Improving the management of hypertension: reconsidering efficacy assessment

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The 2007 guidelines paper and the 2009 update document, even more so, recognize the crucial importance of the assessment of total cardiovascular risk in the management of hypertension and, more specifically, in the decision-making process for treatment initiation. This differentiates European guidelines from American ones, which still mainly appear focused on blood pressure values rather than on global risk.”

**Guidelines on the management of hypertension: where do we stand?**

by G. Mancia and G. Grassi, Italy

The 2007 guidelines document on the diagnosis and management of hypertension, jointly issued by the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC),¹ and the recently published update paper² make a number of statements and recommendations on how to handle essential hypertension in current clinical practice. Along with these recommendations, the two documents also provide an overview of the priorities for hypertension research as well as on the perspectives of hypertension treatment in the next few years, based on the evidence available from clinical trials and meta-analyses. There are four areas of major clinical impact: (i) the assessment of global cardiovascular risk; (ii) blood pressure thresholds and targets for treatment; (iii) the need for combination drug treatment; and (iv) the so-called polypill issue. These four major areas contain novel elements, but also elements of controversy. Both will be addressed in a concise way by this editorial.

**Novel elements**

The 2007 guidelines paper and the 2009 update document, even more so, recognize the crucial importance of the assessment of total cardiovascular risk in the management of hypertension and, more specifically, in the decision-making process for treatment initiation.¹,² This differentiates European guidelines from American ones,³ which still mainly appear focused on blood pressure values rather than on global risk. In particular, the guidelines update document published a few months ago makes a number of recommendations that can be summarized as follows.

First, quantification of total cardiovascular risk must include a search for subclinical organ damage, which is common in the clinical course of the hypertensive state and retains independent prognostic significance. Second, in hypertension the detection of organ damage brings cardiovascular risk into the high range independently of the severity of blood pressure elevation. Third, several measures of renal, cardiac, and vascular damage can be taken into account for total cardiovascular risk quantification. Measures based on urinary protein excretion (including microalbuminuria) and electrocardiograms can be regarded, nevertheless, as more simple and widely available approaches. In addition, these measures are characterized by limited cost and satisfactory sensitivity.

Several other novel elements provided by the 2007 ESH/ESC guidelines and by the 2009 update on the assessment of organ damage and, more generally, on the evaluation of total cardiovascular risk deserve to be mentioned.¹ ² Both the documents recommend organ damage to be searched for in different organs because of the
Evidence that multiple organ damage (eg, in the kidney and the heart) carries a worse prognosis than damage limited to a single organ. They also recommend organ damage be assessed before and during treatment because data are now available that show that treatment-induced improvement of left ventricular hypertrophy (regression) and decreased urinary protein excretion (antiproteinuric effect) is associated with a reduced incidence of cardiovascular events.

Finally, they critically review the issue of markers of organ damage, which, although not yet recommended in clinical practice, may become of practical use in the not-too-far-distant future, such as pulse wave velocity, central blood pressure, endothelial dysfunction, cardiac and vascular tissue composition, and collagen markers. For some of these markers, it will also be possible to predict in the near future their use as indices of effectiveness of antihypertensive treatment. This is particularly the case for central blood pressure, given the evidence provided by the Conduit Artery Function Evaluation (CAFE) study that the combination amlodipine/perindopril may trigger more favorable effects on central aortic pressure than a β-blocker/diuretic association. This finding may thus represent the pathophysiological background for the evidence provided by the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) that an amlodipine/perindopril combination has a better impact on cardiovascular outcomes than a β-blocker/diuretic association.

Other areas of considerable interest are represented by blood pressure thresholds and treatment goals. Guidelines recommend starting drug treatment in grade 1 hypertensive patients at low or moderate risk when blood pressure is equal to or above 140/90 mm Hg after lifestyle modifications. These thresholds are similar in elderly hypertensives, based on the results of the HyVertension in the Very Elderly Trial (HYVET). Prompter treatment is recommended in grade 2 and 3 hypertension. In patients with high-normal blood pressure (a condition also known by the term "prehypertension"), drug treatment should be delayed when the overall cardiovascular risk is low.

As far as goals of treatment are concerned, the 2009 update document recommends that systolic blood pressure should be lowered below 140 mm Hg (and diastolic to 90 mm Hg) in all hypertensive patients, irrespective of their grade of risk. On the basis of the results of recent clinical studies, it appears prudent to lower blood pressure to values within the 130-139 mm Hg range for systolic and 80-85 mm Hg range for diastolic blood pressure. It thus appears that the concept of pursuing lower blood pressure goals in diabetics or very-high-risk patients is not recommended any more. This is because there is no evidence from trials of a greater benefit being derived from tight blood pressure control, nor can this procedure be regarded as easily achievable in current clinical practice. Lastly, the update document underlines the so-called "J-curve phenomenon" (ie, an increase rather than a reduction in the incidence of coronary events when blood pressure values are below 120-125 mm Hg for systolic and 70-75 mm Hg for diastolic blood pressure), suggesting that blood pressure should not be lowered too much, particularly in patients with a history of a previous coronary event.

Two further questions addressed by the ESH/ESC 2007 guidelines and by the 2009 update document are: (i) whether treatment of individuals at high or very high risk differs from that of lower risk ones only as regards the blood pressure threshold and target values for treatment; and (ii) whether similar treatment recommendations pertain to individuals in whom elevated cardiovascular risk is due to conditions other than diabetes or a history of cardiovascular or renal disease.

The former question has a clear answer because evidence exists that additional treatment peculiarities distinguish high- or very-high-risk individuals from lower-risk ones. For example, in high- and very-high-risk individuals, treatment with a combination of two or more antihypertensive drugs is almost always necessary, given that the size of blood pressure reduction to achieve is greater and that the chance of obtaining it with monotherapy is small. Also, starting treatment with a two-drug antihypertensive combination is advisable because delaying blood pressure control, even by a few months, may lead to an event. Finally, evidence exists that high- or very-high-risk hypertensive patients may obtain additional benefit by the addition of an antplatelet treatment and a statin to an effective antihypertensive drug regimen, the latter independently of whether serum cholesterol values are elevated or not.

The last consideration brings us to the third area of innovation in the guidelines update document, namely the crucial role of combination drug treatment in achieving effective blood pressure control. Indeed, as already mentioned in the 2007 ESH/ESC guidelines, combination drug treatment is the only approach that allows effective blood pressure control to be achieved in current clinical practice. The 2009 guidelines update document recommends this treatment strategy, which
may also offer advantages over monotherapy for treatment initiation, particularly, as mentioned above, in high-risk patients in whom early blood pressure control is indicated. Fixed-drug combinations are indicated, with the possibility of making a choice based on a wide range of two-drug combinations that include an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker with a diuretic, a β-blocker, or a calcium channel blocker. An ACE inhibitor/calcium channel blocker combination, as shown by the results of the Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, may be particularly effective and well tolerated, although further data on the effects of this combination need to be collected. Further data is also needed for the combination between angiotensin II receptor blockers and calcium antagonists, for which at present no outcome data have been provided.

Given the potential dysmetabolic effects of a diuretic/β-blocker combination, this therapeutic strategy should be avoided, but single components of the association can be safely combined to the other drug classes (particularly those acting on the renin-angiotensin system). The same conclusion applies to the combination of an ACE inhibitor and an angiotensin II receptor blocker, in the light of the negative data collected in the OnGoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET), particularly its unfavorable effects on renal function.

In conclusion, the guidelines update document discusses the potential advantages of the polypill (ie, a pill containing three antihypertensive agents—an ACE inhibitor, a β-blocker, and a diuretic—together with a statin and aspirin at low dose). Although promising, the polypill approach requires further evaluation, particularly in the primary prevention of cardiovascular disease.

Elements of controversy
Although providing conclusive answers to a number of questions raised following the publication of recent clinical trials and meta-analyses, the 2009 guidelines update document also focuses on a number of issues that still remain unresolved. This is the case, for example, for the implementation of the clinical use of alternative blood pressure measurements, such as 24-hour ambulatory blood pressure or home blood pressure. This is also the case for the future clinical use of “new” markers of organ damage and for the therapeutic approach to specific clinical states, such as high-normal blood pressure or mild hypertension, ie, conditions in which no clear-cut data based on the results of clinical trials have been provided so far. Due to the lack of act hoc clinical studies, it is also difficult to know whether antihypertensive treatment needs to be started in patients with grade 1 hypertension, even if they are at low risk. These unresolved issues may explain why the agenda for future clinical investigations in the field of hypertension still remains crowded.

References

Keywords: guidelines; cardiovascular risk; blood pressure; antihypertensive treatment; combination treatment; polypill
Directives sur la prise en charge de l'hypertension : où en est-on ?

par G. Mancia et G. Grassi, Italie

Le document des directives de 2007 et plus encore la mise à jour de 2009 reconnaissent l'importance cruciale de l'évaluation du risque cardio-vasculaire global dans la prise en charge de l'hypertension et, plus spécifiquement, dans la décision de mettre en œuvre un traitement. Les directives européennes diffèrent sur ce point des recommandations américaines, qui semblent principalement s'intéresser aux valeurs de la pression artérielle plutôt qu'au risque global.

Nouveaux éléments

Le document des directives de 2007 et plus encore la mise à jour de 2009 reconnaissent l'importance cruciale de l'évaluation du risque cardio-vasculaire global dans la prise en charge de l'hypertension et, plus spécifiquement, dans la décision de mettre en œuvre un traitement. Les directives européennes diffèrent sur ce point des recommandations américaines, qui semblent principalement s'intéresser aux valeurs de la pression artérielle plutôt qu'au risque global. Plus particulièrement, le document de mise à jour des directives publié il y a quelques mois propose un certain nombre de préconisations qui sont résumées ci-dessous.

Tout d'abord, la quantification du risque cardio-vasculaire global doit inclure une recherche des lésions organiques subcliniques, qui sont fréquentes au cours de l'évolution clinique de l'hypertension, et conservent une signification pronostique indépendante. En second lieu, dans l'hypertension, la mise en évidence de lésions organiques confère au risque cardio-vasculaire des valeurs élevées, indépendamment de la sévérité de l'augmentation de la pression artérielle. En troisième lieu, les différentes mesures des lésions rénales, cardiaques et vasculaires peuvent être prises en compte pour la quantification du risque cardio-vasculaire total. Les mesures basées sur l'excrétion des protéines urinaires (y compris la microalbuminurie) et les électrocardiogrammes peuvent être considérées comme les approches les plus...
Les autres domaines suscitant un intérêt considérable sont constitués par les valeurs seuils de pression artérielle et les objectifs thérapeutiques. Les directives recommandent de mettre en œuvre un traitement initial chez les patients atteints d’hypertension de grade 1 présentant un risque faible à modéré lorsque la pression artérielle est supérieure ou égale à 140/90 mm Hg après des modifications du style de vie. Ces valeurs seuils sont similaires chez les patients âgés hypertendus, sur la base des résultats de l’étude HYVET (Hypertension in the Very Elderly Trial). Un traitement plus rapide est recommandé en cas d’hypertension de grades 2 et 3. Chez les patients dont la pression artérielle est à la limite supérieure des valeurs normales (une situation également désignée par le terme de « préhypertension »), le traitement médicamenteux doit être retardé lorsque le risque cardio-vasculaire global est faible.

En ce qui concerne les objectifs thérapeutiques, le document de mise à jour de 2009 recommande que la pression artérielle systolique soit abaissée au-dessous de 140 mm Hg (et la pression diastolique au-dessous de 90 mm Hg) chez tous les patients hypertendus, quel que soit leur degré de risque. Sur la base des résultats d’études cliniques récentes, il paraît prudent d’abaisser la pression artérielle à des valeurs comprises entre 130 et 139 mm Hg pour la pression artérielle systolique et 80 à 85 mm Hg pour la pression artérielle diastolique. Il semble en outre que le concept visant des valeurs de pression artérielle inférieures chez les patients diabétiques ou à très haut risque ne soit plus recommandé. Cela est dû au fait que les études n’ont pas apporté la preuve d’un bénéfice supérieur obtenu avec un contrôle strict de la pression artérielle, et n’ont pas montré la possibilité de mettre en œuvre facilement cette procédure dans la pratique clinique actuelle. Enfin, le document de mise à jour souligne le phénomène dit de « courbe en J » (c’est-à-dire, une augmentation plutôt qu’une réduction de l’incidence des événements coronariens lorsque les valeurs de la pression artérielle sont inférieures à 120-125 mm Hg pour la pression systolique et 70-75 mm Hg pour la pression artérielle diastolique), ce qui suggère que la pression artérielle ne doit pas être abaissée de façon excessive, en particulier chez les patients présentant des antécédents d’événements coronariens.

Deux autres questions ont été abordées par les directives 2007 de l’ESH/ESC 2007 et par le document de mise à jour 2009: (1) le traitement des individus à risque élevé ou très élevé est-il différent de celui des patients à risque plus faible uniquement en ce qui concerne les valeurs seuils de la pression artérielle et les valeurs cibles thérapeutiques ? et (2) des recommandations thérapeutiques similaires peuvent-elles s’appliquer à des individus chez lesquels l’augmentation du risque cardio-vasculaire est due à des affections autres que le diabète ou des antécédents de maladie cardio-vasculaire ou rénale.

La première question peut recevoir une réponse claire dans la mesure où des preuves montrent que, du point de vue des traitements complémentaires, les individus à haut risque ou à très haut risque doivent être distingués des patients à risque plus faible. Par exemple, chez les personnes à haut risque et à très haut risque, le traitement d’association par au moins deux antihypertenseurs est presque toujours nécessaire, dans la mesure où l’ampleur de la réduction de la pression artérielle qui doit être obtenue est supérieure, et que la probabilité de l’obtenir avec une monothérapie est faible. De même, un traitement initial par l’association de deux antihypertenseurs est
recommandé, car retarder le contrôle de la pression artérielle, même de quelques mois, peut conduire à un événement. Enfin, certaines données indiquent que les patients hypertendus à haut risque ou à très haut risque peuvent recueillir un bénéfice supplémentaire grâce à l’addition d’un traitement antiplaquettaire et d’une statine à un schéma antihypertenseur efficace, celui-ci étant mis en œuvre que les concentrations sériques de cholestérol soient augmentées ou non1,2.

Le dernier point nous amène à aborder le troisième domaine d’innovation traité dans le document de mise à jour des directives2, c’est-à-dire le rôle crucial du traitement d’association dans le contrôle efficace de la pression artérielle. En fait, comme cela a déjà été mentionné dans les directives 2007 de l’ESH/ESC1, le traitement d’association est la seule approche qui permet un contrôle efficace de la pression artérielle en pratique clinique. Le document de mise à jour des directives 20092 recommande cette stratégie thérapeutique, qui peut également offrir des avantages par rapport à une monothérapie, en particulier, comme cela a été mentionné ci-dessus, pour les patients à haut risque chez lesquels un contrôle rapide de la pression artérielle est conseillé. Les associations fixes sont indiquées, avec la possibilité de choisir dans une vaste offre d’associations de deux médicaments comprenant un inhibiteur de l’enzyme de conversion de l’angiotensine (ECA) ou un antagoniste des récepteurs de l’angiotensine II avec un diurétique, un bétabloquant ou un inhibiteur calcique. L’association d’un inhibiteur de l’ECA et d’un inhibiteur calcique, comme le montrent les résultats de l’étude ACCOMPLISH (Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension)15, s’avère particulièrement efficace et bien tolérée, bien que des données complémentaires sur les effets de cette association doivent encore être collectées. Des résultats additionnels sont également nécessaires sur l’association des antagonistes des récepteurs de l’angiotensine II et des inhibiteurs calciques, pour laquelle aucune évaluation n’a été fournie jusqu’à présent.

En conclusion, le document de mise à jour des directives aborde les avantages potentiels de la polypilule (c’est-à-dire, un comprimé contenant trois antihypertenseurs – un inhibiteur de l’ECA, un bétabloquant et un diurétique – associés à une statine et de l’aspirine à faible dose)18. Malgré les promesses qu’elle peut porter, la polypilule nécessite des évaluations complémentaires, en particulier sur la prévention primaire des maladies cardio-vasculaires.

Éléments de controverse

Bien qu’il apporte des réponses concluantes à un certain nombre de questions soulevées à la suite de la publication de récentes études cliniques et méta-analyses, le document de mise à jour des directives de 2009 souligne également différents problèmes restés sans réponse2. C’est le cas, par exemple, de l’utilisation clinique de mesures alternatives de la pression artérielle, notamment la pression artérielle ambulatoire sur 24 heures ou l’automesure de la pression artérielle à domicile. C’est également le cas de la future utilisation clinique des « nouveaux » marqueurs des lésions organiques, et de l’approche thérapeutique appliquée à des situations cliniques spécifiques, par exemple une pression artérielle à la limite supérieure de la normale ou une légère hypertension, c’est-à-dire des situations dans lesquelles aucune donnée seuil déterminée sur la base de résultats d’études cliniques n’a été fournie jusqu’à présent. Compte tenu de l’absence d’études cliniques ad hoc, il est également difficile de savoir si un traitement antihypertenseur doit être mis en œuvre chez des patients présentant une hypertension de grade 1, même s’ils sont exposés à des risques faibles. Ces problèmes non résolus peuvent expliquer pourquoi le programme des futures investigations cliniques dans le domaine de l’hypertension reste particulièrement chargé.
Can we improve BP control rates? Lessons from the Health Survey for England 2006

by N. Poulter, United Kingdom

National and international surveys are consistent in showing that the management of hypertension is suboptimal, with a minority of hypertension patients getting their blood pressures (BPs) controlled to currently recommended targets. Raised BP is currently the biggest single contributor to global death, and the prevalence of hypertension is expected to increase over the next 2 decades. It is therefore critical to improve the management of raised BP, so that the dreadful toll on global health caused by raised BP is reduced. The reasons for the poor BP control observed around the world are multiple and various, but include inadequate use of antihypertensive agents as a result of physician inertia, drug side effects and drug costs, which adversely affect adherence to therapy, and drug resistance. Every year in England, a nationally representative survey of various aspects of health of the noninstitutionalized population takes place. Intermittently—approximately every 4 years—the focus of investigation is cardiovascular (CV) disease, which includes a systematical evaluation of BP. This database provides an invaluable source of data about mean BP levels, the prevalence of hypertension, and how BP is managed in the English adult population. In the most recent CV focus year, 2006, results showed that raised BP was being managed more effectively than in previous years (1994, 1998, and 2003), with higher rates of awareness, treatment, and control. Taking these 4 surveys into account, the key explanation for improving BP management appears to be raised levels of education among doctors and patients, which leads to raised levels of awareness, treatment, and the use of dietary measures. In addition, among those treated with drugs, more antihypertensive agents are being used to greater effect.

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changes are associated with raised BP. Despite our increasing knowledge of the pathophysiology of CV diseases and the major risk factors for these disorders, such as hypertension, we face a major increase in the prevalence of hypertension, which currently generates more deaths than any other risk factor, due to the adverse effects of the process of development.

It is therefore critical that major efforts are devised for trying to prevent the currently anticipated increases in the prevalence of hypertension and that improvements in the treatment for those with hypertension are made.

It is apparent from national and international survey data from all over the world that the management of hypertension is suboptimal. Although there are clear variations by age, sex, and geography in the proportion of patients with hypertension who get their BPs controlled to current targets, overall a minority of patients are controlled to what is currently considered optimal. The reasons for this are multiple and vary from patient to patient, but explanations include inadequate drugs, drug side effects, poor adherence to therapy, drug costs, confusing guidelines, resistant hypertension, and physician inertia. Physicians favor all except the last of these reasons as plausible, but in reality the failure of physicians to act on currently available knowledge with currently available drugs is undoubtedly a major contributor to the suboptimal hypertension management that prevails worldwide.

This article reviews how BP treatment may be improved in terms of achieving better BP control based on evidence from the latest in the series of annual national surveys carried out in England (the Health Survey for England).

### Health Survey for England: methods

The Health Survey for England (HSE) is an annual, nationally representative sample of the noninstitutionalized population of all ages randomly selected from residential addresses in England. The primary focus of the survey varies from year to year, but in 1994, 1998, 2003, and 2006, the focus was on CV disease. The detailed sampling and data collection methods have been described elsewhere.

Data collection took place throughout the year and was essentially the same in all the CV focus years. It involved an interview, which was followed by a visit by a nurse, who measured BP, took a blood sample, and recorded the use of medicines. Sitting BP readings were taken on the right arm after 5 minutes of rest using an Omron HEM 907 and an appropriately sized cuff. BP data presented here are based on the means of the last 2 of 3 measurement. Participants were excluded if they had exercised, eaten, drunk alcohol, or smoked in the 30 minutes before BP measurement. The interviewers collected sociodemographic information, including self-assigned ethnicity, and participants were asked if they had been told by a doctor or a nurse that they had high BP. Information about diabetes mellitus and history of CV disease (angina, heart attack, or stroke) was also collected. Research ethics approval was obtained from the appropriate committees before each survey.

Hypertension was defined as systolic blood pressure (SBP) ≥140 mm Hg, diastolic blood pressure (DBP) ≥90 mm Hg, or being on treatment for blood pressure. Isolated systolic hypertension was defined as follows: stage 1 was defined as an SBP of 140 to 159 mm Hg and DBP <90 mm Hg; and stage 2 was defined as SBP ≥160 mm Hg and DBP <90 mm Hg. Details of antihypertensive agents being taken, if any, were recorded by the nurse. Respondents who were not sure whether an antihypertensive drug had been prescribed to treat hypertension were considered a treated hypertensive individual if they also reported a history of hypertension. We examined the use of antihypertensive drugs by class and compared this with the current British guidelines by age and ethnicity. Analyses were restricted to participants aged ≥16 years with no missing data. Samples were weighted to allow for nonresponse differences both to the interview and then to the nurse visit. We computed awareness, treatment, and control rates among hypertensive men and women from HSE 2006 and compared these with data from previous years. Awareness was defined as a self-report of having been diagnosed as hypertensive by a doctor or nurse (excluding women during pregnancy). For control rates, we considered blood pressure target levels: <140/90 mm Hg (the target recommended in most hypertension guidelines).

