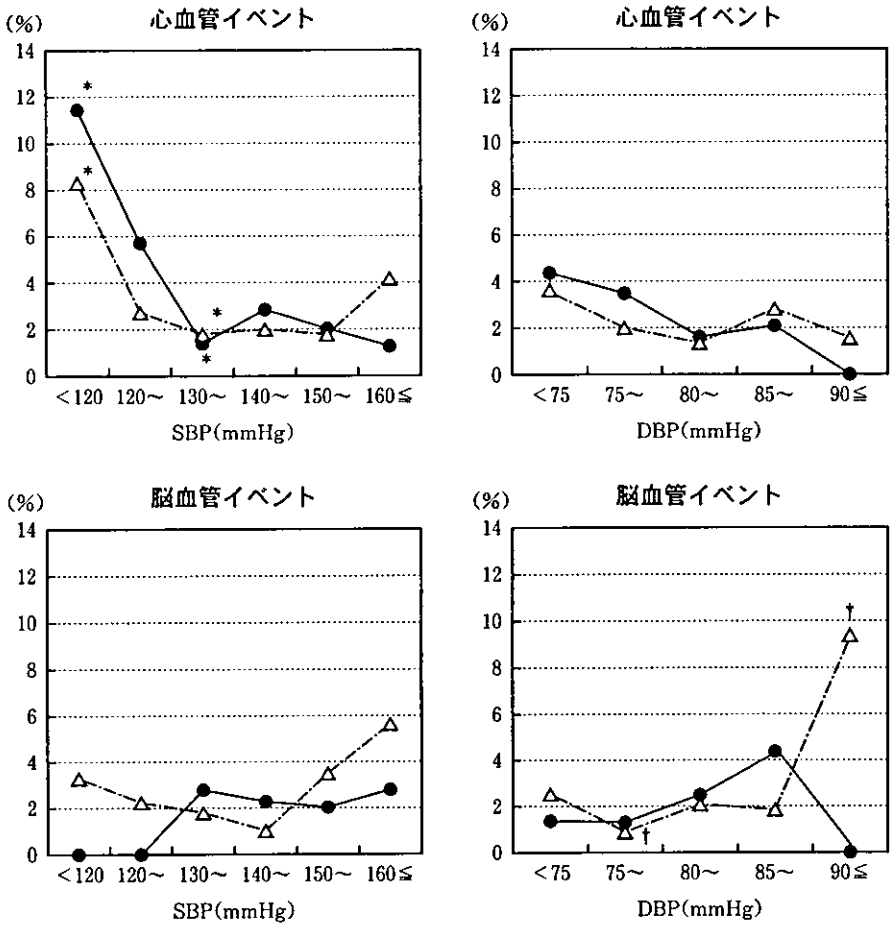

図2　PATE-Hypertension 研究における治療中の血圧値と心血管イベントとの関係

上段：心血管イベントは，収縮期血圧 120mmHg 未満において 130～139mmHg よりも有意に（$p < 0.01$）頻度が高かった．（＊印）．

下段：脳血管イベントは Ca 拮抗薬群においては拡張期血圧 75～79mmHg で，90 mmHg 以上よりも有意に（$p < 0.01$）頻度が低かった．（†印）．ACE 阻害薬群では同様の関係は認められなかった．

●：ACE 阻害薬群，△：Ca 拮抗薬群，上段：心血管イベント，下段：脳血管イベント

PATE-Hypertension：Practitioner's Trial on the Efficacy of Antihypertensive Treatment in the Elderly Hypertension，SBP：収縮期血圧，DBP：拡張期血圧

（文献 4 より）

度の降圧でも発症率の上昇を認める，いわゆる J-curve を呈した。副作用は，Ca 拮抗薬群よりも ACE 阻害薬群で多かった。

この研究は，目標降圧レベルが設定されていないが，ACE 阻害薬と Ca 拮抗薬は，高齢者高血圧における予後には差がなく，ACE 阻害薬は忍容性で劣ることを示唆している。また，過度の降圧は有害である可能性が示唆された。（図2）。