### Results

In 2006, 10,489 adults aged ≥16 years were interviewed and had a nurse visit. Of these, 7478 had valid blood pressure readings (3314 men and 4164 women) with a mean age of 47 years in both sexes. The full results relating to BP and hypertension of the 2006 survey have been published previously. Mean SBP rose across the whole age range in both men and women, but was higher in men than women until the age of 70 years (Figure 1). DBPs also rose with age in both sexes, but only until the age of 60 years, above which blood pressures
fell systematically. DBPs were generally, but not always, higher in men than women. Overall mean BP levels were 130.8/74.2 mm Hg in men and 124.0/72.4 mm Hg in women. Hypertension rates increased with age in both sexes and were more prevalent in men than women, except in the age range 70 to 79 years.

Overall, hypertension was observed in 30% of informants (32% of men and 29% of women), and in those aged <30 years, almost half of this hypertension (16% of men and 12% of women) was stage 1 isolated systolic hypertension. Mean BP levels and prevalences of hypertension in 2006 compared favorably with those reported in 2003 when mean blood pressures were 131.4/74.5 mm Hg in men and 125.7/73.3 mm Hg in women, and overall hypertension rates were 33% and 30%, respectively.

In 2006, two thirds of those classified as hypertensive were aware of their diagnosis, awareness being more common among women than men in all age groups (Table I; and Figure 2, page 230). Among the hypertensive population, more than 60% of women, but fewer than half of the men were on treatment for hypertension. Similarly, control rates to <140/90 mm Hg were higher overall among women than men, with approximately one third and one quarter, respectively, having controlled BP levels.

In 2006, of those on treatment for hypertension, 52% of informants (52% of men and 53% of women) had controlled BP (Table II, page 230). This compared with 46% (48% and 44%, respectively) for the equivalent populations in 2003. Similarly, the rates of awareness, treatment, and control observed in 2006 were all consistently greater than the equivalent figure reported in 2003, particularly among women.

About three quarters of patients with a self-reported history of CV or diabetes mellitus or an estimated 10-year risk of CV disease of ≥20% were hypertensive (Table II). Of those hypertensive patients who had CV disease or diabetes mellitus, about 85% were treated and about 44% had their BPs controlled to <140/90 mm Hg. However, for those hypertensives

<table>
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<th>Awareness/Treatment/Control in hypertensives</th>
<th>2003 Total</th>
<th>2006 Total</th>
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</tr>
<tr>
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<td>54*</td>
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<tr>
<td><strong>Control among hypertensives</strong></td>
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<td></td>
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<tr>
<td>BP &lt;140/90 mm Hg (%)</td>
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</tr>
<tr>
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<td>53*</td>
</tr>
<tr>
<td>Total</td>
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<td>52*</td>
</tr>
</tbody>
</table>

*P<0.001 for comparisons between 2003 and 2006.

Table I. Awareness, treatment, and control among those with hypertension (≥140/90 mm Hg or on medication) in HSE 2003 and HSE 2006.

Abbreviation: BP, blood pressure.

who did not have coronary heart disease or stroke, but whose estimated CV risk was ≥20%, only 55% were treated and 17% controlled. These rates are all greater than the equivalent figures in 2003. More than 60% of patients on treatment for hypertension were receiving ≥2 antihypertensive drugs (Table III), which compares with 56% in 2003. For those receiving monotherapy, the most common agents used were blockers of the renin-angiotensin system (RAS), either angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers. Overall, diuretics, β-blockers, and calcium channel blockers (CCBs) were the second, third, and fourth most commonly used agents, with similar levels of usage. However, this order changed when stratified by age and ethnicity (data not shown): β-blockers were clearly the second most commonly used agents for those <55 years of age, but diuretics and CCBs were more frequently used than β-blockers among older patients or those of African origin (data not shown). The most common combination of drugs among those taking 2 agents

Table II. Management of hypertension among those with past history of angina, heart attack, or stroke; diabetes mellitus; and CVD risk ≥20%.

<table>
<thead>
<tr>
<th>Treatment/Control in hypertensives</th>
<th>Past history of angina, heart attack, or stroke</th>
<th>Diabetes mellitus*</th>
<th>CVD risk ≥20% (Age ≥30 years only)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All with condition (n)</td>
<td>460</td>
<td>380</td>
<td>830</td>
</tr>
<tr>
<td>Hypertensive (n, [%])</td>
<td>377 (82)</td>
<td>284 (75)</td>
<td>626 (75)</td>
</tr>
<tr>
<td>Treated (%)</td>
<td>86</td>
<td>85</td>
<td>55</td>
</tr>
<tr>
<td>Controlled (&lt;140/90 mm Hg [%])</td>
<td>47</td>
<td>42</td>
<td>17</td>
</tr>
</tbody>
</table>

*Data include doctor diagnosed and exclude pregnancy.

Table III. Type of drugs used in the Health Survey for England 2006.

<table>
<thead>
<tr>
<th>Type of drug</th>
<th>Total (%)</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>One drug (39%, n=543)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic</td>
<td>23 (1.8)</td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>21 (1.8)</td>
<td></td>
</tr>
<tr>
<td>RAS blocker</td>
<td>34 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>19 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Other drug affecting BP</td>
<td>3 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Two drugs (40%, n=552)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics + β-blocker</td>
<td>13 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Diuretics + calcium antagonist</td>
<td>16 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Diuretics + RAS blocker</td>
<td>26 (1.9)</td>
<td></td>
</tr>
<tr>
<td>β-Blocker + RAS blocker</td>
<td>16 (1.5)</td>
<td></td>
</tr>
<tr>
<td>β-Blocker + calcium antagonist</td>
<td>6 (1.0)</td>
<td></td>
</tr>
<tr>
<td>RAS blocker + calcium antagonist</td>
<td>15 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>8 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Three drugs (16%, n=220)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic + β-blocker + calcium antagonist</td>
<td>17 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Diuretic + β-blocker + RAS blocker</td>
<td>28 (3.0)</td>
<td></td>
</tr>
<tr>
<td>Diuretic + RAS blocker + calcium antagonist</td>
<td>31 (3.1)</td>
<td></td>
</tr>
<tr>
<td>β-Blocker + RAS blocker + calcium antagonist</td>
<td>8 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>16 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Four drugs (4%, n=60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic + β-blockers + calcium antagonist + RAS blocker</td>
<td>37 (6.2)</td>
<td></td>
</tr>
<tr>
<td>Diuretic + calcium antagonist + RAS blocker + α-blocker</td>
<td>17 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Diuretic + β-blocker + RAS blocker + α-blocker</td>
<td>8 (3.5)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>38 (6.3)</td>
<td></td>
</tr>
</tbody>
</table>
was a RAS blocker plus a diuretic, with a diuretic plus a CCB, a RAS blocker plus a \(\beta\)-blocker, and a RAS blocker plus a CCB having similar but lower levels of usage than a RAS blocker plus a diuretic (Table III). Again, when stratified by age and ethnicity, the order of preference changed for those aged <55 years, with greater use of RAS blockade plus \(\beta\)-blockers, whereas diuretics plus CCBs were used together relatively less often in this age group (data not shown). When 3 agents were used, the most common combination of agents was a RAS blocker, diuretic, and CCB, with a RAS blocker, diuretic, and \(\beta\)-blocker a close second.

Discussion

The HSE 2006 data show that for the first time in England, the majority of those treated for hypertension were controlled to the target of <140/90 mm Hg. These results represent improvements compared with HSE data from 1994, 1998, and 2003 in terms of awareness and treatment and control rates, for men and women.\(^6,7\) In the UK, the local hypertension guidelines recommend treating all BPs greater than 160/90 mm Hg, but for BPs >140/90 mm Hg treatment should only be initiated if the estimated 10-year CV risk is \(\geq 20\%\) and/or if the patient has diabetes or established CV disease.\(^9,10\) However, using 140/90 mm Hg as the recommended treatment threshold—in keeping with the latest European\(^11\) and American guidelines\(^12\)—only 54\% of those above this threshold were treated and, therefore overall, only 28\% are controlled. Nevertheless, this compares favorably with overall control rates (using the 140/90 mm Hg definition for treatment threshold and target) in several other countries\(^13\) and with English data in earlier years.\(^6,8\) Taking the British recommendation to treat those at \(\geq 20\%\) 10-year risk, only 55\% were treated and of those less than one third were controlled. Clearly using the more aggressive target of <130/80 mm Hg for patients with diabetes, significant renal dysfunction, or established CV disease, control rates are worse than those shown in Table II.

One of the major reasons for improved hypertension management in the UK between 1994 and 2006 is the increased use of two or more agents. In 1994, only 40\% of treated patients were on \(\geq 2\) drugs for hypertension, whereas in 2006, 61\% were on \(\geq 2\) drugs. The improvements reported between 1994 and 1998 were thought, in part at least, to be attributable to improved uptake of nonpharmacological advice.\(^7\) It may also be that better BP control is partly attributable to better selection of antihypertensive agents and combinations of agents, which in turn may reflect successes of the guidelines produced by the British Hypertension Society (BHS)\(^9,10,14\) and latterly by the BHS in collaboration with the National Institute for Health and Clinical Excellence (NICE).\(^10\)

These guidelines currently recommend the use of either an “A+C” (where “A” stands for ACE inhibitors or angiotensin receptor blockers and “C” for CCBs) or “A+D” (where “D” stands for diuretics) combination. In contrast with the results in 1994\(^4\) and in contradiction to the latest British Guidance, the most common first-line agent was a RAS blocker—“A” drug, using the terminology used in the British Guidelines.\(^9,10\) The most common second-line drug was a diuretic (or “D” drug), being used by 55\% of patients using two agents, and the most common combination of drugs used by those using two agents was “A+D.” However, the results of the recent Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial\(^15\) show that benazepril plus amlodipine (“A+C”) was significantly superior to benazepril plus hydrochlorothiazide (“A+D”) in terms of preventing major CV events.

Furthermore, the Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure–Lowering Arm (ASCOT-BPLA) trial provided evidence of the superiority of an antihypertensive regimen using the CCB amlodipine and adding the ACE inhibitor perindopril over a regimen using a \(\beta\)-blocker and adding a low-dose thiazide diuretic, in terms of preventing both all-cause and CV mortality and major CV events. It may be therefore that practice changes in England to reflect the evidence base, and the combination of “A+C” may increase from its current position as the fourth most common combination used.

It is hard to tell how far the improvements in BP management that occurred between 2003 and 2006 reflect the new contract to which general practitioners have been working since April 2004,\(^16\) because improvements had been apparent between 1994 and 1998\(^7\) and between 1998 and 2003.\(^8\) However, the pattern of treatment and control rates for those targets that attracted financial rewards suggests that the contract is likely to have contributed to improvements.

Meanwhile, whatever the reasons for the improvements that did occur during this 3-year period, we estimate that between 4000 and 8000 fatal or major nonfatal CV events were prevented as a result of the improved BP control apparent in Table I.

Summary and conclusions

Progressive improvement in several aspects of hypertension management—rates of awareness, treatment, and control—has been apparent in England between 1994 and 2006, as witnessed by data from four of the annual HSEs that focused on CV disease and associated risk factors. These four surveys in 1994,\(^8\) 1998,\(^1\) 2003,\(^3\) and 2006\(^6\) provide high-quality and standardized nationally representative data on BP levels and the management of hypertension.

The determinants of the improvements observed cannot be definitively identified, but appear to include:

- The increased use of nonpharmacological advice.
- The increased use of more antihypertensive agents and different classes of agents.
The stimuli for these changes are again not certain, but are likely to include at least two major factors. Firstly, the publication of a series of guidelines by the BHS,13,14 and the attempts of this society to disseminate and implement the recommendations included in the guidelines. Secondly the new GP contract, the new General Medical Services (nGMS) contract, which included a pay-for-performance component for aspects of hypertension management, including BP control.16

During the last 15 years, the critical role that raised BP plays in terms of contributions to global death has become increasingly clear and increasing trial evidence17-19 has become available. Both types of data have helped guide and encourage improved hypertension management.

Looking to the future, “more of the same” is required—that is, continued improvements are required particularly with regard to those who are at high estimated CV risk, but who have not yet experienced CV symptoms and are not diabetic (Table II).

Meanwhile, more data are required to confirm that treating raised BP in the systolic range 140-159 mm Hg and diastolic range 90-99 mm Hg is cost-effective for subjects at low estimated CV risk. Furthermore, more data are needed to confirm which combinations of therapy are best when two, three, and four drugs are combined. Current best evidence based on two major trials ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) and ACCOMPLISH suggests “A+C” drugs are likely to be the most effective at preventing CV events,20,21 but only observational data are available to advise drug sequencing thereafter.

Whether any new drug classes—currently available (direct renin inhibitor) or in the pipeline—will impact importantly on optimal drug sequencing remains to be seen, but trials are in progress evaluating the management of resistant hypertension.

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References

Keywords: national survey; hypertension; awareness; treatment; control
Peut-on améliorer les taux de contrôle de la pression artérielle ? Les leçons de la Health Survey 2006 pour l'Angleterre

Les études nationales et internationales s'accordent à considérer que la prise en charge de l’hypertension reste sous-optimale, la pression artérielle (PA) n’étant contrôlée de façon conforme aux recommandations actuelles que chez une minorité de patients hypertendus. Une PA élevée est actuellement le principal facteur de risque de mortalité globale, dans un contexte où l’on s’attend à une augmentation de la prévalence de l’hypertension au cours des 20 prochaines années. Il est donc urgent d’améliorer la prise en charge de l’hypertension, afin de diminuer ses conséquences dramatiques sur la santé publique. Les raisons du mauvais contrôle de la PA dans le monde sont multiples et variées, mais associent en tout état de cause : (1) l’usage inadéquat des antihypertenseurs du fait d’une certaine inertie des médecins ; (2) les effets indésirables et la cherté des médicaments (qui diminuent l’observance au traitement) ; et (3) la résistance au traitement. En Angleterre, chaque année, a lieu une étude représentative à l’échelle nationale, portant sur divers aspects de la santé de la population ambulatoire. La maladie cardio-vasculaire (CV) revient environ tous les 4 ans sur la sellette, et son évaluation comprend une mesure systématique de la PA. Il se constitue ainsi une base de données précieuse sur les niveaux moyens de PA, la prévalence de l’hypertension et la qualité de la prise en charge de cette dernière dans la population anglaise adulte. Les résultats les plus récents concernant la maladie CV, publiés en 2006, ont montré une meilleure prise en charge de l’hypertension que par les années précédentes (1994, 1998 et 2003), avec des taux plus importants de sensibilisation à la maladie, de traitement et de contrôle. Les résultats relevés au cours des quatre années citées concordent pour démontrer que la clé de l’amélioration de la prise en charge de la PA réside en une meilleure information des médecins et des patients. Ceci se traduit par une plus grande sensibilisation au problème de l’hypertension et une mise en œuvre de meilleurs traitements et de mesures diététiques plus efficaces. Quant aux médicaments antihypertenseurs, lorsqu’ils sont indiqués, leur éventail s’est élargi, et ils sont utilisés de façon plus efficace.
Destiffening therapy" means that, in controlled therapeutic trials, a significant and selective reduction of systolic blood pressure (BP) has been obtained in long-term treatment by comparison with a control group. The demonstration requires a reduction of central BP in association with a significant decrease of arterial stiffness and/or attenuation of wave reflections. For this purpose, all clinical trials in recent years have used angiotensin II blockade, mainly through angiotensin-converting enzyme inhibition, and frequently in combination with a diuretic and/or a calcium antagonist. Cardiovascular outcomes are significantly better than in controls, particularly when such controls involve a β-blocking agent.

Prospective studies from Framingham have focused attention on brachial systolic blood pressure (SBP) as a better guide than brachial diastolic blood pressure (DBP) for evaluation of cardiovascular (CV) risk. In large populations, antihypertensive drug therapy frequently achieves adequate DBP control (≤90 mm Hg), but SBP control (SBP ≤140 mm Hg) is much more difficult to attain. The findings have focused attention on the factors that modulate central (aortic) SBP and pulse pressure (PP) levels in hypertensive individuals, and therefore on the role of increased arterial stiffness and/or wave reflections in the mechanism of hypertension, and hence CV risk.

A major function of central (aortic) arteries is to change the PP arriving from the heart into a steady pressure at the peripheral level, thus obtaining optimal oxygenation of tissues. This major modification is a consequence of the so-called Windkessel effect. During systole, part of the stroke volume flows directly toward the periphery, causing systolic perfusion. The other part of stroke volume is stored within the elastic thoracic aorta wall and restored during diastole, causing diastolic perfusion. The combination of systolic and diastolic perfusion is responsible for a continuous and steady flow, which contrasts with the alternating cyclic movement initiated by the heart. This Windkessel effect has a major impact on central SBP and PP regulation, through alterations produced by aortic stiffness and wave reflections.

This review consists of 2 parts: (i) the hemodynamic and epidemiological basis of propagation of the pressure wave along the vascular tree; and (ii) the principal strategies to lower large artery stiffness and wave reflections in the treatment of hypertension.
Hemodynamic and epidemiological basis of pressure wave propagation

Components of the BP curve
There are 2 different components of the blood pressure (BP) curve in the arterial tree: a steady component and a pulsatile component. The former is expressed by mean arterial pressure (MAP), the product of blood flow by vascular resistance, which represents the main index reflecting the status of small arteries, mainly their diameter. The latter is PP, the difference between SBP and DBP. This parameter is determined by stroke volume, aortic stiffness, and wave reflections. The two latter factors, but not stroke volume, contribute, through the aorta's elastic properties, to the Windkessel effect. Although MAP and PP are associated within the same BP curve, each of these parameters is a significant and independent predictor of CV risk. Whereas MAP is a predictor of overall CV risk (stroke, heart failure, renal insufficiency), PP is mainly related to the unique presence of coronary risk. Central PP, not brachial PP, is the more powerful predictor in this context.

BP propagation and aortic stiffness
Following ventricular contraction, the pressure pulse generated by the heart travels along the aorta as a wave. The velocity of propagation of this wave (ie, pulse wave velocity [PWV]) along the aorta is calculated from the interval between two BP curves located at two different sites in the aortic tree (Figure 1). Because a fundamental principle is that pulse waves travel faster in stiffer arteries, PWV measurement is considered the best surrogate to evaluate aortic stiffness in man. Its value is 3-5 m/s in young persons at rest, but increases considerably with age. Carotid-femoral (aortic) PWV is nowadays considered as a significant and powerful predictor of CV risk independent of age and MAP. PWV of the upper and lower limbs has no predictive value.

When BP measurements are recorded simultaneously at different points along the aorta, the pressure wave changes shape as it travels down the aorta. Whereas SBP and PP actually rise with distance from the heart, DBP and MAP fall slightly (about 4 mm Hg) during the same course along the aortic pathway (Figure 2). Thus, pressure oscillation amplitude between systole and diastole, ie, PP, nearly doubles. This SBP and PP amplification (Figure 2) is a physiological finding and approximately 14 mm Hg between the thoracic root of the aorta and the brachial artery.

Central wave reflections and age
If an individual's body length is about 2 m at most and aortic PWV is approximately 5 m/s, something must happen to the BP-curve shape within each beat if heart rate is 60 beats/min. What happens is the generation of wave reflections and their summation with the incident wave, as summarized in Figure 3, upper part on the left, page 236). The incident wave is driven away from the heart through highly conductive arteries. However, it encounters impedance mismatch at the junction of the highly conductive artery and high resistance arterioles, blocking its entry into the arterioles, and it is reflected backwards towards the heart. Thus, the shape of every pulse wave results from the summation of the incident (forward-traveling) and reflected (backward-traveling) pressure waves (Figure 3, upper part on the right). Reflected waves initiate from any discontinuity of the arterial or arteriolar wall, but mainly issue from high resistance vessels and their arteriolar bifurcations. Nevertheless, pulse-wave propagation and reflection vary considerably according to age (Figure 3, lower part). In young adults with maximum elasticity of their central arteries (low PWV),
the summation of the incident arterial pressure wave and the reflected wave results in progressive PP amplification, so that SBP is higher in the brachial artery than the ascending aorta. Because PWV is relatively low in the thoracic aorta, the reflected wave comes back during diastole, thereby maintaining DBP and boosting coronary perfusion (Figure 3). Hence, optimal arterial function is obtained along with adequate coronary perfusion.

The development of increasing arterial stiffness (high PWV) and altered wave reflections with aging completely abolishes the differences between central and peripheral PP by the age of 50-60 years, with major consequences on ventricular load and coronary perfusion. The increased PWV means that SBP is elevated by 30-40 mm Hg as a result of the early return of wave reflections. Furthermore, because the backward pressure returns in systole, and not in diastole, as a consequence of enhanced PW, DBP and coronary blood flow tend to be reduced, a situation promoting coronary ischemia. It can be noted that, in clinical practice, several factors can modulate the transit of wave reflections and thus central SBP and PP. First, reduced heart rate shifts wave reflections from diastole to systole, thus increasing "augmentation pressure" and central SBP. Second, angiotensin II inhibition and calcium blockade as well as insulin administration reduce wave reflections and central SBP. Insulin resistance has a reverse effect on central wave reflections.

**Modulation of aortic stiffness and wave reflections**

In the long term, mechanical forces (shear or tensile stress) participate in the modulation of arterial stiffness, wall thickness, and wave reflections. In the absence of drug treatment, hypertensive remodeling is characterized, according to the Laplace law, by an increased wall/lumen ratio of arteries and arterioles, which represent the main site of vascular resistance and microcirculation, but also the origin of wave reflections. Drug-induced regression of arteriolar hypertrophy is associated with a reduction in vascular resistance and reflection coefficients, thereby attenuating wave reflections, and, in the end, decreasing central SBP and PP. This process becomes significant approximately 1 year after the beginning of drug treatment of hypertensive subjects. Reduction of arteriolar hypertrophy is consistently obtained with angiotensin or calcium blockade, but never with β-blocking agents or hydrochlorothiazide. Endothelial dysfunction may affect this process, mainly through attenuation of NO dysfunction and/or oxidative stress under drug treatment.

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**SELECTED ABBREVIATIONS AND ACRONYMS**

- ACE: angiotensin-converting enzyme
- Alx: augmentation index
- ARB: angiotensin receptor blocker
- ASCOT: Anglo-Scandinavian Cardiac Outcomes Trial
- BP: blood pressure
- CAFE: Conduit Artery Function Evaluation
- CCB: calcium channel blocker
- CV: cardiovascular
- DBP: diastolic blood pressure
- MAP: mean arterial pressure
- MBP: mean blood pressure
- PP: pulse pressure
- PWV: pulse wave velocity
- REASON: pREterax in regression of Arterial Stiffness in a contrOlled double-blind study
- SBP: systolic blood pressure
Pulsatile arterial hemodynamics and the basis of risk-reduction strategies in hypertension

Risk reduction strategies should reduce together and independently increased MAP and PP. While the latter is principally sensitive to angiotensin II blockade alone, the former requires the addition of diuretics and/or calcium channel blockers, but not of traditional β-blocking agents (with the exception of coronary ischemic disease). This entire process is explained.

◆ Importance of angiotensin blockade

Renin-angiotensin system blockade either by angiotensin-converting enzyme (ACE) inhibition or, to a lesser extent, AT1 receptor blockade is classically associated with reductions of vascular resistance and MAP. However, the effects on aortic PWV and central and peripheral PP have been incompletely investigated until recently, but are important to develop.

Studies on animal models and hypertensive subjects have shown that angiotensin II blockade, mainly with the ACE inhibitor perindopril, is associated with reverse remodeling of both small and large arteries via specific mechanisms, including anti-inflammatory and antifibrotic effects as well as changes in arterial attachments linking α5β1-integrin to its specific ligand fibronectin.15-17 These mechanisms are very important to consider in order to obtain a significant and selective reduction in central PP and arterial stiffness with angiotensin II blockade. Their effect on mechanotransduction is primarily subject to the mitogen-activated protein kinase system.

In hypertensive rats fed a low-salt diet, angiotensin II blockade by the angiotensin receptor blocker (ARB) valsartan normalizes central PP (<50 mm Hg), whereas MAP is not normalized (>100 mm Hg) with the same drug dosage.15,16 Furthermore, in hypertensive subjects under angiotensin II blockade with a normal sodium diet, not only is PWV decreased, but central BP and wave reflections are also attenuated and carotid-brachial SBP and PP amplifications are increased. Angiotensin II blockade improves or even normalizes the wall thickness of small resistance arteries and, at the same time, reduces carotid wave reflections, suggesting a cause-and-effect relationship between the two factors. This is the basis of all the new strategies using destiffening drug therapy.1-3

However, to further reduce MAP, angiotensin blockade may be given in combination either with diuretics or calcium channel blockers (CCBs), but not usually with conventional β-blockers, as described below.

◆ Angiotensin II blockade and diuretics

The main therapeutic trial demonstrating the predictive role of aortic stiffness in hypertensive subjects was conducted in end-stage renal disease patients on hemodialysis.18 The objective was to lower CV morbidity and mortality through a therapeutic regimen involving successively: salt and water depletion by dialysis; then, after randomization, an ACE inhibitor or CCB; and, finally, the combination of the two agents and/or their association with a β-blocker. Using this protocol, it was possible to evaluate with long-term follow-up (51 months) whether or not the drug-induced mean blood pressure (MBP) reduction was associated with a concomitant decrease in arterial stiffness impacting on CV risk.

During follow-up, it was clearly shown that in survivors, MBP, brachial PP, and aortic PWV were concomitantly lower (Figure 4). In contrast, for patients who died from CV events, MBP had been reduced to the same extent as in survivors, but neither PWV nor brachial PP had been significantly modified by drug treatment (Figure 4). Thus, survival in end-stage renal disease patients was significantly better when aortic
PWV declined in response to BP lowering. The adjusted relative risks for all-cause and CV mortality rates in those with unchanged PWV in response to BP changes were: 2.59 (95% confidence interval [CI], 1.51 to 4.43) and 2.35, respectively (95% CI, 1.23 to 4.51); P<0.01. The prognostic value of PWV sensitivity to BP reduction on survival was independent of age, BP changes, and blood-chemistry abnormalities. The results indicated that arterial stiffness was not only a risk factor contributing to the development of CV disease, but also a marker of established, more advanced, and less reversible arterial lesions. Finally, in this trial, survival seemed to be more closely associated with the use of an ACE inhibitor than other drugs. The use of β-blockers and/or CCB had no direct impact on the outcomes.18

The Complior study was the first study to show the feasibility of a large-scale interventional trial using PWV as the end point in 1703 hypertensive patients (mean age 50±12 years old; mean baseline SBP, 158±15 mm Hg; mean baseline DBP, 98±7 mm Hg; mean baseline carotid-femoral PWV, 11.6±2.4 m/s). Patients were treated for 6 months with the ACE inhibitor perindopril, adding indapamide if BP still was above 140/90 mm Hg. Significant decreases (P<0.001) in BP (SBP, -23.7±16.8 mm Hg; DBP, -14.6±10 mm Hg) and carotid-femoral PWV (-1.1±1.4 m/s) were obtained at 2 and 6 months.19

The REASON (pREterax in regression of Arterial Stiffness in a contrOllEd double-bliNd study) study11,20 was the first study to investigate the long-term interactions between central PP, arterial stiffness, and wave reflections, on the one hand, and drug treatment or end-organ damage (cardiac mass) of hypertensive subjects in middle age, on the other hand. The ACE inhibitor perindopril, combined with low-dose indapamide, was compared for 1 year of treatment with the β-blocker atenolol. For the same DBP and MBP decreases, perindopril/indapamide lowered SBP and PP more than atenolol. This finding was observed using not only routine BP measurement, but also 24-hour BP measurements.21 The reduction was more pronounced centrally (carotid artery) than peripherally (brachial artery). While the two drug regimens lowered PWV equally, only perindopril/indapamide (and not atenolol) reduced central PP and AIx (Figure 3).11,20 In addition, perindopril/indapamide decreased cardiac hypertrophy more than atenolol, and that decrease was attributed to the augmentation index (AIx) decrease, indicating that reduction of cardiac end-organ damage was mainly associated with a reduction of central SBP, PP, and wave reflections.11,20 In contrast, atenolol increased wave reflections and AIx through reduction of heart rate and a shift of the backward pressure wave from diastole to systole, thus excluding this drug from the destiffening strategy. Similar findings were observed when atenolol was compared to the ARB irbesartan.22

Angiotensin II blockade and CCB blockade

The Conduit Artery Function Evaluation (CAFE) study, a sub-analysis of the controlled Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)23 conducted in 2073 subjects showed that aortic PP, recorded noninvasively by radial tonometry and the application of generalized transfer functions, is a determinant of clinical outcomes, independent of age, other traditional CV risk factors, and even peripheral PP. In agreement with the REASON study,11,20 the results of CAFE (Figure 5)23 showed that treating subjects with a regimen based on the β-blocker atenolol and a diuretic versus another strategy based on the CCB amlodipine and the ACE inhibitor perindopril had similar effects on brachial SBP and PP, but differ-
therapy should selectively lower SBP and PP bearing in mind the complex interactions between small and large arteries, thereby opening the way to the development of suitable new long-term CV treatment strategies.

The comparison of effects between a CCB (azelnidipine) and a diuretic (hydrochlorothiazide), each in combination with the same ARB olmesartan, was also studied. Aortic SBP and brachial ambulatory 24-hour SBP were used as criteria of effectiveness. After adjustment for baseline covariates, the extent of reduction in central (aortic) SBP in the olmesartan/azelnidipine group was significantly greater than that in the olmesartan/diuretic group (the difference between groups was 5.2 mm Hg [95% CI, 0.3 to 10.2]; \( P = 0.039 \)), while the difference in the reduction in brachial SBP between the two group was not significant (2.6 mm Hg [95% CI, -2.2 to 7.5]; \( P = 0.29 \)). The aortic PWV showed a significantly greater reduction with the olmesartan/azelnidipine combination than with the olmesartan/hydrochlorothiazide combination (0.8 m/s [95% CI, 0.5 to 1.1]; \( P < 0.001 \)) after adjustment for covariates. The extent of reduction in brachial ambulatory SBP was similar between the groups. These data showed that the combination of olmesartan 20 mg/azelnidipine 16 mg had a more beneficial effect on central SBP and aortic stiffness than the combination of olmesartan 20 mg/hydrochlorothiazide 12.5 mg, despite the lack of a significant difference in brachial SBP reduction between the two treatments.

Recently, in a new substudy of the ASCOT trial, it was investigated whether directly measured carotid SBP differed between subjects randomized to amlodipine/perindopril and atenolol/hydrochlorothiazide therapies and whether this was accounted for by differences in wave reflection patterns. Wave intensity analysis was used to separate and quantify forward and backward waves. Brachial BP did not differ significantly between groups, but carotid SBP (127 mm Hg [12] versus 133 mm Hg [15]; \( P < 0.001 \)), the ratio of backward to forward pressure (0.48 [0.17] versus 0.53 [0.19]; \( P = 0.01 \)), and wave reflection index (19.8% [10.9%] versus 23.3% [13.3%]; \( P = 0.02 \)) were significantly lower in patients randomized to amlodipine/perindopril therapy.

Carotid SBP was lower in subjects randomized to amlodipine-based treatment compared with those randomized to atenolol/hydrochlorothiazide therapies and whether this was accounted for by differences in wave reflection patterns. Wave intensity analysis and wave separation show that the lower carotid SBP is attributable to a lower magnitude of wave reflection and not to changes in the timing of reflected waves, differences in heart rate, or changes in the forward wave reflection index (19.8% [10.9%] versus 23.3% [13.3%]; \( P = 0.02 \)) were significantly lower in patients randomized to amlodipine/perindopril therapy.

Wave-intensity analysis and wave separation show that the lower carotid SBP is attributable to a lower magnitude of wave reflection and not to changes in the timing of reflected waves, differences in heart rate, or changes in the forward wave reflection index (19.8% [10.9%] versus 23.3% [13.3%]; \( P = 0.02 \)) were significantly lower in patients randomized to amlodipine/perindopril therapy.

In conclusion, this report has shown that it is now possible to obtain a selective reduction of brachial and mostly central SBP and PP through changes in aortic stiffness and wave reflections. To achieve this, long-term drug treatment should consistently involve chronic angiotensin blockade. A combination of diuretics or CCB, but not of \( \beta \)-blockers, can simultaneously reduce MAP to a large extent. Nevertheless, \( \beta \)-blockers remain important in cases of associated coronary ischemic disease. All these assumptions taken together correspond to three main objectives: (i) angiotensin II blockade, mainly by ACE inhibition, provides comparable decreases in brachial SBP and PP, but consistent differences exist in central SBP and PP reductions and organ-protection effects; (ii) combined antihypertensive treatment is more beneficial on MAP than monotherapy alone; and (iii) ischemic heart disease should be treated independently.

Because therapeutic trials have shown extensively that CV risk reduction is primarily related to SBP and PP reduction, further therapeutic trials using the destiffening strategy are important to consider for the reduction of CV morbidity and mortality. Finally, in the presence of hypertension, a vicious circle involving macro- and microcirculation (Figure 6) is constantly observed and is important to disrupt using drug treatment. Reduction of central SBP and PP with treatment is the clear beneficial consequence of this disruption.

This study was conducted with the help of INSERM (Institut de la Santé et de la Recherche Médicale) and GPH-CV (Groupe de Pharmacologie et d’Hémodynamique Cardiovasculaire), Paris. We thank Dr Anne Safar for her helpful and stimulating discussions.
**Keywords:** hypertension; pulse pressure; large arteries; destiffening therapy

**Efficacité antihypertensive et stratégies thérapeutiques dirigées contre la rigidité artérielle**

Sous le terme « thérapeutique dirigée contre la rigidité artérielle » on entend un traitement permettant d’obtenir une diminution significative et sélective de la pression artérielle systolique au moyen d’un traitement au long cours, dans le cadre d’études cliniques contrôlées contre groupe témoin. La confirmation d’un tel effet requiert la mise en évidence d’une diminution de la pression artérielle centrale, accompagnée d’une diminution significative de la rigidité artérielle et/ou d’une diminution des ondes de réflexion. C’est pourquoi tous les essais cliniques récents se sont basés sur le blocage de l’angiotensine II, principalement par inhibition de l’enzyme de conversion, et fréquemment en association avec un diurétique et/ou un antagoniste calcique. Les résultats sur les événements cardio-vasculaires sont significativement supérieurs par rapport aux groupes témoins, et ce tout particulièrement lorsque le groupe témoin avait été traité par bêtabloquant.

**References**

Ambulatory blood pressure monitoring: 24-hour blood pressure control as a therapeutic goal for improving cardiovascular prognosis

by E. O’Brien, Ireland

In this review, I discuss the important information that ambulatory blood pressure monitoring can provide in clinical practice and make the case once again for making this technique available to all doctors engaged in managing patients with hypertension. I review the evidence on how nocturnal variation in blood pressure (BP) can influence outcome, consider interesting preliminary evidence that some drug classes may be superior to others in modifying nocturnal BP, and suggest that the time of administration of medication may also have an influence on the correction of abnormal nocturnal patterns. There is a need to direct research to determine if correcting abnormal nocturnal patterns either with drugs specifically targeted at nocturnal BP or by manipulating the time of drug administration will improve outcome.

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The technique for measuring blood pressure (BP) was introduced into clinical medicine in 1896 and has survived largely unchanged for over a century, despite being inherently inaccurate.1 Why, we might ask, have we connived for so long in perpetuating an inaccurate measurement in both clinical practice and hypertension research? The identification of white-coat and masked hypertension and the realization that many patients are being treated needlessly with BP-lowering drugs, whereas others are being denied drugs that could prevent cardiovascular (CV) sequelae, are the latest factors in the growing case against the traditional technique of BP measurement.

ABPM is indispensable to good clinical practice

These concerns have resulted in considerable research into techniques for assessing BP away from the medical environment, foremost among which has been ambulatory blood pressure monitoring (ABPM). Indeed, this technique is now accepted as being indispensable to good clinical practice.1,2 There are guidelines and recommendations laying down the criteria for validation of devices for ABPM and the website www.dableducatinal.org provides up-to-date information on recommended devices.3,4 The advantages of ABPM are many. First and foremost, the technique simply gives more measurements than conventional BP measurement, and real BP is reflected more accurately by repeated measurements. ABPM provides a profile of BP away from the medical environment, thereby allowing identification of individuals with a white-coat response or masked hypertension, who are in need of careful management. ABPM shows BP behavior over a 24-h period rather than giving a snapshot of BP measured with an inaccurate technique under artifi-
cial circumstances. Rather than relying on one or a few conventional measurements confined to a short period of the diurnal cycle, the efficacy of antihypertensive medication over a 24-h period becomes apparent.

ABPM can identify patients with abnormal patterns of nocturnal BP; the technique can demonstrate a number of patterns of BP behavior that may be relevant to clinical practice. Finally and importantly, evidence is now available from longitudinal studies that ABPM is a much stronger predictor of CV morbidity and mortality than conventional measurement. Moreover, evidence is growing that nocturnal BP measured by ABPM may be the most sensitive predictor of CV outcome, from which it follows that the measurement of nighttime BP should be an important part of clinical practice.5

Windows of the 24-hour circadian profile

In contemporary clinical practice, mean daytime and nighttime BPs are generally taken as being the most valuable parameters of ABPM,6-9 but ongoing research indicates that there is much more information to be gleaned from the 24-h BP cycle. First, the 24-h period can be divided into a number of windows (Figures 1 and 2).

◆ White-coat window

The white-coat window is the period that extends from the beginning of ABPM recording and lasts for 1 hour.59 During the white-coat window, BP may be influenced by the medical environment. The most popular definition of white-coat hypertension is that BP measured by conventional techniques in the office, clinic, or surgery exceeds 140 mm Hg systolic or 90 mm Hg diastolic, but when ABPM is performed the average BP is <135 mm Hg systolic and 85 mm Hg diastolic during the daytime period.10 It has been shown that the white-coat window on ABPM recordings cannot only diagnose the white-coat phenomenon, but also allows identification of a white-coat hypertensive subgroup with significantly higher pressures who may be at greater risk and in need of antihypertensive medication.11 ABPM remains the method of choice for diagnosing white-coat hypertension.2,11,12

◆ Daytime window

The daytime window follows the white-coat window and is the period when the subject is away from the medical environment and engaged in usual activities.11 For almost all subjects with hypertension, BPs during this window are lower than conventionally recorded pressures in the office, clinic, or surgery setting.12,13 However, BPs during this period are subject to stress, activity, arm movement, and the effect of exercise and other activities, such as driving, all of which may have an influence on the mean level of BP recorded.14 These effects are largely absent from BP measured during the nocturnal period.6,15

◆ Vesperal window

In the normal individual, there is a decline in BP in the vesperal window from daytime levels of BP that reaches a plateau during the nighttime period. This period (9.01 PM to 0.59 AM on the basis of ABPM commencing at 9 AM) is not included in the estimation of day and night mean pressures because this period represents a time during which bed rest is inconsistent and, therefore, cannot be categorized reliably.16 In hypertensive patients (or some normotensive patients with CV

### SELECTED ABBREVIATIONS AND ACRONYMS

- **ABPM**: ambulatory blood pressure monitoring
- **ACE**: angiotensin-converting enzyme
- **ASCOT**: Anglo-Scandinavian Cardiac Outcomes Trial
- **BP**: blood pressure
- **CV**: cardiovascular
- **DBP**: diastolic blood pressure
- **SBP**: systolic blood pressure

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**Figure 1.** Schema of ambulatory blood pressure.

**Figure 2.** ABPM suggests optimal 24-hour blood pressure (128 mm Hg/78 mm Hg daytime, 110 mm Hg/62 mm Hg nighttime). Normal dipping pattern.
As the decline in BP during the vesperal window may be absent (nondipping) so that BPs do not reach basal levels, BP may even rise in the vesperal window to reach levels that are higher than daytime levels (reverse dipping). Alternatively, there may be a marked fall in BP during the vesperal window to give the phenomenon of extreme dipping. Therefore, what happens to BP in the vesperal window predicts the BP level in the basal window.

**Basal window**

The nighttime window follows the vesperal window and is the period between 1.00 AM and 6.00 AM. BPs in this window are most likely to coincide with sleep (or if not with actual sleep, with the greatest cessation of activity) and are likely, therefore, to represent a steady state. There is compelling evidence that basal BP is superior to casual pressure in predicting outcome. Nighttime BP is superior to all other BP measurements in predicting CV outcome and mortality, which suggests that nighttime BP obtained by ABPM is similar to basal BP. Moreover, it has also been shown that the use of a mild sedative during ABPM may help in identifying patients with a very high CV risk, namely those patients who continue to manifest a blunted nocturnal dip despite sedation.

Valuable though the information derived from the basal window may be, there are a number of methodological limitations to recording BP at night. Ironically, despite doubts about reproducibility of the night-to-day ratio, it may be that nighttime BP is more standardized and consequently more reproducible than daytime BP (sleep being a more stable state than activity) and that it is this feature that gives nocturnal BP its predictive value. In clinical practice when the sleep and awakening periods are clearly defined, nocturnal changes in BP are surprisingly reproducible.

**Matinal window**

The matinal window extends from the end of the basal window to the commencement of daytime activities following rising. This period (6.01 AM to 8.59 AM) is not included in the estimation of day and night mean pressures because this period represents a time during which bed rest is inconsistent and, therefore, cannot be categorized reliably. However, the magnitude of the rise in BP in the matinal window may yield the most valuable prognostic information. In normal subjects, a modest rise in BP occurs in the matinal window preceding awakening from sleep to merely restore the previous daytime level of BP. However, this preawakening rise in BP in hypertensive patients may exceed the daytime average—the pre-awakening or morning surge—and this phenomenon is associated with a poor CV outcome.

**Patterns of ABPM**

Within the windows of the 24-h BP profile, several variations of BP behavior may be discerned, allowing differentiation of patients into subforms and patterns. ABPM may also be used to gauge the severity of BP—the higher the initial 24-h ABPM, the more frequent the occurrence of cardiovascular events.

**White-coat hypertension**

The risk associated with white-coat hypertension remains controversial, but there is general agreement that the condition should not be regarded as benign, with the risk of developing sustained hypertension at some time being almost inevitable.
Ambulatory hypotension
Hypotension is particularly common in the elderly, who may have autonomic or baroreceptor failure and who may also experience postprandial and postural hypotension. ABPM may also be useful in identifying hypotensive episodes in young patients in whom hypotension is suspected of causing symptoms. In treated hypertensive patients, ABPM may also demonstrate drug-induced decreases in BP that may have untoward effects in patients with compromised arterial circulation, such as individuals with coronary and cerebrovascular disease (Figure 5). In women with CV disease, SBP is most strongly related to the risk of secondary CV events (Figure 6).

Daytime systo-diastolic hypertension
Many patterns of BP behavior can be discerned from ABPM. By far the most common pattern is systo-diastolic hypertension. Generally, mean daytime levels of BP are superior to clinic BPs in predicting outcome, but inferior to nocturnal BP.

Isolated systolic hypertension
Isolated systolic hypertension can be apparent on clinic BP measurement, but it can be overestimated. ABPM allows for confirmation of the diagnosis as well as predicting outcome more accurately. The results of the ABPM substudy of the Systolic Hypertension in Europe Trial showed that systolic blood pressure (SBP) measured conventionally in the elderly may average 20 mm Hg more than daytime ABPM, thereby leading to the inevitable overestimation of isolated systolic hypertension in the elderly and probable excessive treatment of the condition. In women with CV disease, SBP is most strongly related to the risk of secondary CV events (Figure 6).

Isolated diastolic hypertension
Isolated diastolic hypertension, which can be present on clinic measurement, can be more readily studied with ABPM. The prevalence of the condition in one study was 3.6%. It is generally accepted that if SBP is normal, high diastolic blood pressure (DBP) is not associated with an adverse prognosis.