5．JATE および JATE Ⅱ

JATE(Japanese Trial on the Efficacy of Antihypertensive Treatment in the Elderly)研究は，高齢者（70～80 歳）軽症高血圧に対する治療効果を評価するために，Ca 拮抗薬（nitrendipine，nisoldipine，manidipine）のプラセボ対照の無作為二重盲検試験として，1992 年に開始された[5]。目

標登録患者数は2,000例と設定されたが，329例が登録されたのみで，1998年に追跡を終了した。

心血管イベントの発生率では，明らかな差はなかった。参加表明医師へのアンケート調査も行われ，症例登録が困難であった理由として，プラセボ対照試験に対する国民・医師両者のコンセンサスが得られていなかったこと，患者に利益がないことなどがあげられた。

この研究では十分な症例登録が得られず，本邦でプラセボを用いた臨床試験を実施することの困難さが示された[6]。

JATE Ⅱは，JATEの後を受けて行われた，高齢者高血圧を対象とするオープンの臨床試験である。プラセボは用いられず，Ca拮抗薬(上記3種に後にnifedipine CRが追加)を基礎薬として，治療期間は3年間である。661例が登録され，頭部CT(computed tomography)を含む臓器障害や心血管イベント，QOL (quality of life) などが評価された。2002年に終了し，解析結果の発表が予定されている。

6．J-MIND

J-MIND (Japan Multicenter Intervention of Antihypertensive Treatment for Nephropathy in Diabetics)は，高血圧を伴う2型糖尿病患者における尿アルブミン排泄量(AER)，および心血管イベントに対するCa拮抗薬（nifedipine持効錠）とACE阻害薬(enalapril)の効果を，2年間にわたり検討した研究である[7]。対象は，尿蛋白正常または微量アルブミン尿を伴う436例で，nefedipine持効錠群（N群），enalapril群（E群）に無作為に割り付けられた。目標血圧は140/90mmHg未満とし，目標に達しない場合はfurosemideまたはα遮断薬を追加した。

AERはN群（45→64mg/日），E群（42→74mg/日）と，ともに増加した。両群間で差はなかった。脳心血管イベントはN群で5例（2.2%），E群で8例（3.8%）に認められ，有意な差はなかった。この研究は，糖尿病性腎症の進展に対する効果は，Ca拮抗薬とACE阻害薬との間にあまり差がないことを示唆している。しかし，両者ともに腎症の進行を阻止できなかった。

7．J-MIC（B）

J-MIC（B）(Japan Multicenter Intervention for Cardiovascular Disease(B))は，冠動脈疾患を有する高血圧患者に，nifedipineとACE阻害薬を無作為に割り付け，予後を比較したものである[8]。観察期間は3年で，一次エンドポイントは心臓死，虚血性心疾患発症，冠動脈血行再建術および重症不整脈とし，二次エンドポイントは脳卒中，腎障害，心血管疾患以外の疾患および総死亡である。

Nifedipine群（N群）828例，ACE阻害薬群（A群）822例が解析対象となり，一次エンドポイントの発症率はN群で8.13/1,000例/年，A群で9.24で両群に有意差はなかった。虚血性心疾患を伴う高血圧患者の予後への効果は，Ca拮抗薬とACE阻害薬との間に差がないことが示唆された。

8．進行中の大規模臨床試験

1) JATOS

JATOS (Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients)は，高齢者高血圧治療における至適降圧レベルを検討するために企画された[9]。65～85歳の本態性高血圧患者を対象に，efonidipineを基礎薬として，降圧目標を収縮期血圧140mmHg未満，140～160mmHgの二群に分け，2年間の脳心血管疾患および腎障害の発症を評価比較する無作為臨床試験である。目標登録症例数は4,000例で，2001年4月に開始され，既に登録症例数は目標を達成している。2004年12月に終了する予定である。この研究は，ガイドラインにより異なっている，高齢者高血圧の降圧目標への答えになるものとして注目される。