Dipping and nondipping
The “dipper/non-dipper” classification was first introduced in 1988 when a retrospective analysis suggested that nondipping hypertensive patients had a higher risk of stroke than the majority of patients with a dipping pattern. It is generally accepted that a diminished nocturnal BP fall is associated with a poor prognosis. For example, blunted nighttime dipping of BP is independently associated with angiographic coronary artery stenosis in men. In elderly people with long-standing hypertension, a blunted nocturnal dip in BP is independently
associated with lower cognitive performance. Among elderly patients with recently diagnosed isolated systolic hypertension, those with a nondipping nocturnal pattern have been shown to have significantly higher left ventricular masses on echocardiography than dippers. A nondipping nocturnal pattern is also associated with renal and cardiac target organ involvement. Moreover, nocturnal BP is now known to be an independent risk factor for CV outcome over and above all other measures of BP. For example, in the Dublin Outcome Study for each 10-mm Hg increase in mean nighttime SBP, the mortality risk increased by 21% (Figures 6 and 7).

**Reverse dipping**

In some patients, BP rises above daytime pressures rather than falling during the night. These patients (also referred to as risers, or extreme nondippers) have the worst CV prognosis, both for stroke and cardiac events (Figure 5).

**Extreme dipping**

Patients with a marked nocturnal fall in BP—known as extreme dippers—are at risk for nonfatal ischemic stroke and silent myocardial ischemia. This is particularly likely in extreme dippers who already have atherosclerotic disease and in whom excessive BP reduction is induced by injudicious antihypertensive medication. This possibility was originally enunciated by Floras as long ago as 1988. Extreme dipping is closely associated with an excessive morning surge in BP, which is associated with cerebral infarction and a high risk of future stroke (Figure 8).

**Siesta dipping**

A siesta dip in BP on ABPM is common in societies in which an afternoon siesta is an established practice, but in many elderly patients regardless of cultural practice a siesta is often part of the daily routine. There is evidence that ignoring the dipping pattern associated with a siesta distorts the day/night ratio of ABPM, and the magnitude of the siesta dip may have prognostic implications (Figure 8).

**Nocturnal hypertension**

Although daytime ambulatory hypertension is a good predictor of outcome, a number of studies have shown that ambulatory nocturnal hypertension is associated with a worse CV outcome. Further confirmation of the importance of nocturnal hypertension comes from a recent study showing that a nondipping pattern and increased nighttime DBP predicted the occurrence of congestive heart failure independently of antihypertensive treatment and established risk factors for cardiac failure (Figures 4 to 8).

**The morning surge**

CV events, such as myocardial infarction, ischemia, and stroke, are more frequent in the morning hours soon after waking than at other times of day. Circadian variations in biochemical and physiological parameters help to explain the link between acute CV events and the early morning BP surge. The occurrence of stroke and heart attack is more common during this period than at any other time of the day. In older hypertensive subjects, a morning surge in BP—defined as a rise in BP >55 mm Hg from the lowest nighttime reading—carries a risk of stroke almost three times greater than that seen in patients without a morning surge. Greater carotid intima-media thickness and circulating inflammatory markers coexist in hypertensive patients with a morning BP surge and might contribute to the increased CV risk in these patients (Figure 8).

**Indices of risk in the circadian profile**

ABPM can also provide interesting and informative indices that are associated with outcome. The subject has been reviewed.
lower rate of events in patients treated with amlodipine/perindopril (Figure 9). Nocturnal ABPM values complemented clinical BP values for the prediction of CV risk in hypertensive patients receiving treatment. These data reinforce the concept that BP-lowering treatment should be directed towards the reduction of nocturnal BP.

Can drugs be targeted to reduce BP in circadian periods of greatest risk?
Traditionally, BP-lowering drugs with a once-daily regimen of administration are taken in the morning. The hypertension guidelines require that antihypertensive medication with once-daily administration should possess at least a 50% trough-to-peak (T/P) ratio to ensure a 24-hour duration of action. It is surprising how little attention has been paid to the possibility of achieving a more beneficial effect on CV outcome by reducing nocturnal BP either by nighttime dosing or by designing drugs aimed specifically to reduce nocturnal BP.

In the main study, the group receiving ramipril had approximately 35% fewer CV events, despite an insignificant reduction in BP of 3/2 mm Hg; the outcome benefit was attributed to angiotensin-converting enzyme (ACE) inhibition, which was recommended in all high-risk patients regardless of baseline BP. However, it became evident from a later analysis of the ABPM substudy that ramipril (T/P ratio 50%-63%) was actually taken in the evening with outpatient BP measured some 10 to 14 hours later the following day. The reported insignifi-
significant change in BP in the main study gave no indication of a “whopping” 17/8 mm Hg reduction in BP during the nighttime period, which translated into a 10/4 mm Hg average reduction in BP over the entire 24-hour period.63

Interestingly from a historical perspective, the first paper to describe the effects of antihypertensive medication on 24-hour BP was in 1982, when Flora and his colleagues demonstrated using direct intra-arterial BP measurement that atenolol and slow-release propranolol lowered nighttime BP, whereas metoprolol and pindolol did not.64 A few years later, we presented data showing a discrepancy between antihypertensive drug efficacy when measured by clinic and noninvasive ambulatory daytime measurement methods. We concluded that “noninvasive ambulatory blood pressure measurement should be considered an essential part of the evaluation of antihypertensive drugs.”65 Why, we might ask, have we had to wait nearly a quarter of a century to explore the therapeutic potential of nocturnal BP lowering and the differing effects of drugs on ambulatory BP?

Efficacies of the various classes of antihypertensive drugs for restoring normal dipping are not well studied. However, diuretics, ACE inhibitors, angiotensin II receptor blockers, and calcium channel blockers appear to be superior to α- and β-blockers.46,67 Individualized antihypertensive medication targeting abnormal diurnal patterns may offer particularly good protection in high-risk groups, such as patients with a rise in nocturnal BP and in extreme dippers.68,69

As much of the morning surge may be mediated by involvement of the renin-angiotensin system, it would seem logical to assess agents targeting angiotensin II.70,71 Another mechanism worthy of manipulation to enhance nocturnal pharmacological therapy is dietary potassium supplementation and sodium restriction to restore normal dipping.46 The consistent lowering of nocturnal BPs by the renin inhibitor aliskiren in combination with a thiazide diuretic, an ACE inhibitor, or an angiotensin receptor blocker is a potential therapeutic strategy for reducing nocturnal hypertension.72

The evidence to date clearly suggests that pharmacological research should be directed towards designing drugs with the primary purpose of modifying nocturnal manifestations of hypertension. However, it should also be possible to modify nocturnal BP using the drugs or drug combinations presently available with 24-hour BP coverage. Hermida and colleagues examined the hypothesis that nondipping in hypertensive patients might be due, at least in part, to the absence of 24-hour therapeutic coverage in patients treated with single morning doses. They showed that in patients taking morning medication, ABPM control was double that of patients taking morning medication. Moreover, in patients with true resistant hypertension, bedtime medication resulted in a significant reduction in the 24-hour mean of SBP and DBP, and this reduction was much more prominent at nighttime.73 Bedtime dosing with an ACE inhibitor in patients with a nondipping pattern of hypertension improves efficacy during the nocturnal period.74 Antihypertensive medication directed at nighttime BP may not necessarily alter nocturnal hypertension patterns for the better. For example, a nondipping or dipping pattern could be transformed into an extreme dipping pattern with injurious therapy. The objective should be to reduce BP at the same time as preserving the physiological circadian dipping pattern. This is particularly important in stroke survivors, in whom ABPM is mandatory because it determines the appropriate dose of antihypertensive drug and the optimum time of administration to avoid inducing non-dipper, riser, and extreme dipper circadian profiles with treatment.75

Given the extensive evidence for the increased prevalence of CV events in the early morning hours, antihypertensive drugs that provide BP control during the early morning surge should provide greater protection against target-organ damage and enhance patient prognosis. This period has been dubbed the “blind spot” in current clinical practice.76 Pharmacological research into ways of altering the morning surge is limited.77 However, reduction of the morning surge in BP may be beneficial in preventing target-organ involvement in hypertension.78

From the evidence available there is a need in clinical practice to use antihypertensive therapies with proven 24-hour duration of action and with superior nighttime BP coverage, as demonstrated in the ASCOT trial with an amlodipine/perindopril regimen. There is a need for pharmaceutical research to develop drugs that correct nocturnal BP abnormalities and for clinical research to determine if correcting nocturnal BP abnormalities will result in improved outcomes.

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**Keywords:** ambulatory blood pressure monitoring; blood pressure control; cardiovascular outcome; nocturnal blood pressure

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**Mesure ambulatoire de la pression artérielle : le contrôle de la pression artérielle sur 24 H, un objectif thérapeutique pour améliorer le pronostic cardio-vasculaire**

Cet article analyse les informations importantes délivrées en pratique clinique par la mesure ambulatoire de la pression artérielle, et défend une fois de plus l’intérêt de mettre cette technique à disposition de tous les médecins impliqués dans la prise en charge des hypertendus. L’article fait également le point sur la façon dont les variations nocturnes de la pression artérielle (PA) influent sur l’évolution de la maladie ; il examine d’intéressants arguments préliminaires suggérant la supériorité de certaines classes thérapeutiques sur d’autres quant à l’action sur la PA nocturne ; et enfin conclut en avançant l’hypothèse que l’horaire de la prise médicamenteuse pourrait avoir une influence sur la correction des schémas tensionnels nocturnes anormaux. Ce dernier point nécessite plus ample étude afin de déterminer si cette correction serait plus efficace en termes d’amélioration du pronostic en utilisant des médicaments spécifiquement orientés vers la PA nocturne ou en modifiant l’horaire de la prise.
The preeminence of systolic blood pressure measurement in the management of patients with high blood pressure

by P. Sever, United Kingdom

Recent years have seen a switch in the focus of blood pressure measurement from diastolic to systolic pressure. A historical review of the subject reveals that early statements about raised systolic pressure having no pathological significance led to erroneous beliefs that diastolic pressures were all-important and should form the basis of blood pressure assessment. However, an extensive evidence base exists that confirms that systolic pressure is a more important prognostic determinant of cardiovascular disease, particularly in those over the age of 50 years. Systolic hypertension is by far the most common type of hypertension in the middle-aged and elderly, in whom diastolic pressures are frequently not elevated. A focus on diastolic pressure and use of it to determine thresholds and goals for treatment in these age groups is therefore misleading and irrelevant, and leads to inadequate treatment of most hypertensive subjects. For the majority of people, thresholds for diagnosis and treatment should be based on a single number—the systolic pressure. This will help to communicate an important health message to patients and policy makers, simplify treatment decisions for physicians, and lead to improvements in blood pressure control with accompanying reductions in cardiovascular morbidity and mortality.

For almost 100 years of blood pressure measurement, the focus has been on diastolic blood pressure. This is clearly an accident of history: research into the writings of the teachers of the early 20th century revealed that an editorial insertion into the posthumous 3rd edition (1926) of MacKenzie’s classic book Principles of Diagnosis and Treatment in Heart Affections led to the widespread misconception that increased diastolic pressure resulted from elevated peripheral vascular resistance, and that high systolic pressure was an indicator of the strength of the heart. In Nichol-son’s text (1915), the author’s view was also that the maximum systolic pressure was believed to indicate the strength of the heart. In 1926, Halls Dally reported that:

“It is of the greatest importance to remember that of the two pressures, the minimal pressure is the more valuable, in that it is a measure of the burden which the arteries and valves must continuously bear, and from which there is no escape… Records of systolic pressure alone are of no value… Transitory systolic elevations which form the pulse represent only an intermittent and superadded load.”

The consequence of these widely disseminated beliefs was that generations of physicians embraced the all-too-simple explanation of blood pressure and were subse-
The preeminence of systolic BP measurement in the management of high BP – Sever

**Switch from preeminence of diastolic pressure to systolic pressure**

The switch to the preeminence of systolic pressure, which has occurred gradually over the past 10-15 years, has been brought about because of overwhelming evidence from observational studies that systolic pressure is a more important prognostic determinant of cardiovascular disease end points than diastolic pressure, particularly in those over the age of 50 years. Systolic pressure rises with age, but diastolic pressure, which rises with age until around 50 years, thereafter falls (Figure 1) during a time period when cardiovascular disease incidence rises (Figure 2).

The prevalence of systolic hypertension is high in those over the age of 50 years, and accounts for more than 80% of hypertension in the older age group. Any focus on diastolic pressure in the middle-aged and elderly is, therefore, totally misleading. Higher levels of blood pressure in younger people are largely accounted for by an increase in peripheral vascular resistance, which, in turn, is due to functional and structural narrowing of small arteries and arterioles. With advancing age, increasing rigidity in larger arteries generates higher levels of systolic pressure, but is associated with lower diastolic pressures.7,8

Whilst systolic and diastolic pressures are both strong predictors of cardiovascular morbidity and mortality, as age advances, systolic pressure becomes a far more important determinant of future cardiovascular events, and should thus be the figure upon which therapeutic decisions are made.

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**Figure 1.** The changes in systolic and diastolic blood pressure with age in three North American populations.


**Figure 2.** Prevalence of isolated systolic hypertension, systolic-diastolic hypertension, and isolated diastolic hypertension in different age groups.

The switch to the preeminence of systolic pressure is also supported by overwhelming evidence from intervention trials that lowering systolic pressure confers substantial benefits on cardiovascular outcomes.9-12 Regrettably, this evidence base has been accompanied by a slow and disappointing rate of uptake in clinical practice in the management of raised systolic pressure and the achievement of systolic blood pressure targets. As recently as 2004, control of blood pressure to the target levels set by national and international guidelines (<140/90 mm Hg) was achieved in only 5%-15% of people in Europe, and even fewer in those at higher risk, such as those with diabetes, for whom a lower target is set (<130/80 mm Hg).13

Explanations for failure to achieve systolic blood pressure goals certainly include the historical focus on the physiology of the circulation and the perceived role of diastolic pressure, but this has been compounded by evidence from trials that have been mainly based on diastolic pressure thresholds for intervention and for treatment goals. Widespread teaching on the importance of diastolic pressure together with an outdated but long-held view that “normal” systolic pressure is “100 plus age” have also contributed. Such traditions have clearly shackled progress in this important field of medicine.

Current proposals

The current proposals, therefore, are that for the majority of people, thresholds for diagnosis and treatment should be based on a single number—the systolic blood pressure14-16—simply because systolic blood pressure is the defining feature of hypertension in those over the age of 50 years (when most hypertension occurs), and that a continuing focus on diastolic blood pressure is misleading and irrelevant and leads to inadequate treatment of most hypertensive subjects. Systolic pressure is easier to measure (and can be more accurately measured), and distilling the risk of high blood pressure into a single number will greatly assist communication of the all-important public health message to patients and policy makers and the simplification of thresholds and targets for physicians.

For those less than 50 years of age, diastolic blood pressure should be considered along with systolic blood pressure, but the latter should be the main target. One issue arising from this recommendation is whether those with isolated diastolic hypertension (diastolic blood pressure >90 mm Hg, systolic blood pressure <140 mm Hg) warrant therapeutic intervention in the light of the questionable benefits of treatment in this low-risk group.

Concerns have been raised that a switch to a focus on systolic blood pressure and the abandonment of consideration of diastolic blood pressure levels could lead to harmful outcomes in selected patient subgroups. Such concerns have been largely ameliorated following observations in high-risk patients with isolated systolic hypertension undergoing antihypertensive treatment in placebo-controlled trials such as the Systolic Hypertension in the Elderly Programme,9 the Syst-EUR Trial,10 the Hypertension in the Very Elderly Trial,11 and the Medical Research Council Trial in Older Patients with Hypertension.12 In these studies, substantial reductions in systolic blood pressure were accompanied by falls in diastolic pressures to levels as low as 60 mm Hg, which were not associated with adverse outcomes. However, other studies that included patients with established coronary disease suggested that those achieving the lowest diastolic pressures (50-70 mm Hg) were at higher risk of subsequent ischemic coronary events (observations compatible with the “J-curve” hypothesis).17 Whilst these data are understandable, the extrapolation of the concept of a J-curve relationship to older hypertensive patients in general, and particularly those with isolated systolic hypertension, has led to the reluctance of some physicians to aggressively treat systolic blood pressure, with the result that the protection of a small minority of patients with established coronary disease is accompanied by failure to achieve systolic blood pressure goals in the vast majority for whom low diastolic pressures do not confer an additional risk.

The final issue concerns those patients in the younger age group (<50 years) in whom elevated diastolic pressure is not associated with raised systolic pressure (isolated diastolic hypertension). In some observational studies18 but not others,19 raised isolated diastolic pressure does confer an increased cardiovascular risk in the longer term, but the absolute risk associated with isolated diastolic hypertension is extremely small and would be far below any threshold advocated by contemporary guidelines for therapeutic intervention. It may be that in some patient subgroups, such as those with obesity, isolated diastolic hypertension predicts the development of combined systolic and diastolic hypertension in later years.20 However, for reasons stated above, the absolute risks in this group are very low, and nonpharmacological, ie, lifestyle, measures would be a more appropriate course of intervention.

Following “My Personal View” published in the BMJ in 1999,14 a large general practice in South Wales implemented a policy of treatment decisions based solely on systolic pressure measurements. Over the following 4 years, repeated practice audits showed blood pressure control to targets increased by more than 20% in those over 60 years, and by more than 30% in those less than 60 years (Glyn Elwyn personal communication).

Conclusion

Hypertension must be one of the most extensively studied areas of medicine, with a wealth of observational data and outcomes from randomized intervention trials establishing the risks and benefits of treatment. It is, therefore, a great disappointment that translation of this extensive database and its conclusions into better models of patient care has not been
achieved. Whilst those of us involved in producing national and international guidelines must bear some responsibility for ignoring the all-important question of why guidelines have not been implemented (too long, too detailed, too complicated, and at times inconsistent), it is likely that difficulties associated with managing two numbers—systolic blood pressure and diastolic blood pressure—have led to uncertainties and confusion in the minds of practicing physicians, with the inevitable outcome of poor systolic control and high residual cardiovascular morbidity and mortality. As the late Geoffrey Rose once stated, “One sometimes wishes that Nikolai Rotkov had never described the fourth and fifth phases…”

References

Keywords: systolic; diastolic; blood pressure; measurement; treatment guideline; cardiovascular disease; predictor

**PRÉÉMINENCE DE LA MESURE DE LA PRESSION ARTÉRIELLE SYSTOLIQUE DANS LA PRISE EN CHARGE DES PATIENTS HYPERTENDUS**

Depuis quelques années, la mesure de la pression artérielle diastolique est remplacée par celle de la pression artérielle systolique. Une revue historique sur le sujet montre que la croyance, dans le passé, selon laquelle l’élévation de la pression systolique n’avait aucune signification pathologique avait conduit à l’opinion erronée que la pression diastolique devait former la base de l’évaluation de la pression artérielle. Il existe cependant un solide faisceau d’arguments confirmant que la pression systolique est un déterminant pronostique plus important vis-à-vis de la mortalité cardiovasculaire que la pression diastolique, en particulier chez les plus de 50 ans. L’hypertension systolique est de loin le type le plus courant d’hypertension chez les patients d’âge moyen et avancé, chez qui les pressions diastoliques sont rarement élevées. Une focalisation sur la pression diastolique et sur son utilisation pour déterminer les seuils et les objectifs du traitement dans ces groupes d’âge est donc trompeuse et non pertinente, et conduit à un traitement inadapté chez la plupart des hypertendus. Pour la majorité d’entre eux, les seuils pour le diagnostic et le traitement devraient être fondés sur un seuil chiffre, celui de la pression systolique. La prise en compte d’un tel point de vue aimerait à communiquer un important message de santé aux patients et aux responsables des politiques de santé, simplifierait les décisions thérapeutiques des médecins et devrait conduire à l’amélioration du contrôle de la pression artérielle avec une diminution concomitante de la morbidité et de la mortalité cardiovasculaires.
The recorded blood pressure (BP) waveform at each arterial site derives from the “summation” of the forward and backward traveling waves. As a consequence of arterial stiffness/diameter gradient and pressure wave reflections along the arterial bed, the final pattern of the waveform varies substantially between the peripheral and central arteries. Its amplitude (pulse pressure [PP]) increases gradually as it propagates distally. PP amplification between two arterial sites is not constant. It depends on “vascular age” (ie, arterial stiffness and wave reflections), heart rate, cardiovascular (CV) risk factors, and vasoactive substances. Although limitations exist regarding non-invasive central blood pressure (CBP) assessment, accumulating data from clinical studies suggest that it is associated with CV risk more closely than peripheral blood pressure (PBP); thus PP amplification is emerging as a new biomarker of CV risk. Current evidence indicates, beyond any doubt, that antihypertensive drugs affect PBP and CBP differentially and alter PP amplification. It is also becoming evident that important differences between classes of antihypertensive drug exist regarding their effects on PP amplification, due to different modes of action and effects on arterial stiffness and wave reflections. A review of the current data suggest that newer antihypertensive drugs with vasodilating properties (such as the angiotensin-converting enzyme inhibitors and dihydropyridine calcium channel blockers), as well as their combinations, appear to have a more beneficial effect on PP amplification than older drugs (particularly β-blockers, but also diuretics) by decreasing CBP over and above PBP.

Medicographia. 2010;32:254-261 (see French abstract on page 261)

In the mid fifties, invasive studies which were curried out at the laboratories of Earl Wood at the Mayo Clinic and patients undergoing diagnostic catheterizations showed that the contour of the pressure waveform changes dramatically from the central (aortic/carotid) to the peripheral (brachial/radial) arteries. This was also true for the arterial segment between the subclavian and brachial/radial arteries, which is conventionally used for blood pressure (BP) recording in clinical practice and clinical trials. The main qualitative differences regarding the shape of the pressure waveform between the central and peripheral arteries that were observed in early studies were (Figure 1): (i) The presence of an early (S1) and a late systolic peak (S2) of the central arteries in contrast to a blunt second systolic peak (S2) and at the same time an accentuated diastolic wave (D) of the brachial and radial arteries.
(ii) A clear widening (amplification) of the pulse pressure (PP) from the subclavian towards the brachial/radial sites.

In those early days, the so-called pressure amplification phenomenon, due to the amplification of the amplitude (ie, the PP) of the pressure waveform from the aorta to the radial artery, was attributed principally to the presence of multiple peripheral pressure wave reflections.1

It is now accepted that the pressure waveform is distorted as it travels distally from the aorta to the upper limb, however without substantial energy loss (Figure 1).2 This was clearly stated in the recently published experts’ opinion statement, which reviewed the available data.3 The characteristics of the contour as well as the PP of the waveform change substantially between the central and peripheral arterial sites.

It is important to note that, as described by both invasive and noninvasive studies1:4; (i) the mean BP (as well as diastolic blood pressure [DBP]) remain almost constant, ie, the energy is preserved. In contrast, systolic blood pressure (SBP) gradually increases as the wave travels distally; and (ii) for that reason, there is a gradual widening of the amplitude of the pressure wave. In practice, PP amplification is quantified as the ratio of the PP amplitude between a distal (eg, brachial [PP2]) and a proximal (eg, aorta [PP1]) location, ie, PP2/PP1, or as their difference, ie, PP2-PP1.

Figure 1. Schematic representation of: (i) the morphological differences of the pulse wave between the aorta and the brachial artery in young healthy subjects (upper panel [A]); and (ii) the effect of heart rate (upper panel [A] versus lower panel [B]) on systolic blood pressure augmentation and pulse wave amplification, for the same reflected pressure wave and similar pulse height of the forward ejected pressure wave.

Abbreviations: aortic S1, 1st systolic peak attributed to the forward wave; aortic S2: 2nd late systolic peak due to the augmentation by the reflected pressure wave; brachial S1, 1st systolic peak attributed to the forward wave; brachial S2, systolic peak due to the reflected wave from the upper limb; D, accentuated diastolic wave due to the delayed arrival of the reflected wave from the lower body; ED, ejection duration; T0, onset of the forward ejected wave; Tr, time to return at the aorta of the backward reflected wave from T0.

Additional data from invasive as well as noninvasive studies are needed in order to further verify the applicability of these basic physiological concepts in various ages, as well as various cardiovascular (CV) states and diseases.

**Pathophysiology of pulse pressure amplification**

The physiology of this phenomenon is not fully elucidated. Its genesis follows the principal laws of biophysics regarding wave travel and reflection.\(^5\) In terms of the currently available methodology and data,\(^3\) pressure amplification is attributed to:

1. the presence of stiffness and diameter gradient across the arterial tree;
2. the presence of wave reflections (originating from various sites due to arterial bifurcations, calcification, and impedance mismatch); and
3. to the spatial variation that is observed in the timing of the incident (forward traveling) and reflected (backward traveling) pressure waves.

Therefore, apart from total peripheral resistance, the arterial properties of the micro- and the macrocirculation, ie, large artery stiffness (commonly assessed by pulse wave velocity [PWV])\(^5\) and wave reflections (commonly assessed as augmentation pressure or augmentation index [AI])\(^6\) are the principal modulators of the amplification phenomenon.\(^2\) Two other cardinal modulators of PP amplification are:

1. the “distance”; and
2. the heart rate. The notion of “distance” should be appreciated as the length between the site of wave recording and the site of generation of the wave reflection (ie, the “effective reflecting distance,” which is more a statistical notion than an actual one). In synergy with the alterations in heart rate (ejection phase duration), the “distance” covered by the backward reflected pressure wave regulates the “timing/synchronization” with the forward traveling wave (ejected wave from the heart). “Early timing” in the systolic phase of the ejected wave is associated with augmentation of the systolic area of the pressure waveform, whereas “late timing” leads to the opposite effect (**Figure 1**).\(^2\)

PP amplification is affected by several nonmodifiable and modifiable factors. Aging (mainly due to “normal vascular aging,” ie, large artery stiffening and increased wave reflections) is the main nonmodifiable factor leading to attenuation of PP amplification, as suggested by cross-sectional data in healthy subjects (**Figure 2**).\(^6,8\) Gender is the second important nonmodifiable determinant; for all ages, females exhibit lower PP amplification than males (**Figure 2**).\(^6,8\) Modifiable traditional CV risk factors, including high blood pressure, diabetes mellitus, hypercholesterolemia, smoking, and established CV disease, are also associated with lower PP amplification,\(^6,9\) and vasoactive substances can alter PP amplification.\(^3\) As a consequence, PP amplification presents substantial variability within and between subjects\(^3,7\), it may vary enormously (from 0 to more than 30 mm Hg).\(^3,6,8\) The actual magnitude of PP amplification is an issue of debate and it depends on the method-
Clinical implications of blood pressure amplification

More and more data are accumulating regarding the superiority of central blood pressure (CBP) over peripheral blood pressure (PBP) in the prognosis of CV disease. The European Society of Hypertension has acknowledged this emerging possibility in the latest guidelines. Recent findings in an unselected geriatric population showed that CBP, compared to brachial BP, was associated more closely with CV events. These data imply that even in the elderly, who are characterized by low PP amplification, central BP is superior to brachial BP for the prognosis of CV events.

From the point of view of pathophysiology, lower PP amplification is expected to be associated with unfavorable hemodynamic effects on the central arteries and the heart. For a given peripheral PP, a person with low PP amplification when compared to another with high PP amplification is subject: (i) per se to higher left ventricular afterload and potentially to lower subendocardial viability (systolic/diastolic area under the pressure waveform); as well as (ii) to more intense cyclic stress imposed on the renal and cerebral micro- and macrovessels.

Prospective data in subjects with end-stage renal disease show that the reduction (disappearance) of PP amplification is an independent predictor of both all-cause and CV mortality. Data from a cross-sectional observational study in hypertensive subjects (with or without metabolic syndrome) have also shown that PP amplification was associated with a calculated risk for myocardial infarction. A more recent cross-sectional study verified the association of low PP amplification with target-organ damage and CV risk, as assessed by the Framingham equation. Additional data regarding the association of PP amplification with target-organ damage has also been presented in untreated subjects with essential hypertension, associating a regression of left ventricular mass index after one year of treatment with an increase in PP amplification, and not with brachial BP reduction.

Although prospective data regarding the association of PP amplification and CV risk are still limited, PP amplification is emerging as a new biomarker of CV disease.

Antihypertensive drugs: theoretical mode of action on central BP over and above peripheral BP

Available antihypertensive drugs have been designed to decrease PBP by reducing total peripheral resistance, via vasodilatation at the level of the arterioles (microcirculation) and by decreasing cardiac output, through reduction of the stroke volume, heart rate, or both. Currently, there is no drug specifically designed to improve intrinsic elasticity-related arterial wall properties. Theoretically, an increase in PP amplification can be achieved by two potential mechanisms: (i) a reduction in the intensity of the wave (reduction of the reflection coefficient); or (ii) a resynchronization of the timing of the reflected wave within systole, in such a way that peak SBP is less enhanced (Figure 1). The latter mechanism may be a result of: (i) the delayed arrival of the reflected wave (Tr) (Figure 1) due to either decreased PWV or distal shift of the origin of the reflected wave (effective reflecting distance); or (ii) shortening of the left ventricular ejection time (due to acceleration of the heart rate) (Figure 1).

PWV is, at least in some cases, passively reduced as a consequence of BP lowering due to attenuation of arterial wall passive distension. In this respect, all drugs exert potential further favorable actions on CBP, over and above PBP.

Evidence of class-related effects of antihypertensive drugs on pulse pressure amplification

There is now solid evidence suggesting that important differences between classes of antihypertensive drugs exist regarding their direct effect on the arterial wall and elasticity-associated arterial properties (arterial compliance and reflection coefficient). These differences underlie the differential effect of antihypertensive drugs on PP amplification, as will be briefly addressed below.

- Diuretics
  The available evidence on diuretics (six studies with 457 subjects in total) suggests that diuretics (as monotherapy or single add-on therapy) have no additional effect on CBP over and above PBP (Tables I and II, page 258). This conclusion is in line with the reviewed data elsewhere regarding the effect of diuretics on aortic stiffness and pressure wave reflections that show that diuretics have no, or a minimal, beneficial effect on these two arterial parameters when used as monotherapy.

- β-Blockers
  The data regarding the effect of β-blockers derive from studies (six studies with 193 subjects in total) that have almost exclusively evaluated atenolol, whereas inadequate data are available for newer β-blockers with vasodilating properties (Tables I and II). These results clearly show that atenolol decreases central PP less than the observed reduction at the level of the brachial artery. Most importantly, in two of the studies, central PP actually increased, although peripheral PP decreased. In three studies, proof of substantial clinical increase of left ventricular afterload was provided. All the six available studies, as well as a recent post hoc analysis of the Anglo-Scandinavian Cardiac Outcomes Trial Conduit Artery Function Evaluation (ASCOT-CAFE), verify that the principal mechanism explaining the nonfavorable effect of β-blocker on CBP is the increase of AI due to the deceleration of heart rate and the resynchronizing of the reflected pressure wave earlier in the systolic phase (thus increasing AI) (Tables I and II). A decrease in the heart rate by 10 beats/min, induced by atenolol, is associated with an increase in aortic AI of 4%.
Wave reflections, even in the presence of bradycardia.28 Pyridine CCBs increase PP amplification by reducing pressure. The available data (4 studies with 175 subjects in total) imply an effect of dihydropyridine CCBs on the reflection coefficient of the peripheral arteries and/or a distal shift of the effective reflecting distance, which delays the arrival of the reflected wave at the central artery, as previously reported in a number of studies.29

This implies an effect of dihydropyridine CCBs on the reflection coefficient of the peripheral arteries and/or a distal shift of the effective reflecting distance, which delays the arrival of the reflected wave at the central artery, as previously reported in a number of studies.29 This action is related to the main mode of action of dihydropyridine CCBs, ie, the vasodilator effect at the level of the conduit arteries.30 Additionally, substantial aortic stiffness reduction has been reported with CCBs in studies that lasted more than 4–6 weeks.28,30,32,39

### Table I. Studies classified according to group of antihypertensive drug and outcome (positive/negative/neutral/missing data) regarding the effect on central blood pressure over and above peripheral blood pressure, as well as mode of action (aortic stiffness, pressure wave reflections, heart rate, left ventricular function, and synchronization of the pressure [forward and backward] traveling waves).

<table>
<thead>
<tr>
<th>Class of antihypertensive drug (number of available studies)</th>
<th>Reduction of central BP over and above peripheral BP</th>
<th>Reduction of arterial stiffness†</th>
<th>Reduction of pressure wave reflections†</th>
<th>Delay of the arrival of the reflected wave</th>
<th>Increase of heart rate</th>
<th>Decrease of left ventricular systolic function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics (6)</td>
<td>1/2/3/0</td>
<td>1/0/1/4</td>
<td>1/0/4/1</td>
<td>1/0/2/3</td>
<td>0/0/6/0</td>
<td>0/0/0/6</td>
</tr>
<tr>
<td>β-Blockers (6)</td>
<td>0/6/0/0</td>
<td>3/0/1/2</td>
<td>0/6/0/0</td>
<td>1/0/0/5</td>
<td>0/6/0/0</td>
<td>0/0/0/6</td>
</tr>
<tr>
<td>ACE inhibitors (11)</td>
<td>8/1/2/0</td>
<td>3/0/3/5</td>
<td>9/0/1/1</td>
<td>1/0/2/8</td>
<td>0/0/0/2</td>
<td>0/0/1/10</td>
</tr>
<tr>
<td>ARBs (5)</td>
<td>2/1/2/0</td>
<td>1/0/1/3</td>
<td>3/0/2/0</td>
<td>0/0/0/5</td>
<td>0/0/5/0</td>
<td>0/0/0/5</td>
</tr>
<tr>
<td>CCBs (4)</td>
<td>3/0/1/0</td>
<td>2/0/0/2</td>
<td>4/0/0/0</td>
<td>0/1/2/1</td>
<td>0/1/3/0</td>
<td>0/0/1/3</td>
</tr>
</tbody>
</table>

* Assessed by direct methods, eg, pulse wave velocity, or indirect methods, eg, change at the time of the arrival of the reflected wave at the central arterial site
† Assessed by: (i) change in augmentation index or augmentation pressure; and (ii) substantial transformation of the pattern of the central pressure waveform

### Table II. Summary of the available evidence on the effects of antihypertensive drug classes on central blood pressure–lowering capacity over and above peripheral blood pressure–lowering (ie, increase of blood pressure amplification).

<table>
<thead>
<tr>
<th>Antihypertensive drug classes (number of available studies)</th>
<th>Change in BP amplification</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics (6)</td>
<td>Neutral/decrease</td>
<td>More data needed</td>
</tr>
<tr>
<td>β-Blockers (6)</td>
<td>Decrease</td>
<td>Compelling</td>
</tr>
<tr>
<td>ACE inhibitors (11)</td>
<td>Increase</td>
<td>Convincing</td>
</tr>
<tr>
<td>ARBs (5)</td>
<td>Increase/neutral</td>
<td>Suggestive</td>
</tr>
<tr>
<td>CCBs (4)</td>
<td>Increase</td>
<td>Convincing</td>
</tr>
</tbody>
</table>

### Dihydropyridine calcium channel blockers

The available data (4 studies with 175 subjects in total) imply that dihydropyridine calcium channel blockers (CCBs) increase PP amplification by decreasing CBP over and above PBP (Tables I and II).24,25,26,30,32 All the studies suggested that dihydropyridine CCBs increase PP amplification by reducing pressure wave reflections, even in the presence of bradycardia.28

### Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are the most extensively studied class of antihypertensive drug regarding the ability to reduce CBP over and above PBP.24,27,35,36,41-45 The weight of evidence (Tables I and II) clearly supports the presence of additional CBP-lowering capacity by ACE inhibitors over and above PBP. This effect was observed in eight out of the eleven available studies and it was associated, in almost all of the studies, with a reduction in the reflected pressure wave. Data on concomitant arterial stiffness reduction and resynchronization of the reflected wave were not widely available in these studies. However, revised data from a large number of studies on arterial properties22,30,32 suggest that ACE inhibitors have a beneficial action on both arterial stiffness and wave reflections. These actions are in part mediated by the classic vasodilating effect due to angiotensin II inhibition leading to smooth muscle relaxation and collagen/elastin fiber rearrangement. Yet several other mechanisms of action exist and are at least partly independent of angiotensin II reduction, including the reduction of oxidative stress and inflammation, which leads to direct beneficial effects on the endothelium, smooth muscle cells, the collagen/elastin ratio, and extracellular matrix composition.20,46

### Angiotensin receptor blockers

Five noninvasive studies23,38,43,44,47 (95 subjects in total) (Tables I and II) have evaluated the effect of angiotensin receptor blockers (ARBs), as monotherapy or single add-on therapy, on CBP over and above PBP. Although the literature regarding the effect of ARBs on pressure wave reflections and aortic stiffness30,32 suggests that this class of drugs can reduce
both parameters, the available evidence on the effect of ARBs on CBP reduction over and above PBP is still very weak. Only two studies provided positive evidence. Given the fact that only small differences between ACE inhibitors and ARBs have so far been documented and pleiotropic effects have been attributed to both classes, further clinical proof is awaited from larger studies.

Direct evidence regarding the inferiority of β-blockers versus the new classes of antihypertensive drugs (ACE inhibitors, ARBs, and CCBs) has been presented in four studies. Similarly, direct comparison of diuretics with ACE inhibitors and CCBs verified the superiority of the latter.

Evidence regarding the effect of combination treatment on pulse pressure amplification
The Conduit Artery Function Evaluation (CAFE) study, a substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), showed for the first time that the combination of new antihypertensive drugs, i.e., an ACE inhibitor (perindopril) with a dihydropyridine CCB (amlodipine) has more favorable effects on PP amplification than the combination of a diuretic (benidropiumbendiazide) with a β-blocker (atenolol). In 2199 subjects after almost 6 years of follow-up, it was clearly shown that subjects in the amiodipine/perindopril regimen arm had significantly lower levels of central SBP and PP during the study than subjects on the atenolol/benidropiumbendiazide regimen. Most importantly, it was clearly shown that these differences could not be detected at the level of the brachial artery. This clear beneficial effect on BP amplification (ratio) (atenolol/diuretic vs amiodipine/perindopril, 1.21 vs 1.31; P=0.001) in the amiodipine-based combination was attributed to the significant decrease of pressure wave reflections (expressed by AI) rather than PWV (aortic stiffness was available only in 114 subjects), and mostly to a change in the timing of the reflected wave (taking place earlier in the systolic phase of the ejected aortic wave due to the slowing of the heart rate by the β-blocker).

Limitations and conclusions
There are considerable limitations regarding the extrapolation of the above data in daily clinical practice due to the fact that most of the data derive from small and short-term studies, which differ in design, primary end points, dosage of active drug, and the applied methodology for CBP and PBP assessment. Nevertheless, several conclusions can be drawn based on the consistency of the results.

First, it is clear that there are important differences between the classes of antihypertensive drugs regarding their effects on BP amplification. These differences are based on the differential effects of drugs on arterial wall properties and the autonomic nervous system.

Second, it seems that the newer antihypertensive drugs (especially ACE inhibitors and dihydropyridine CCBs) have a more beneficial effect on BP amplification than the older drugs (diuretics and particularly β-blockers). The common features of these newer classes of drugs appear to be their arterial dilating capacity and their ability to reduce pressure wave reflections, as expressed by AI. Third, there is compelling evidence regarding the detrimental effect of β-blockers (mainly atenolol) on CBP. This is largely attributable to the bradycardia induced, which leads to augmentation of aortic SBP primarily due to the earlier timing of the reflected pressure within the systolic phase of the ejected wave. Whether newer β-blockers with vasodilating properties are devoid of these effects remains to be proven. Fourth, among newer drug classes, ACE inhibitors are by far the best studied regarding their effects on CBP.

There is convincing evidence that ACE inhibitors increase BP amplification, mainly by decreasing wave reflections. The most probable mode of action includes chronic remodeling of the small arteries leading to reduced reflection coefficients. Finally, the combination of ACE inhibitors and dihydropyridine CCBs appears to be the most promising treatment for CBP reduction at the moment, over and above PBP.

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Keywords: central blood pressure; pulse pressure amplification; arterial stiffness; wave reflections; antihypertensive drug treatment
EFFET DES ANTIHYPERTENSEURS SUR LA PRESSION ARTÉRIELLE CENTRALE INDÉPENDAMMENT DE LA PRESSION ARTÉRIELLE BRACHIALE : MISE AU POINT SUR L’AMPLIFICATION DE LA PRESSION ARTÉRIELLE

La forme d’onde de pression artérielle (PA) enregistrée à chaque site artériel résulte de la « somme » des ondes antérogrades et rétrogrades. L’aspect final de cette forme d’onde varie considérablement entre les artères périphériques et centrales en fonction de la rigidité artérielle et du gradient du diamètre artériel, d’une part, et de la réflexion de l’onde de pression le long du lit artériel d’autre part. Son amplitude (pression pulsée [PP]) croît progressivement au fur et à mesure de sa propagation. Toutefois, l’amplification de la PP entre deux sites artériels n’est pas constante, mais dépend de « l’âge vasculaire » (par ex. rigidité artérielle et réflexion de l’onde), de la fréquence cardiaque, des facteurs de risque cardio-vasculaires (CV) et des substances vasoactives. Malgré les limites de l’évaluation non invasive de la pression artérielle centrale (PAC), un nombre grandissant de résultats d’études cliniques suggèrent que celle-ci est plus étroitement associée au risque CV que la pression artérielle périphérique (PAP). L’amplification de la PP apparaît ainsi comme un nouveau biomarqueur du risque CV. Les données actuelles montrent de façon indubitable que les antihypertenseurs agissent différemment sur la PAP et la PAC et qu’ils modifient l’amplification de la PP. Il devient également de plus en plus clair qu’il existe des différences importantes vis-à-vis des effets sur l’amplification de la PP entre les classes d’antihypertenseurs, en ce qui concerne leurs modes d’action et leurs effets sur la rigidité artérielle et la réflexion de l’onde de pression artérielle. Une revue des données actuelles suggère que les nouveaux antihypertenseurs vasodilatateurs (inhibiteurs de l’enzyme de conversion de l’angiotensine et inhibiteurs calciques dihydropyridiniques), ainsi que leurs associations, semblent avoir un effet bénéfique plus important sur l’amplification de la PP que les antihypertenseurs plus anciens (en particulier les β-bloquants, mais aussi les diurétiques), du fait de leur capacité à diminuer la PAC indépendamment de la PAP.
Need for fixed-dose–combination therapy in the early phases of hypertension

by S. Julius, USA

Stage 1 hypertension is the most prevalent form of hypertension and because of its frequency it has a large impact on public health. Nearly two thirds of all hypertension-related coronary deaths occur in stage 1 hypertension. Current treatment of stage 1 hypertension is based on old studies, when the side effects of drugs dictated a slow, stepwise increase in medication dosage. This might not be necessary with new, effective, and fast-acting fixed-combination pills. Hypertension is a self-accelerating condition. Early brisk blood pressure lowering with fixed-combination pills may prevent the development of high-risk hypertension later. Many patients perceive the current approach of repeated clinic visits for dose adjustments in stage 1 hypertension as a failure to achieve blood pressure goals. This discourages adherence to treatment. Physicians’ fear of hypotension with the use of effective drugs in stage 1 hypertension is unwarranted. Blood pressure decrease is proportional to baseline blood pressure level, and the response in stage 1 hypertension is less than that in advanced hypertension. Currently, fixed-combination pills are not approved for treatment of stage 1 hypertension. However, the worldwide failure to control hypertension calls for new approaches. Fixed-combination pills promise safe and fast BP control, better adherence to treatment, and a larger reduction in cardiovascular events in stage 1 hypertension. Changes in clinical practice cannot be implemented without evidence, so there is a need for a trial to verify that the conceptual advantages of fixed-combination pills translate into better outcomes in stage 1 hypertension.