2) CASE-J

CASE-J (Candesartan Antihypertensive Survival Evaluation in Japan)研究は，アンジオテンシンⅡ受容体拮抗薬（ARB）であるcandesartanと，Ca拮抗薬のamlodipineの効果を比較する試験である[10]。糖尿病，脳血管障害，冠動脈疾患，または腎障害を持つ，20～85歳の高リスク本態性高血圧患者が対象である。目標症例数は4,000例で，2001年9月に開始され，2005年12月に終

表2　海外と日本の高齢者高血圧の臨床試験における心血管イベントの発症率
わが国では欧米に比べて心血管イベントが少ない傾向がある．

	臨床試験	年齢（歳）	脳心血管合併イベント		脳血管イベント		心血管イベント	
			プラセボ	実薬*	プラセボ	実薬*	プラセボ	実薬*
海外	EWPHE	60～96	114.8	74.2‡	36.3	20.7†	22.0	18.5
	SHEP	≧60	68.3	49.3‡	14.9	9.7§	20.2	14.8‡
	STOP-Hypertension	70～84	55.5	33.5‡	31.3	16.8‡	16.5	14.4
	MRC Ⅱ	65～74	25.2	21.0†	10.8	8.1‡	12.7	10.3
	臨床試験	年齢（歳）	プラセボ	カルシウム拮抗薬	プラセボ	カルシウム拮抗薬	プラセボ	カルシウム拮抗薬
	Syst-Eur	68～98	33.9	23.3¶	13.7	7.9‡	20.5	15.1†
	Syst-China	≧60	33.3	21.4‡	20.8	13.0‡	10.8	6.9
日本	臨床試験	年齢（歳）	ACE阻害薬	カルシウム拮抗薬	ACE阻害薬	カルシウム拮抗薬	ACE阻害薬	カルシウム拮抗薬
	GLANT	60±10	12.7	22.7	4.9†	14.7	4.9	2.9
	PATE-Hypertension	70±7	22.5	19.7	9.3	9.1	13.3	10.7

*利尿薬またはβ遮断薬，‡$P < 0.01$，†$P < 0.05$，§$P < 0.001$

EWPHE：European Working Party on High Blood Pressure in the Elderly trial

SHEP：The Systolic Hypertension in the Elderly Program

STOP-Hypertension：Swedish Trial in Old Patients with Hypertension

MRC Ⅱ：Medical Research Council Trial of treatment of hypertension in older adults

Syst-Eur：Systolic Hypertension in Europe，Syst-China：Systolic Hypertension in China

GLANT：The evaluation Group of Long-term Antihypertensive Treatment

PATE-Hypertension：Practitioner's Trial on the Efficacy of Antihypertensive Treatment in the Elderly Hypertension

（文献4より）

了する予定である。この研究においても，既に目標症例数は達成されている。ARBとCa拮抗薬を比較する大規模臨床試験は海外でも進行中であるが，日本人におけるエビデンスをもたらすであろう。

3）HOMED-BP

HOMED-BP（Hypertension Objective Treatment based on Measurement by Electrical Devices of Blood Pressure Study）は，家庭血圧をベースに，降圧レベルと降圧薬の効果を評価する大規模研究である[11]。40～80歳の高血圧患者9,000例を登録し，それら患者をCa拮抗薬，ACE阻害薬，ARBいずれかの薬剤群と，家庭血圧135/85 mmHg未満と125/80mmHg未満の降圧目標とに無作為に割り付け，7年間追跡する。また，すべての参加施設をインターネットでホストコンピュータに接続し，降圧薬の処方や増・減量の判断を中央で管理するという，新しい手法がとられている。

2001年5月よりパイロット研究が開始され，2002年3月に本試験が開始された。2002年末で約1,400人が登録されている。この研究は，家庭血圧による至適降圧レベルと降圧薬の効果についての，重要な知見を提供してくれるであろう。

4）HOSP

HOSP（Hypertension Control Based on Home Systolic Pressure Study）研究は，家庭収縮期血圧の至適血圧レベルを検討し，同時にCa拮抗薬amlodipineと，ARBのlosartanの効果を比較する無作為臨床試験である[12]。パイロット研究が2000年4月に開始され，約170例が登録された。本試験は，国立循環器病センターと全国の国立病