In this review I will argue that in order to further decrease adverse cardiovascular outcomes, we ought to focus on the treatment of stage 1 hypertension. There are three major reasons why this stage of hypertension deserves renewed attention:

1. Public health impact of stage 1 hypertension

The huge impact of stage 1 hypertension on public health is illustrated in Figure 1, adapted from the impressive Multiple Risk Factor Intervention Trial (MRFIT) follow-up of 122 086 subjects with hypertension on initial screening. Over a 15-year observation period, 6293 people in the hypertension group died from coronary heart disease. In MRFIT, hypertension was classified according to the USA Joint National Committee (JNC) 6 guidelines. This classification has been superseded by the JNC 7 grading of hypertension, but the diastolic blood pressure (DBP) range for stage 1 classification is the same in JNC 6 and JNC 7. In the left panel of Figure 1,
the death rate from coronary heart disease is lowest in stage 1 hypertension. The rate increases in a stepwise fashion with each subsequent grade. By stage 4, coronary deaths are three times more likely to occur than in stage 1. However, as the middle panel shows, stage 1 hypertension is the most prevalent form of hypertension (74%), while stage 4 is extremely rare (1.2%). The net result of this is shown in the right panel. The sheer size of the stage 1 group is so overwhelming that despite a relatively low individual risk, most coronary deaths are found in stage 1 hypertension. Conversely, the group with the highest risk is so small that it barely impacts total hypertension-related coronary deaths (3%).

In clinical practice highly endangered patients command immediate attention, and this fact is partially reflected in hypertension guidelines. Thus JNC 7 guidelines recognize that most patients require two drugs to reach their blood pressure (BP) goals, but suggest initiating treatment of stage 1 hypertension with one drug. More effective treatment with combination pills containing 2 drugs is reserved for stage 2 hypertension. This inadvertently creates the impression that BP control in stage 1 is less important. In fact the reverse is true; to decrease adverse cardiovascular events, we ought to focus on BP control in stage 1 hypertension.

2. Lack of new information about therapy in stage 1 hypertension

Present approaches to stage 1 hypertension are based on outcomes from old studies. The last paper about stage 1 hypertension was published 17 years ago. Present strategies are based on outcomes from old studies. The last paper about stage 1 hypertension was published 17 years ago. Since then nothing new has been published about the treatment of stage 1 hypertension.

The first report about mortality in stage 1 hypertension was published 70 years ago. Longitudinal observations of millions of people with life insurance policies in the USA clearly demonstrated that longevity negatively correlates with BP levels (Figure 2, page 264). Since effective antihypertensive agents had not yet been invented in 1939, this observation provides a unique view of the natural history of untreated hypertension. What would today be classified as stage 1 hypertension (DBP, 93 to 97 mm Hg) was associated with a 100% increase in total mortality.

Thirty years after the life insurance companies’ report, the US Veterans Administration (VA) published the first in a series of seminal treatment trials in hypertension. They first showed that BP can effectively be reduced with pharmacological treatment and next reported that pharmacological BP lowering reduced “terminating morbid events” in patients with DBPs of 115 to 129 mm Hg. The effect of treatment was so dramatic that after one year patients receiving placebo were switched to active treatment. The picture was not so clear for DBP in the 90 to 114 mm Hg range, and in this group the trial was continued.

**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>MRFIT</td>
<td>Multiple Risk Factor Intervention Trial</td>
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<tr>
<td>JNC</td>
<td>Joint National Committee</td>
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<tr>
<td>DBP</td>
<td>diastolic blood pressure</td>
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<tr>
<td>BP</td>
<td>blood pressure</td>
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<tr>
<td>VA</td>
<td>Veterans Administration (trial)</td>
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<tr>
<td>TOMH</td>
<td>Treatment Of Mild Hypertension (study)</td>
</tr>
<tr>
<td>HDP</td>
<td>Hypertension Detection and Follow-up Program</td>
</tr>
<tr>
<td>MRC</td>
<td>Medical Research Council</td>
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<tr>
<td>ALLHAT</td>
<td>Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial</td>
</tr>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ARB</td>
<td>angiotensin receptor blocker</td>
</tr>
<tr>
<td>ASCOT-BPLA</td>
<td>Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure–Lowering Arm</td>
</tr>
<tr>
<td>CCB</td>
<td>calcium channel blocker</td>
</tr>
<tr>
<td>SHEP</td>
<td>Systolic Hypertension in the Elderly Programme</td>
</tr>
<tr>
<td>ASCOT</td>
<td>Anglo-Scandinavian Cardiac Outcomes Trial</td>
</tr>
<tr>
<td>TROPHY</td>
<td>Trial Of Preventing Hypertension</td>
</tr>
<tr>
<td>RAS</td>
<td>renin-angiotensin system</td>
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**Figure 1. The impact of stage 1 hypertension on coronary heart disease mortality.**

Abbreviation: CHD, coronary heart disease.

Three years later the VA study reported that patients receiving placebo with DBPs of 90 to 114 mm Hg had a significantly higher incidence of cerebrovascular accidents, congestive heart failure, and accelerated hypertension.7 The incidence of coronary artery events was similar in both arms of the study. The relative risk reduction in morbidity events was 75% in patients with prerandomization DBPs of 105 to 114 mm Hg, but only 35% in the group with DBPs of 90 to 104 mm Hg, a difference that was not statistically significant.

Active drug treatment in the VA study was associated with substantial side effects. Two patients were lost due to the toxicity of apresoline, while serious central nervous side effects of reserpine and α-methyldopa led to the discontinuation of treatment in 29 additional patients.

The unclear results of VA trial participants with DBPs of 90 to 104 mm Hg shaped subsequent outcome studies, and three major new trials were launched to resolve the issue.8-10 Because of the VA experience with treatment-related side effects, the treatment schemes in these trials included careful and slow titration of drug dosages.

The upper DBP limit for enrollment in studies of “mild” hypertension (Table I) published from 1979 till 1985 was 5 to 9 mm Hg higher than the current DBP limit for stage 1 hypertension. These older studies used stepwise uptitrations and/or the addition of drugs—starting with diuretics, adding α-methyldopa or apresoline, and eventually adding other drugs—to reach BP goals.

The most recent trial in Table I was substantially different from the other trials.11 Importantly, the enrollment criterion (DBP , 90 to 99 mm Hg) in the Treatment Of Mild Hypertension (TOMH)
study was consistent with the current definition of stage 1 hypertension. Furthermore, TOMH patients were randomized either to placebo or to one of four monotherapies with different active antihypertensive agents. The TOMH study introduced an important innovation to the definition of events by also adding other clinical events (hospitalization for transient ischemic attacks, development of angina or intermittent claudication, and signs of peripheral arterial disease) to the usual “hard” end points. Since the population in TOMH was too small to compare the effect of different drugs, the four active treatment groups were pooled and compared to the placebo group.

In all the trials reviewed in Table I, rates of events in the active treatment groups were lower than in the placebo group. In the Hypertension Detection and Follow-up Program (HDFP), total mortality was significantly reduced in the stepped-care group. In the Australian study, significantly lower rates of cardiovascular events were seen in the treatment group. In the Medical Research Council (MRC) trial, strokes and cardiovascular events were reduced in the active treatment groups. In TOMH, the rate was significantly lower in the active treatment group only after “hard” and “other” events were merged into a composite index of events.

Significance levels in these studies were not overwhelming ($P<0.01$ to $P<0.05$). It was hoped that TOMH would open the door to studies exploring whether the use of modern, more effective, and better-tolerated antihypertensive agents in stage 1 hypertension would yield superior and more convincing results. The small TOMH study was designed to test the feasibility of a larger trial in “mild” hypertension, but eventually it became the model for ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial) in high-risk hypertension.

3. The exponential nature of untreated hypertension

We have shown in the Tecumseh study (Figure 3) that hypertension starts very early and that with the passage of time BP begins to increase in a steep, nonlinear fashion. Subjects that in 1990 were classified as having “borderline” hypertension would currently be classified as having stage 1 diastolic hypertension (average DBP, 93 mm Hg). This group already had a significantly higher BP level at 6 years of age. In the second decade of life their BP remained higher than that of the normotensive group, but did not reach the hypertensive range.

However, in subjects destined to become hypertensive, BP increased steeply from normal values in the second decade of life to hypertensive values at 31 years of age. We call this abrupt increase in BP, “self-acceleration,” as it largely reflects the consequences of previous milder BP elevation. Prolonged mild BP elevation suffices to elicit a restructuring of resistance vessels (arterioles) and to cause endothelial damage in these vessels. Restructured arterioles in stage 1 hypertension respond excessively to all constrictive stimuli. These structural changes also reduce the arteriolar lumen and render arterioles less responsive to vasodilation. The ensuing endothelial dysfunction further reduces vasodilation capacity in the early phases of hypertension. Thus patients with stage 1 hypertension are already on the path to further hypertension acceleration, and early BP lowering is the only way to interrupt the process. If the BP in these subjects is not lowered in a timely fashion, target-organ consequences of hypertension are bound to develop.

Since the processes described above reflect previous BP elevation, it stands to reason that the earlier treatment is started and the faster BP is controlled, the better the patient’s prognosis. New better tolerated, more effective drugs promise better BP control, quicker BP lowering, and improved patient adherence to treatment. Unfortunately, the subsequent research focus jumped from stage 1 to high-risk hypertension, and we have no information about new therapeutic approaches to stage 1 hypertension.

![Figure 3. Longitudinal blood pressure trends in the Tecumseh study.](image-url)

Subjects were classified as having borderline hypertension or normal blood pressure when they were 31 years old. Their previous blood pressures values were retrieved from records of preceding Tecumseh health exams. Modified after reference 13. Julius et al. JAMA. 1990;264:354-358. © 1990, American Medical Association.

In the absence of new data, the US JNC 7 guidelines extrapolated findings from studies of advanced high-risk hypertension and applied them to the treatment of stage 1 hypertension. This is plainly wrong. There is a world of difference between stage 1 and high-risk hypertension. The treatment goal in stage 1 hypertension is to prevent vascular damage caused by high BP. In high-risk patients the goal is to postpone the clinical consequences of preexisting vascular damage. Hypertension is a disease of multiple competing cardiovascular risk factors. In the early phases of hypertension a higher BP is already associated with pressure-independent cardiovascular risk factors, such as obesity, high hematocrit,
Need for fixed-dose–combination therapy in the early phases of hypertension

Julius

Tachycardia, higher glucose and insulin levels, and dyslipidemia. Over the course of hypertension, the progression of most of these abnormalities accelerates, and target organ damage starts to develop in parallel. If target organ changes such as arteriolar and left ventricular hypertrophy, coronary atherosclerosis, nephrosclerosis, and decreased distensibility of large conduit arteries have already developed, the patient may have reached the point of no return. Beyond this point, BP lowering will ameliorate and postpone cardiovascular events, but will not fully reverse the underlying processes. Moreover, life expectancy in these aged patients is substantially shorter than in stage 1 hypertension.

Admittedly, during the short observation period in ALLHAT, new-onset diabetes was not associated with more adverse cardiovascular events, but does that mean that inducing abnormalities of glucose metabolism in stage 1 hypertension will prove to be innocuous? Typically stage 1 hypertension is diagnosed in the third decade of life and the patient will subsequently require 30 to 40 years of treatment. Nevertheless observations in ALLHAT provided the basis for the JNC 7 recommendation that diabetes-inducing diuretics similar to the one used in ALLHAT be avoided. Other combinations, particularly those containing a small amount of diuretic and offer a wide range of RAS inhibition are preferable. In selecting such a pill the physician must evaluate the dose and the type of diuretic used. Some potent diuretics, are less useful.

A positive example of clinical need changing a treatment paradigm in younger patients with arterial hypertension comes from the latest UK guidelines reported by the National Institute for Clinical Excellence and the British Hypertension Society. These guidelines called for the selection of first-line drugs based on the age of hypertensive patients, advocating treatment with a drug that blocks the renin system (angiotensin-converting enzyme [ACE] inhibitor or angiotensin receptor blocker [ARB], in the case of ACE inhibitor intolerance) in younger subjects (<55 years), whereas in older subjects and blacks, in whom a low renin status is more common, a calcium channel blocker (CCB) or thiazide diuretic is recommended. The reason for these changes come from the Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure–Lowering Arm (ASCOT-BPLA), which although not specifically designed in stage 1 hypertension nevertheless recruited 19 257 hypertensive patients at mild risk of experiencing a cardiovascular event without clinical evidence of coronary artery disease or heart failure. The ASCOT-BPLA trial was terminated prematurely due to significantly lesser rates of all-cause mortality (11%), cardiovascular mortality (24%), stroke events (30%), and new-onset diabetes (32%) in patients allocated an amiodipine-perindopril regimen compared to those allocated an atenolol-bendroflumethiazide regimen (Table II).

<table>
<thead>
<tr>
<th>Study end point</th>
<th>RRR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal MI + CHD death</td>
<td>-10%</td>
<td>0.12</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>-14%</td>
<td>0.247</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>-24%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total coronary events</td>
<td>-14%</td>
<td>0.007</td>
</tr>
<tr>
<td>Fatal and nonfatal strokes</td>
<td>-23%</td>
<td>&lt;0.0003</td>
</tr>
<tr>
<td>Total CV events and procedures</td>
<td>-16%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>New-onset diabetes</td>
<td>-32%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Development of renal impairment</td>
<td>-15%</td>
<td>0.0187</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>-35%</td>
<td>0.0001</td>
</tr>
</tbody>
</table>


Fixed-dose–combination pills in stage 1 hypertension

Fixed-combination pills, which are currently denied to stage 1 patients, are well tolerated, decrease BP in a very efficient fashion, and provide quicker BP control. Two categories of currently available fixed-dose medications are of particular interest. First are pills that contain a diuretic and a drug that interferes with the renin-angiotensin system (RAS), like ACE inhibitors, ARBs, or renin inhibitors. The second group are pills that combine a CCB with a drug that interferes with the RAS. Both these categories decrease BP efficiently and are well tolerated. Other combinations, particularly those containing β-blockers, are less useful.

It is unlikely that all pills combining diuretics with RAS blockers are equal. In selecting such a pill the physician must evaluate the dose and the type of diuretic used. Some potent diuretics in larger doses invariably interfere with glucose metabolism. Particularly notorious is chlorthalidone. In the large Systolic Hypertension in the Elderly Programme (SHEP) and in ALLHAT, chlorthalidone was associated with an increase in new-onset diabetes. Combinations that contain a small amount of diuretic and offer a wide range of RAS inhibition are preferable. Some diuretics are “glucose friendly” and are very efficacious when combined with drugs that interfere with the RAS. There are also substantial differences between the var-
ious RAS and CCB combinations. Tablets containing a long-acting dihydropyridine CCB are likely to be more efficacious—especially when combined with a long-acting RAS inhibitor (for example, the amlodipine/perindopril regimen of ASCOT [Anglo-Scandinavian Cardiac Outcomes Trial]—than ones containing verapamil or diltiazem. In an attempt to imitate habitual stepwise uptitration, some products are composed of numerous tablets, each with a different dose of basic ingredient. This defeats the purpose of a combination pill. Combination products should efficiently decrease BP and require no more than a single uptitration step.

Experts in the field agree that quick BP lowering is also a physiological imperative in stage 1 hypertension. BP-related target-organ damage is seen in prehypertension and is widespread in stage 1 hypertension. Decreased maximal forearm vasodilation, an early sign of vascular restructuring, has been documented in patients with borderline hypertension and, to a larger degree, also in stage 1 hypertension. Inadequate vasodilation was also documented in a physical exercise study of subjects with borderline hypertension. During exercise, cardiac output increased and vascular resistance decreased with increasing workload. In other words, exercise induces generalized vasodilation to accommodate the increased blood flow. At the point of maximum achievable exercise, subjects with borderline hypertension had much higher vascular resistance than healthy volunteers. Thus, the strong stimulus of exercise failed to elicit appropriate vasodilation in subjects with borderline hypertension.

Many subjects with borderline hypertension and stage 1 hypertension show signs of cardiac restructuring. A decrease in stroke volume has been described in prehypertension and stage 1 hypertension. Prehypertension and stage 1 hypertension are associated with tachycardia, which may limit stroke volume. However, an even more substantial stroke volume decrease was seen after blockade of cardiac autonomic nervous receptors. Cardiopulmonary blood volume, a measure of cardiac venous filling, was normal in these patients. Thus low stroke volume after chemical denervation of the heart is due to increased cardiac stiffness. Higher cardiac stiffness in early phases of hypertension is associated with echocardiographic signs of impaired ventricular diastolic relaxation (E/A ratio). Importantly, longitudinal observation has demonstrated a further and more prominent decrease of stroke volume over the course of hypertension. Long-standing BP differences between the placebo and actively treated groups in the TOMH study of stage 1 hypertension were associated with electrocardiographic changes indicative of increased left ventricular mass in the placebo group.

With this background in mind, one must conclude that nothing will be gained by postponing effective antihypertensive treatment in stage 1 hypertension. Similarly, slow stepwise uptitration of medication offers no advantage. The stepwise approach was justified when drugs were poorly tolerated and physicians had to search for the lowest possible effective dose. Besides the conceptual rationale suggesting that early, brisk BP lowering is advantageous, there is also a practical reason to embrace a more aggressive stance in the treatment of stage 1 hypertension. Patients’ poor adherence to prescribed medication is a notorious problem in the treatment of hypertension. The problem is even greater in patients who perceive that their BP is just a “little bit elevated” because they feel healthy and are not convinced that treatment is necessary. The earlier physicians can tell patients that their BPs have been brought under control, the more likely they are to comply with taking their medication. We live in a success-oriented environment where failure is not welcome. Many a patient disappointed by his doctor’s slow search for the right dose will either find another practitioner or will simply give up.

Nevertheless, fear of hypotension may deter physicians from using fixed-dose—combination pills for the treatment of stage 1 hypertension. This is a legitimate concern that needs to be resolved with a clinical trial. However, I will dare to predict that patients with stage 1 hypertension tolerate combination pills very well. It is not generally appreciated that the higher the baseline BP, the bigger the BP decrease for a given dose of antihypertensive medication. By the same token, the lower the baseline BP, the lower the BP lowering. Contrary to the general perception that lowering BP in “mild” hypertension is easy, it is actually quite difficult to reach the target BP decrease in stage 1 hypertension. It seems that the closer one gets to a BP reading of 120/80 mm Hg, the more the body opposes further BP lowering. I am particularly encouraged by the results of TROPHY (TRial Of Preventing HYpertension) in prehypertension, where treatment elicited BP lowering of 10/5 mm Hg and none of the patients reported major signs of hypotension. In summary, prompt BP lowering in highly prevalent stage 1 hypertension may have a major positive impact on public health and is likely to be well tolerated.

References

Nécessité d’un traitement par association à dose fixe dans les phases initiales de l’hypertension

La prévalence de l’hypertension de stade 1 est celle qui est la plus forte ; il en résulte que sa fréquence a un impact important sur la santé publique. Presque 2/3 de tous les décès coronariens liés à l’hypertension incombent à l’hypertension de stade 1. Son traitement actuel est basé sur des études anciennes, à une époque où les effets indésirables des médicaments obligeaient à une augmentation lente et progressive de la posologie. Il semble qu’une telle prudence puisse être abandonnée aujourd’hui avec les nouvelles associations efficaces à dose fixe et d’action rapide. L’hypertension est une pathologie auto-aggravante : son abaissement rapide à l’aide d’associations fixes au début de l’hypertension pourrait éviter le développement ultérieur d’une hypertension à haut risque. De nombreux patients perçoivent l’approche actuelle basée sur des visites répétées chez le médecin afin d’ajuster la posologie comme un échec à l’obtention du contrôle de la PA, ce qui diminue d’autant l’observance du traitement. La crainte de la part du médecin de voir apparaître une hypertension due à l’utilisation des médicaments actuellement disponibles dans l’hypertension de stade 1 devient injustifiée. La diminution de la pression artérielle est proportionnelle au niveau de pression initiale et la réponse dans l’hypertension de stade 1 est inférieure à celle des stades avancés. Actuellement, les associations fixes ne sont pas indiquées dans le traitement de l’hypertension de stade 1. Cependant, l’échec mondial du contrôle de l’hypertension appelle de nouvelles approches. Les associations à dose fixe ouvrent des perspectives prometteuses en termes de contrôle surs et rapide de la PA, de meilleure observance du traitement et de réduction plus importante des événements cardio-vasculaires dans l’hypertension de stade 1. Cependant, les modifications de la pratique clinique ne pouvant être instaurées sans preuves, nous avons besoin d’un essai thérapeutique en bonne et due forme pour vérifier que les avantages imputés aux associations fixes se traduisent effectivement par de meilleurs résultats dans l’hypertension de stade 1.
For many years, diastolic blood pressure was considered as the most important determinant of cardiovascular complications. This was explained by the relationship between diastole and coronary perfusion. However, recent cohort studies have reported that it is systolic blood pressure that carries the greatest responsibility in terms of major cardiovascular events. This begs the question: has the time now come for us to forget all about diastolic blood pressure when faced with a patient with hypertension?

**THE QUESTION**

**Management of hypertension in clinical practice: can we forget about diastolic blood pressure?**

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4. S. A. Golwalla, *India*
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Management of hypertension in clinical practice: can we forget about diastolic blood pressure?

1. T. Albassam, Saudia Arabia

Until early middle age, systolic and diastolic blood pressure (SBP/DBP) move in parallel, both tending to increase. However, at about the age of 55 years, their paths diverge. The two components of blood pressure (BP) move in opposite directions: SBP tends to climb on upwards, while DBP tends to decline. The resulting increase in pulse pressure (PP) has attracted attention as a risk factor in its own right.

In the last two decades, SBP has been coming to the fore as the main BP variable, in particular in the elderly, in whom isolated systolic hypertension is the most important BP abnormality. However, the picture is not simple. One complication is the J-curve phenomenon, according to which patients with very low DBP are also at increased age of cardiovascular death. The introduction of ambulatory BP generated a fresh profusion of parameters: daytime BP, nocturnal BP, morning surge BP, average 24-hour BP, and masked hypertension. These were supplemented by central BP, pulse wave velocity, and augmentation index. Consequently, it was good news to hear that international hypertensives experts wanted to simplify life for the practicing physician. They recommended focusing mainly on SBP, with less emphasis on DBP. This view was also supported by studies showing that SBP is the more difficult parameter to control. In addition, SBP contributes more to the global burden of BP-related disease than DBP. However, a number of concerns remain.

Arguments against ignoring DBP

1. DBP data come free of charge with every BP measurement device. There are no instruments that solely record SBP. Thus no cost saving is involved in concentrating on a single parameter; indeed, there may be wastage in ignoring the free contribution of DBP.
2. Blood pressure clinics are typically attended by a mix of young, middle-aged, and elderly. We need to maintain the DBP parameter in the minds of physicians so that they can offer optimal treatment to these heterogeneous hypertensive populations.
3. The J-curve phenomenon relates to DBP levels in the many hypertensive patients who have coronary artery disease. The concern is that DBP levels may fall too low to provide adequate myocardial perfusion. It is therefore important to monitor DBP carefully in order to prevent unnecessary coronary accidents.
4. Cardiovascular risk assessment in young and middle-aged hypertensives is more accurate if informed by SBP and DBP together than by SBP, DBP, or PP alone.
5. Combining SBP with DBP and PP with mean arterial pressure produces models that are superior to single BP components for predicting cardiovascular disease.
6. Systolic and diastolic hypertension differ in their pathogenesis. The first is related mainly to large artery stiffness while the second relates to arteriolar vasoconstriction. It is important to bear this difference in mind in order to provide optimal patient care.
7. Both SBP and DBP are used in the definition of hypertensive emergencies.
8. We currently stage hypertension using systolic and diastolic values, either separately or in combination. Will the new emphasis on SBP require revision of the staging conventions?

Personally, I feel it is too early to drop the DBP component. The time is not yet ripe. DBP is a simple and easy parameter to measure and remember. Physicians were brought up with it. Taking DBP into account enhances the view of overall risk when combined with SBP, improves hypertensive care, and does so at no extra charge.

References

The history of clinical medicine shows how advances in scientific knowledge have shaped physician attitudes to disease and treatment objectives. In cardiovascular medicine, clinicians traditionally gave more importance to diastolic blood pressure (DBP) than to systolic blood pressure (SBP) in the induction and maintenance of arterial disease and its complications in target organs. This was because DBP was viewed as reflecting the systemic resistance offered by small arterioles. An increase in this resistance was considered the fundamental pathophysiological mechanism of hypertension. In addition, in clinic or home blood pressure (BP) measurements, DBP was much more stable and reproducible than SBP. For these and other reasons, even though epidemiologic studies had shown a direct linear relationship between both BP components and cardiovascular mortality and morbidity, the first operative definition of hypertension by the World Health Organization in 1978 included DBP as the most important distinctive element in hypertension and its classification of severity. SBP was assumed to be less important. It is not therefore surprising that, in all studies on the prevention of morbidity and mortality by antihypertensive treatment carried out during these years, efficacy should have been evaluated by changes in DBP and that regulatory agencies such as the Food and Drug Administration or the European Medicines Agency use this type of design to the present day. Thus the Hypertension Optimal Treatment (HOT) study was designed to determine the optimal DBP treatment objective, regardless of the SBP levels achieved.

These concepts strongly influenced physician education in hypertension in the final 30 years of the 20th century. All therapeutic options considered by physicians were designed to normalize DBP. Once this objective was achieved it was generally considered that the patient was controlled, regardless of SBP levels. Due to the training received and hence physicians’ mind-sets, current control rates for DBP are practically double those for SBP in all countries. The disparity between SBP and DBP control is also due to the fact that hypertension affects >60% of over 65s, isolated systolic hypertension affects between 10% and 20%, and while the control of DBP increases with age, that of SBP declines.

For these reasons, in recent years, SBP control has been promoted as the great challenge in hypertension. The importance of DBP risks being forgotten. Evidence of this importance can be found in the Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation (ADVANCE) study, in which patients treated with the fixed combination of perindopril and indapamide for a mean of 4.3 years had a mean reduction of 5.6 mm Hg in SBP and 2.2 mm Hg in DBP compared with those receiving placebo plus standard therapy. Strikingly, this reduction of only 2.2 mm Hg in DBP was associated with a significant relative risk reduction of 9% (P=0.04) in combined major macrovascular or microvascular events, with significant reductions of 21% in renal events (P<0.0001) and microalbuminuria (P<0.0001). The relative risk of cardiovascular death was also significantly reduced by 18% (P=0.03) and all-cause mortality by 14% (P=0.03).

In summary: Both components of BP are important in lowering morbidity and mortality. Normalization of DBP should therefore continue to be a priority, in addition to normalization of SBP.

References
3. S. Filipova, Slovakia

In the core trio of hemodynamic values that govern clinical practice (systolic blood pressure [SBP], diastolic blood pressure [DBP], and heart rate), DBP is—to use a fairy-tale analogy—the less favored princess, the one whose story evokes less interest. We have less clinical information and evidence-based medicine data on the role of normal and elevated DBP. On the other hand, the physiology and pathophysiology of DBP contain a mine of information on blood pressure (BP) regulation and the development of all types of hypertension: essentially, DBP rises with increased systemic vascular resistance and falls with increased arterial stiffness.

Isolated diastolic hypertension resulting from dysautoregulation of systemic vascular resistance and elevated pulse pressure is more frequent in younger and middle-aged hypertensives (typically 30 to 50 years old). DBP elevation with a normal SBP is the classic presentation of essential hypertension, progressing to systo-diastolic hypertension if untreated. The underlying hemodynamic abnormality is the elevation of systemic vascular resistance and hence of mean arterial pressure, with no corresponding increase in cardiac output. The result is an isolated increase in DBP. Such diastolic hypertensives are frequently obese and exhibit higher sympathetic and renin-angiotensin-aldosterone system activation. The condition has been characterized as prehypertension, but is unfortunately rarely picked up in everyday practice.

Extensive trial data have shown a close and continuous relationship between coronary risk and DBP: risk is continuous over the range 115/75 to 185/115 mm Hg, and doubles with each 20/10 mm Hg increment. Although lower DBP generally reflects lower risk, a level below the lower limit of coronary autoregulation may actually increase coronary risk, presumably due to lower coronary filling pressures. This would produce a J shape for the DBP coronary risk curve, except for no such shape has yet been satisfactorily confirmed. In patients with coronary artery disease, hypertension, and left ventricular hypertrophy, DBP levels either above or below the normal range increase myocardial oxygen demand. Data are too few to characterize the autoregulatory threshold. The Hypertension Optimal Treatment (HOT) trial found a minimal increase in major cardiovascular events (myocardial infarction, cardiovascular mortality, but not stroke or renal failure) at DBP levels below 70 mm Hg. Such myocardial susceptibility to low diastolic perfusion pressures is consistent with the data that stroke morbidity and mortality are best correlated with SBP, while the best predictor of coronary events may be pulse pressure.

There are no data for characterizing the appropriate rate of DBP lowering or target DBP values in patients with coronary heart disease. The consensus is that DBP should be lowered continuously, but maintained above 60 mm Hg if the patient has diabetes or is over 60 years of age. In older hypertensive patients with a wide pulse pressure, lowering SBP may lower DBP below 60 mm Hg, thereby accentuating myocardial ischemia.

An important clinical consideration is the relationship between hypothyroidism and hypertension. Many patients with hypothyroidism have DBP elevation, even in the early stages of the disorder, although no relationship between thyroid-stimulating hormone levels and DBP has been found, at least in the elderly. Thyroxine replacement lowers both SBP and DBP in hypertensive patients with hypothyroidism, including during the subclinical (or oligosymptomatic) phase of disorder. Diastolic hypertension could be a marker of incipient hypothyroidism.

Conclusion: The differential diagnosis of hypertension comprises many syndromes other than essential hypertension that influence DBP. They form an important part of everyday practice in internal medicine, cardiology, and geriatrics.

References
Meta-analysis of prospective epidemiologic observations in a total of one million adults with no previous vascular disease recorded at baseline has shown an association between an increased risk of vascular mortality, essentially from ischemic heart disease and stroke, and elevation of both diastolic blood pressure (DBP) and systolic blood pressure (SBP). Although the average of DBP and SBP is slightly more informative than either alone in predicting vascular mortality from a single blood pressure measurement, the evidence also suggests that risk lies more with SBP than with DBP.

Presently, the definition of essential hypertension is based on the level of both DBP and SBP. As with other biological characteristics, these pressures change with an individual’s age. Whereas SBP increases continuously with age, DBP rises till about the age of 50 years and decreases thereafter. It is for this reason that after the fifth decade of life the frequency of high SBP in the community is much greater than that of high DBP. The majority of hypertensive patients are above the age of 50 years, and because of an increasing lifespan, the distribution of hypertension is likely to shift further towards the later decades. This is why the burden of elevated cardiovascular risk rests more with SBP than it does with DBP.

As age advances, atherosclerotic changes to conduit arteries become a more important determinant of blood pressure (reflected in the SBP) than peripheral resistance (which determines DBP). Clinical trials in the elderly with predominantly isolated systolic hypertension have shown the benefit of cardiovascular risk reduction by concentrating on the reduction of SBP. A particularly large trial, the randomized, double-blind, placebo-controlled Hypertension in the Very Elderly Trial (HYVET), was performed in 3845 patients aged 80 years or above with hypertension defined essentially by SBP (160 mm Hg or higher). DBP was initially required to be between 90 and 109 mm Hg, but this was subsequently relaxed to include any value below 110 mm Hg, allowing the inclusion of many patients with isolated SBP. Treatment with a sustained release formulation of the diuretic indapamide 1.5 mg, augmented as necessary with the angiotensin-converting enzyme inhibitor perindopril 2 mg or 4 mg, was targeted to a BP of <150/80 mm Hg. Active treatment was associated with a 39% reduction in the rate of fatal stroke (P = 0.05), a 21% reduction in the rate of death from any cause (P = 0.02), and most strikingly a 64% reduction in the rate of heart failure (P = 0.001). Serious adverse events were also fewer in the active-treatment group (P = 0.001). Such a study provides evidence of the vascular benefits of treatment targeted primarily at SBP in the very elderly.

It has also been observed that it is more difficult to lower SBP than it is to reduce DBP. The control rate of SBP is about half that achieved with DBP. This suggests that control of both would be achieved in more patients if SBP were targeted rather than DBP. Presently, physicians and patients are expected to monitor two parameters of blood pressure. It would be simpler and more practical for all concerned to base management decisions on a single parameter. This is particularly important because despite treatment, about a third of all patients fail to achieve long-term blood pressure control. Perhaps the time has now come to jettison DBP in the day to day management of essential hypertension, and focus our energies on the control of SBP alone.

References
5. I. Barna, Hungary

Diastolic blood pressure (DBP) increases with age to 55 years, then decreases, whereas systolic blood pressure (SBP) increases steadily with age to at least 80 years. Elevated DBP is thus more common in youth and middle age.

Other physiological determinants of BP fluctuation include pregnancy and weight reduction. Early in the first trimester, active vasodilatation induced by local mediators such as prostacyclin and nitric oxide lowers blood pressure (BP), primarily DBP. A drop of 10 mm Hg is usual by 13 to 20 weeks, reaching a nadir at 20 to 24 weeks; fluctuation is similar in both normotensive and hypertensive women. As for weight reduction, a review of randomized controlled trials reported a both normotensive and hypertensive women. As for weight reaching a nadir at 20 to 24 weeks; fluctuation is similar in

mature DBP. A drop of 10 mm Hg is usual by 13 to 20 weeks, reaching a nadir at 20 to 24 weeks; fluctuation is similar in both normotensive and hypertensive women. As for weight reduction, a review of randomized controlled trials reported a short-term fall in DBP of 0.92 mm Hg per kg weight lost1; in the longer term, despite a clear linear relationship, this effect is attenuated: 10 kg weight loss decreases DBP by only 4.6 mm Hg, while decreasing SBP by 6.0 mm Hg (r=0.702; P≤0.01); the results are similar to those for absolute differences (r=0.661; P≤0.07)2.

The simple direct relationship between SBP/DBP and cardiovascular risk has recently been complicated by observing that risk is directly proportional to SBP in the elderly and that for any given SBP level, outcome is inversely proportional to DBP, with pulse pressure (PP) proving strongly predictive. PP increases due to stiffening of the major arteries. BP fails to increase during diastole. Left ventricular workload is increased, while the lower DBP reduces coronary flow. Arterial stiffening and the resulting increase of PP with age are well-recognized. PP was first reported as a cardiovascular risk marker in 1989 and confirmed as such in several epidemiologic studies. It is associated with other risk factors for atherosclerotic vascular disease, such as obesity, inflammation, the micro- and macrovascular complications of type 2 diabetes, and plasma natriuretic peptide levels. There are several theoretical reasons for considering PP an excellent indicator of cardiovascular and mortality risk.

The Veterans Administration and other treatment studies were based on DBP, although SBP may well also have been clearly increased at baseline. The classic meta-analyses of BP and cardiovascular risk similarly used DBP. However, for over 30 years the Framingham investigators have been telling us that SBP is the more important component. Three large placebo-controlled interventional studies—Systolic Hypertension in the Elderly Program (SHEP), Systolic Hypertension in Europe (Syst-Eur), and Systolic Hypertension in China (Syst-China)—reinforced this idea during the 1990s, showing that drug treatment of isolated systolic hypertension reduced cardiovascular events in elderly patients. Elevated SBP is the main target of antihypertensive therapy. It is also the most common and poorly treated component. In the largest available meta-analysis of observational data (61 studies in one million subjects, 70% from Europe, without overt cardiovascular disease), both SBP and DBP were independently and similarly predictive of stroke and coronary mortality. The contribution of PP in this case was slight, particularly in those under 55 years.4

Adequate SBP therapy normally corrects DBP simultaneously. Patients with elevation of SBP and PP are at special risk. Central PP as assessed from the augmentation index is significantly related to cardiovascular events. However, more large-scale observational and interventional studies are required to confirm the prognostic role of central as opposed to peripheral BP. Elevation of SBP, DBP, and PP causes target organ damage and increases cardiovascular morbidity and mortality, but SBP is a superior predictor of coronary heart disease and congestive heart failure than DBP5.6

Conclusion: An increase in SBP is made more dangerous by either a concomitant increase or concomitant reduction in DBP (especially in the elderly), whereas pure diastolic hypertension may be less harmful. ■

References
For decades, hypertension was classified on the basis of diastolic blood pressure (DBP) and the consensus was that DBP was the main determinant of cardiovascular risk (CVR). More recently, however, prospective epidemiological studies, clinical trials, and meta-analyses have focused attention on systolic blood pressure (SBP), showing a stronger association with CVR and suggesting that SBP is a better guide to risk than DBP, especially in older subjects.2,6

Although there is no doubt that lowering elevated blood pressure is highly effective in reducing CVR, the relative importance of pressure components as determinants of risk and the possible existence of J-shaped relationships between mortality and pressure levels have prompted considerable debate.2-5,6

Resolving these issues is methodologically complex, which explains why we still have no conclusive answer about the importance of DBP as a CVR predictor. Elements of the answer include: (i) the linear correlation between SBP, DBP, and pulse pressure; (ii) the age dependency of normal BP levels, reflecting aging of the arterial system: SBP increases to the eighth/ninth decade, whereas DBP increases only until the sixth decade, then decreases slightly; (iii) the contrasting effects on DBP of increases in peripheral arterial resistance and large conduit artery stiffness; (iv) the close correlation between SBP and DBP in subjects aged ≤55 years—increased arterial resistance is the hallmark of systo-diastolic hypertension; (v) increased arterial stiffness as the dominant hemodynamic factor with advancing age, leading to a fall in DBP and hence isolated systolic hypertension; (vi) difficulties in interpreting the effect of BP components due to their interdependency (if only one component is used to model risk, it is unclear how much of the effect is due to its correlation with the other—if both are introduced in a regression model, the interpretation of coefficients is uncertain because they partly reflect the effect of pulse pressure); (vii) the dynamic effect of aging on the complex interactions between BP and cardiovascular disease (coronary heart disease is much commoner in old age, and the absolute annual difference in coronary mortality associated with a given difference in BP increases with increasing age); (viii) the failure of arterial stiffness to respond readily to drug treatment, with the result that antihypertensive drugs often reduce DBP more than SBP in the elderly; (ix) the possibility in interventional studies that a fall in DBP can be due to aging as well as to active treatment; (x) absence of a proven J-shaped relationship between cardiovascular risk and DBP in coronary patients receiving antihypertensive therapy (several mechanisms may be involved); and (xi) failure of conventional (brachial artery) BP determination to take into account the difference between peripheral and central BP and the age-related amplification of SBP.

At present, the levels of evidence for answers to the initial question are low, there are serious gaps in the data available, and many specific issues remain open to debate. In particular, no matter how difficult they may be to design, clinical studies are needed to determine the importance of DBP in determining CVR. In the meantime, DBP levels remain important for (i) classifying hypertension; (ii) targeting specific interventions; (iii) informing antihypertensive therapy options (differing effects in peripheral and central arteries); and (iv) guarding against excessive reduction in the elderly (especially those with comorbidity) since a low DBP may increase coronary risk and related mortality.

On this basis our short answer is: no, we cannot neglect DBP in clinical practice!

References
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D iastolic blood pressure (DBP) came to be considered the most important determinant of cardiovascular risk in the mid-20th century. The first three Reports of the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure staged hypertension according to DBP levels.\(^1\) DBP was viewed as a better predictor of cardiovascular risk than systolic blood pressure (SBP), which was seen as a natural corollary of aging, while DBP was seen as dependent on peripheral resistance. It remained clinical scientists’ focus for many decades.

Reporting the Framingham data in 1971, Kannel et al showed clearly that SBP was more accurate than DBP in predicting cardiovascular risk,\(^2\) but it took nearly 20 years before the JNC used SBP in staging hypertension. The Fourth JNC Report acknowledged the prognostic role of isolated systolic hypertension in 1988.\(^3\)

Since the Fifth JNC Report, hypertension has been staged according to the elevation of SBP and/or DBP, with both pressure components being accepted as indices of increased cardiovascular risk.\(^4\) The key messages of the Seventh JNC Report published in 2003 were that SBP levels over 140 mm Hg are a more important cardiovascular risk factor than DBP in subjects over 50 years of age: risk begins at 115/75 mm Hg and doubles for each 20/10 mm Hg increment of SBP/DBP; until age 50, DBP is the more potent cardiovascular risk factor; it is then overtaken by SBP with systolic hypertension becoming the most common form of hypertension in the over-50s.\(^5\)

In 2008, Williams et al proposed expressing the thresholds for the diagnosis and treatment of hypertension in the single dimension of SBP on the grounds that this is far the more important of the two blood pressure components, especially among the over-50s.\(^6\) They argued that with population aging and hence an increase in the number of subjects with systolic hypertension, it was reasonable to classify and treat hypertension solely on the basis of SBP in the over-50s. However, the 2007 guidelines of the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and European Society of Cardiology stressed the importance of high cardiovascular risk in patients with a high SBP and low DBP, ie, a high pulse pressure. More recently still, in 2009, the European Society of Hypertension Task Force Reappraisal of European Guidelines on Hypertension Management also expressed treatment targets in terms of SBP and DBP.\(^7\)

In 2008, Kelly et al published a Chinese database comprising 169,871 men and women aged ≥40 years. Compared with normotensives, the relative risks of cardiovascular disease and mortality in patients with isolated diastolic hypertension (≥90 mm Hg and SBP <140 mm Hg) were 1.59 and 1.45, respectively, thus confirming DBP as an independent cardiovascular risk factor.\(^8\)

A 2009 analysis by Franklin et al of the Framingham data in 9557 individuals, all free of cardiovascular events and antihypertensive therapy at baseline, showed the combination of high SBP and low DBP to be a superior predictor of future adverse cardiovascular events. As to be expected, given the role of pulse pressure, lowering DBP below 70 mm Hg increased cardiovascular risk.\(^9\)

**Conclusion:** In evaluating, detecting, and treating hypertensive patients, the combination of SBP and DBP remains superior to either component alone in predicting cardiovascular risk. Although there is considerable evidence to suggest that SBP outperforms DBP in gauging cardiovascular risk in the over-50s, the time has not yet come to jettison DBP.

**References**

The short answer is no. Although the paradigm has shifted over the last decade with regard to the relative importance of the blood pressure (BP) components, elevated diastolic blood pressure (DBP) does have prognostic implications. For example, although a relatively large study in 1913 subjects aged >40 years using home BP measurement showed that isolated DBP had the same prognosis as normotension, a larger study in the elderly (>65 years; n=5888) showed otherwise: systolic blood pressure (SBP) was indeed the best individual predictor of cardiovascular (CV) events, but DBP was also strongly and directly related to the risk of coronary and CV events.

Furthermore, clinical trials up to the end of the last decade using DBP as the surrogate end point showed clear clinical benefit, in particular for high-risk patients. Some may argue that over-reliance on DBP as the surrogate may have contributed to the somewhat attenuated benefits of BP reduction seen in many earlier trials. Others will say that SBP is not only prognostically more important, it is also more difficult to control and therefore deserves more emphasis. While these viewpoints have merits, it does not mean that they should be pursued at the expense of neglecting diastolic control.

In clinical practice, we encounter patients whose SBP is controlled, but whose diastolic readings remain suboptimal, particularly among younger patients. We do not currently have enough evidence to allow us to neglect such cases of isolated diastolic hypertension. On the contrary, forgetting that their DBP remains suboptimal is likely to expose such patients to higher than acceptable long-term risk. Admittedly, we also have no hard evidence of clinical benefit from lowering DBP in this category of patient, but there is epidemiologic evidence that neglecting their DBP could expose them to unnecessary risk. It must also be remembered that in contrast to the case with DBP, there have never been any outcome trials examining the benefits of lowering SBP to different pressure levels. Indeed, recent trials have shown that aggressive BP lowering in high-risk patients is more likely to optimize DBP than SBP.

Overreliance on SBP control at the expense of diastolic control has the indirect effect of focusing excessive attention on the elderly as the archetypal patients in whom diastolic control is seldom an issue. However, even in this group, DBP cannot be forgotten, albeit for a slightly different reason: too low a DBP may signify a stiffer conduit artery system, and a worse prognosis. So whichever way one looks at it, neglecting DBP and its importance may not be such a wise step “forward.”

References
D o you treat a patient who has a blood pressure of 130/100 mm Hg on repeated measurement and no other risk factors? This question may seem silly for many, yet profound for those familiar with the epidemiologic data on hypertension and cardiovascular (CV) risk reduction.

Current hypertension guidelines (Joint National Committee 7, European Society of Hypertension 2007, European Association for Cardiovascular Prevention and Rehabilitation 2007) focus on systolic blood pressure (SBP) as the more accurate predictor of CV outcome and mortality.1,2 Many well-designed clinical trials and observational cohort studies have indeed shown strong associations between SBP and CV events, and between SBP treatment and event reduction.3 Diastolic blood pressure (DBP) was predictive only in cases of combined systolic and diastolic hypertension, but not in isolated diastolic hypertension.4 These findings influenced the current guidelines. As a result, the global risk scoring index of individual patients includes only SBP.1,2

However, DBP remains an integral part of the description of hypertensive status, eg, >140 and/or >90 mm Hg.1,2 Nor do the guidelines rule out a potential contribution of diastolic hypertension to CV risk. The attitude is that hypertension is defined as elevated SBP and/or DBP, but that it is SBP that must be treated. This is not the message that the data are giving us: an elevated DBP is a predictor of CV events. It is simply that SBP is more predictive. Meta-analysis has shown a doubling of CV mortality for every 20/10 mm Hg increase in blood pressure.4 There are many explanations for the discordance between SBP and DBP. For a start, the absolute difference in untreated SBP between hypertensive and control groups exceeds that in DBP. In cohort studies most (but not all) patients were already being treated for hypertension before enrolment and classification into different risk categories. DBP is much easier to control than SBP. This further reduces the absolute difference in DBP while maintaining a relatively high difference in SBP. Naturally, those with uncontrolled SBP will remain at high risk for the entire duration of observation. The same is true in randomized placebo-controlled trials; we see big differences in SBP and small differences in DBP. There is therefore less scope for DBP to predict CV events. In addition, many trials (except those in isolated systolic hypertension) had an inclusion criterion for DBP (eg, >95 mm Hg), but no threshold for SBP. As expected, large falls in SBP were paralleled by much smaller falls in DBP (eg, 30 mm Hg SBP vs 11 mm Hg DBP). Nonetheless, compared with placebo or no treatment, and basing recruitment on DBP alone, treatment reduced CV events and mortality.5

For these reasons, we should not yet recommend the discarding of DBP as a risk factor and treatment target. We also need DBP for determining proven strong predictors of CV events, such as pulse pressure and mean arterial pressure. On this basis, the guidelines recommend treating everyone with stage 1 and 2 hypertension, and point out that DBP is a stronger CV risk factor than SBP in younger hypertensives. In the over-50s, on the other hand, SBP is the more important predictor and the more important treatment target.1

A final point: Few, if any, would disagree with the need to treat DBP to normal levels in any patient with a history of coronary heart disease or stroke and a blood pressure of 130/100 mm Hg. In the final analysis, blood pressure is just one of the multiple risk factors that influence CV outcome and its treatment should be approached in an individualized manner. ■

References
10. B. Trimarco, Italy

Diastolic blood pressure (DBP) was long considered the key determinant of the cardiovascular risk associated with hypertension. It was documented as such in the early Reports from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, which defined hypertension and graded its severity in terms of DBP only. The concept was derived from the knowledge that DBP represents the resistance that the heart has to overcome in order to pump blood into the systemic circulation and also from the strong relationship between diastolic and coronary perfusion.

The subsequent finding that systolic blood pressure (SBP) correlates better than DBP with coronary heart disease, stroke, and heart failure have challenged this view, suggesting that SBP outweighs DBP as a predictor of cardiovascular morbidity and mortality. In 1988, the Joint National Committee Report acknowledged the prognostic role of isolated systolic hypertension, and since the Fifth Report published in 1993, hypertension has been defined as elevation of SBP and/or DBP. On the evidence that SBP has greater prognostic value than DBP, Williams et al proposed in 2008 a simplified definition of hypertension, basing the threshold for the diagnosis and treatment of hypertension on SBP only, discarding DBP values altogether, at least in the 50+ age group that accounts for the great majority of hypertensive patients.

Age plays an important role in modifying the relationship between blood pressure components and cardiovascular risk. In particular, with increasing age, there is a gradual shift from DBP to SBP and eventually pulse pressure as predictors of cardiovascular events. Under 50 years of age, DBP is a stronger predictor of cardiovascular risk than SBP or pulse pressure. The sixth decade is a transition state during which all three indices are comparable. From age 60 years on, when considered together with SBP, DBP becomes inversely related to cardiovascular risk and pulse pressure emerges as the best predictor. The fact that SBP and DBP both predict risk in the under-50s confirms the concept that increased peripheral resistance is dominant in determining cardiovascular risk in young hypertensives. In the same way, the emergence of pulse pressure and SBP as the dominant predictors of risk from the seventh decade onwards is consistent with the contribution of large artery stiffness to risk in older patients.

Yet despite the findings relating to age, controversy persists over which blood pressure component is the superior predictor of cardiovascular events. A recent follow-up study of the Framingham data tested the utility of a combination of blood pressure components instead of a single component in predicting cardiovascular risk. In a model adjusted for age, sex, and other covariates, the odds of cardiovascular events increased with increasing SBP and DBP, but the relationship between DBP and cardiovascular risk was quadratic and nonlinear. Thus for any given SBP value greater than 120 mm Hg, the odds of cardiovascular events are increased at both the high and low extremes of DBP. In particular, high DBP values are pathogenic because they represent increased vascular resistance, while low DBP values are pathogenic because they reflect increased arterial stiffness.

Conclusion: We cannot ignore DBP because it has been demonstrated that in patients with isolated diastolic hypertension, who account for 14% of the hypertensive population, cardiovascular risk is twice that in subjects with normal blood pressure. Furthermore, while subjects with SBP $\geq 180$ mm Hg and normal DBP have a 2.4-fold adjusted cardiovascular risk compared to normotensives, those with identical SBP but DBP $\geq 110$ mm Hg have an odds ratio for cardiovascular events of 7.7, which more than qualifies DBP as a treatment target.

References
L ong-term epidemiologic studies have shown a relationship between blood pressure (BP) and the risk of cardiovascular (CV) complications. Treatment of high BP reduces mortality, morbidity and risk of CV events. According to current guidelines all hypertensive patients should be treated to a target BP of <140/90 mm Hg and those at high risk to a target BP of <130/80 mm Hg. More intensive BP lowering in high-risk patients has been questioned by the recent reappraisal of the European Society of Hypertension guidelines on hypertension management.

The risks of hypertension were ascribed mainly to DBP until the mid-1980s when SBP also began to be recognized as an important predictor of CV morbidity-mortality. However, meta-analysis of data from over one million adults in 61 prospective studies indicated that the absolute risk of death from ischemic heart disease at least doubled with every decade, with a line of progression that was similar for both SBP and DBP. Data from various trials of antihypertensive treatment showed clear clinical benefit and fewer CV complications as a result of lowering DBP. More intensive DBP lowering also translated into clear benefit (especially in diabetics) in the Hypertension Optimal Treatment trial. But treating to DBP levels below 65-70 mm Hg appeared to increase coronary risk. The evidence suggests that this J-curve relationship between DBP and coronary risk applies mainly to older subjects with isolated systolic hypertension.

DBP peaks around 50 years of age and then steadily declines. In younger subjects it depends mainly on peripheral resistance, i.e., low DBP means low peripheral resistance. In younger subjects with a hyperkinetic circulation, DBP is less variable than SBP. Isolated diastolic hypertension exists in subjects under 50 years of age, but is uncommon. In older subjects, low DBP means high arterial stiffness, and is usually associated with high SBP, high pulse pressure, and high CV risk. DBP thus appears a better predictor of CV mortality in younger subjects, while SBP and pulse pressure better reflect CV risk in the older population.

Conclusion: DBP is an important predictor of CV morbidity/mortality in subjects under 50 years of age. Above this age, and in particular from age 60 onwards, SBP (and pulse pressure) become the more important determinants of total risk. However, given the relative importance of each component, treatment of hypertension should continue to focus on lowering both SBP and DBP (where raised), as recommended by the current European guidelines.

References
The ultimate goal of antihypertensive therapy is to minimize the risk of hypertension-related death and morbidity. Reappraisal of European guidelines on hypertension has underlined the importance of blood pressure (BP) reduction per se, and highlighted the fact that systolic pressure, 24-hour BP profile, and central BP are strong predictors of cardiovascular events. Guidelines now recommend tailored management of hypertension adapted to each individual patient’s needs, and to initiate treatment with combination antihypertensive therapy. Based on recent evidence from the Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure–Lowering Arm (ASCOT-BPLA), the combination of an angiotensin-converting enzyme inhibitor with a calcium channel blocker (CCB) is one of the preferred therapeutic options. ASCOT-BPLA was a breakthrough as it showed that antihypertensive strategies could differ in cardiovascular outcomes despite producing comparable brachial BP decreases. The amlodipine/perindopril regimen was more effective than atenolol/bendroflumethiazide in preventing death and major cardiovascular events. More efficient control of central BP, BP variability, and nocturnal hypertension with amlodipine/perindopril contributed to the difference in outcomes. Following the ASCOT trial results, Coveram was developed as a fixed combination of perindopril and amlodipine, and has already received consistent evidence-based support. Coveram provides rapid and effective brachial BP reduction in a broad range of hypertensive patients and acts synergistically on each and every component of antihypertensive efficacy: central BP, 24-hour BP, BP variability, and nocturnal hypertension. Coveram, indicated for both hypertension and coronary artery disease, stands out among currently available combinations of renin-angiotensin system inhibitors and CCBs, as it has been shown to decrease the risk of death and cardiovascular events.

Hypertension is the leading risk factor for premature death, responsible for 12.8% (7.5 million) of deaths worldwide, as well as causing up to 54% of cardiovascular deaths, according to a report from the World Health Organization published in 2010. At the same time, a so-called hypertension paradox was described, consisting of an increase in the number of uncontrolled hypertensive patients, despite therapeutic advances. More than two thirds of hypertensive adults in the United States fail to reach the blood pressure (BP) goal of <140/90 mm Hg, and over 80% of patients in Canada and Europe show suboptimal BP control.

Coveram in the management of hypertension: improving each and every component of antihypertensive efficacy for lifesaving benefits

by V. Vandzhura, France
However, hypertension, as a disease whose defining feature is elevated blood pressure, has as many faces as the patients it impacts. In practice, physicians have to treat patients with systolic and/or diastolic hypertension, those whose BP increases in the evening or at night, and BP that “jumps” several times a day. Thus, a patient’s specific BP profile as well as concomitant risk factors and diseases determine each patient’s risk.

To improve the management of hypertension, the Reappraisal of European Guidelines on Hypertension Management: A European Society of Hypertension Task Force Document emphasizes the need for overall cardiovascular risk evaluation and the importance of BP reduction per se. Furthermore, guidelines recognize that central blood pressure and 24-hour BP profile are more informative than clinic (brachial) BP in determining cardiovascular risk as well as the treatment decision.

Based on evidence from clinical trials, use of antihypertensive drug combinations for treatment initiation, “particularly in patients at high cardiovascular risk in which early blood pressure control may be desirable” is recommended. The combination of an angiotensin-converting enzyme (ACE) inhibitor and a calcium channel blocker (CCB) is one of the regimens preferentially recommended, as the guidelines point out. Data on morbidity-mortality for angiotensin receptor blocker (ARB)/CCB combinations are lacking.

The Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure-Lowering Arm (ASCOT-BPLA) was the first, and is still the only, clinical trial to demonstrate effective reduction in mortality among hypertensive patients treated with a CCB in combination with a renin-angiotensin system (RAS) inhibitor. A significant decrease of 11% in deaths from all causes and of 24% in cardiovascular mortality was achieved with an amiodipine/perindopril regimen, despite almost comparable lowering of brachial BP with a β-blocker/diuretic combination. In addition, ASCOT substudies have demonstrated that a better prognosis is directly associated with more effective reduction in central aortic and central carotid BP as well as BP variability and true 24-h efficacy with nighttime hypertension reduction by the amiodipine/perindopril regimen.

Furthermore, the recent subanalysis of the European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) provided evidence that patients receiving perindopril (Coversyl) together with a CCB benefited from a markedly greater decrease in the risk of cardiovascular mortality and morbidity.

Following the results of the ASCOT and EUROPA trials, Coveram, a fixed-dose combination of Coversyl (perindopril) and amiodipine, was developed. Coveram is the focus of this review. Representing a type of exception among antihypertensive treatments, Coveram:

- Was introduced into clinical practice as a consequence of evidence-based support in clinical trials (ASCOT, EUROPA);
- Decreases elevated BP rapidly and markedly (SafeTy and efficacy analysis of coversyl amiodipine in uncontrolled and Newly diagnosed hypertension [STRONG], Study of optimized Blood pressure lowering therapy with fixedCombination perindopril/amiodipine [SYMBIO]); and
- On top of its superior BP reduction, Coveram improves central and nocturnal BP control and BP variability, thus providing lifesaving benefits for a broad range of patients with hypertension.

Evidence for Coveram in mortality and cardiovascular morbidity prevention: a primary objective of antihypertensive treatment

- **ASCOT-BPLA**

ASCOT-BPLA was a landmark multicenter prospective randomized controlled trial in 19 257 patients with hypertension (mean BP at baseline was roughly 164/94 mm Hg), 40 to 79 years of age, and who had at least three other cardiovascular risk factors, but were still free from coronary artery dis-
ease (CAD). Patients were assigned either to amlodipine plus perindopril as required to achieve target BP or atenolol plus bendroflumethiazide as required.

The rationale for the ASCOT study was the lack of morbidity or mortality evidence on optimum combinations of antihypertensive agents. In addition, for a given reduction in blood pressure, some authors suggested that newer agents such as amlodipine with perindopril (Coversyl) would confer advantages over the traditional approach of diuretics and β-blockers. The study was discontinued prematurely because of a significant reduction in cardiovascular mortality (RRR, –24%; P=0.001), all-cause mortality (RRR, –11%; P=0.02), and in stroke (RRR, –23%; P=0.0003) in favor of the amlodipine/perindopril group, even though the necessary number of primary end point events was not reached due to early termination. The amlodipine/perindopril group also had a significantly lower incidence of new-onset diabetes (RRR, 31%; P<0.0001) as well as fatal and nonfatal stroke, total cardiovascular events, and renal impairment (Figure 1).

Mean brachial BP reduction vs baseline was 27.5/17.7 mm Hg with the amlodipine/perindopril regimen and 25.7/15.6 mm Hg with β-blocker/diuretic with a mean difference of 2.7 mm Hg in systolic blood pressure (SBP). Based on long-term observational data, this systolic difference should translate into a difference in the rate of coronary events of about 8% and in the rate of stroke of about 11%, while the actual differences in coronary and stroke events reported in ASCOT-BPLA were 14% and 23%, respectively. Yet, in 2005, the ASCOT investigators demonstrated that the adjustment for BP difference only explained about half of the differences in coronary and stroke events. They suggested, that some of the benefits of the amlodipine/Coversyl regimen might relate to differences in other variables on blood pressure, such as blood pressure variability or central blood pressure, or to other treatment benefits not related to blood pressure. This hypothesis has been recently confirmed by additional results of ASCOT-BPLA sub-studies, detailed here below.

◆ The EUROPA study
The clinical synergy of Coversyl and a CCB in the prevention of cardiac events and mortality in CAD patients was investigated to determine the effects of addition of Coversyl to long-term continuous treatment with a CCB on cardiac outcomes in the stable CAD population of the European trial on Reduction Of cardiac events With Perindopril in stable coronary Artery disease (EUROPA), and explore the presence of synergy between Coversyl and CCB in secondary prevention. Patients receiving a CCB at every visit during the 4.2-year follow-up were identified and the effect of adding perindopril was analyzed (n=1022 perindopril/CCB versus n=1100 placebo/CCB). Addition of Coversyl to CCB significantly reduced total mortality by 46% (P<0.01 versus placebo+CCB) and the primary end point (a composite of cardiovascular mortality, nonfatal myocardial infarction, and resuscitated cardiac arrest) by 35% (P<0.05 versus placebo+CCB). There were 41%, 54%, and 28% reductions in cardiovascular mortality, hospitalization for heart failure, and myocardial infarction, respectively (Figure 2, page 284). The magnitude of benefits suggests the existence of a clinical synergy between perindopril and CCB. The synergy of Coversyl with CCB was observed independently of baseline BP. It must therefore be related to other “beyond BP” mechanisms, similar to those observed with perindopril in the overall EUROPA population.

It was concluded that the addition of Coversyl to a CCB in patients with stable CAD had a significant additional impact on decreasing the risk of cardiovascular mortality and other cardiovascular complications, suggesting the potential for lifesaving benefits as well for the use of the perindopril/amlodipine fixed-dose combination (Coveram) in hypertensive coronary patients.

Synergy is one of the most widely mentioned properties of combinations of two different drug classes, particularly in the field of hypertension. The additive efficacy of an ACE inhibitor and a CCB in terms of vasorelaxation and BP lowering is well known. One possible mechanism is the potentiation of each drug’s efficacy on reduction of central aortic BP. A preference reduction in central aortic BP was postulated as a...
source of benefit on cardiac outcomes with amlodipine/perindopril vs the β-blocker/thiazide diuretic in ASCOT.7 Other mechanisms exist underlying the pharmacodynamic synergy between Coversyl and CCB, where one component counteracts effects of the other. For example, CCBs stimulate the sympathetic nervous system and, indirectly, the RAS, whereas ACE inhibition with perindopril has the opposite effect. We could also summarize the synergy of perindopril and CCB on atherosclerosis. In this context, the positive impact of perindopril on endothelial function was demonstrated in the EUROPA population,14,15 together with a reduction in the size of early noncalcified plaque.16 A trend has been detected toward reduced progression of atherosclerosis with amlodipine versus placebo in the Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT) trial.17

Synergistic effects also have a positive impact on side effects. ACE inhibitors reduce lower-limb edema associated with use of CCBs. Clinical synergy may also be expected given the combination of the cardioprotective properties of Coversyl with the anti-ischemic and antiangiotal activity of amlodipine.13

Evidence for Coveram in blood pressure lowering: an early clinical criterion of antihypertensive therapy

**Blood pressure–lowering efficacy of Coveram simply assessed by brachial tonometry**

The pronounced antihypertensive efficacy of Coveram was demonstrated in the STRONG study. STRONG, a multicenter observational study, evaluated the efficacy and safety of Coveram at a dose equivalent to that of perindopril arginine/amldipine 5 mg/5 mg in 1250 patients with stage 2 hypertension (newly diagnosed or untreated at baseline, patients uncontrolled on monotherapy, those inadequately managed on another free- or fixed-combination therapy) in a real-world clinical practice setting.18

No additional antihypertensive drugs were permitted throughout the 2-month study period. Coveram decreased BP rapidly and progressively during the study with a significant reduction of mean SBP/DBP from 167.4±15.2/101.4±8.1 mm Hg to 125.4±33.1/78.2±20.3 mm Hg (both P<0.0001 vs baseline), representing a decrease of 25.0% and 22.9% in SBP and diastolic blood pressure (DBP), respectively.16 Overall, 66.1% of patients reached the BP target of ≤140/90 mm Hg (≤130/80 mm Hg in diabetics).18 The combination was well tolerated. During the study, treatment was discontinued by 0.4% of patients because of cough, and by 0.2% because of ankle edema. Treatment-related adverse events not resulting in withdrawal were mild cough (1.1%), ankle edema (0.5%), headache with dizziness (0.3%), and nausea (0.2%).18 A longitudinal Study of optimiZed Blood pressure lowering therapy with fixed combination perindopril/amlodipine (the SYMBIO study) evaluated efficacy of Coveram in 2132 patients (age 60.8±11.9 years, 49% female, BMI 29.7±5.1) with treated but uncontrolled hypertension (ie, SBP/DBP ≥140/90 mm Hg or ≥130/80 mm Hg in the presence of high cardiovascular risk) from 223 healthcare centers. At study inclusion, patients receiving an angiotensin-converting enzyme inhibitor (77% of patients) and/or CCBs (59%), either as individual drugs or in combination, were switched to treatment with Coveram (5/5 mg, 5/10 mg, 10/5 mg, or 10/10 mg). Dosages were determined at the discretion of the treating physician and were titrated to optimize management of hypertension. Other antihypertensive treatments remained unchanged.19

At baseline, SBP and DBP values were 158.5±17.5 mm Hg and 93.6±9.8 mm Hg, respectively. Cardiovascular risk factors included dyslipidemia (70% of patients), smoking (24%), and diabetes (23%). Notable medical histories included coronary heart disease (34%), myocardial infarction (8% of patients), left ventricular hypertrophy (34%), and stroke (8%). At month 3, BP had decreased to 132.9±10.6/80.6±6.3 mm Hg (ΔBP = -25.9/-13 mm Hg vs baseline; P<0.00001). Furthermore, 74% of patients achieved recommended target BP levels. According to the grade of hypertension, 84% of patients with previously uncontrolled grade 1 hypertension achieved target BP, and 72% and 52% of those with grade 2 and grade 3 hypertension, respectively. Lower-limb edema was reported in 5.4% of patients.

**Effective BP normalization: the Coveram solution to the contemporary emphasis on SBP**

The rise in SBP is linear throughout life, starting from the age of 30 years, while DBP falls progressively from the age of 50

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**Figure 2. Results of a post hoc subanalysis of the EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) study. Clinical synergy of a therapeutic regimen including Coversyl and calcium channel blocker (CCB) showing greater magnitude of morbidity-mortality benefits vs placebo + CCB.**

years. As more than 75% of people with hypertension are over the age of 50, the burden of disease is mainly due to elevated SBP. Moreover, systolic hypertension is a better predictor of stroke, coronary heart disease, heart failure, as well as all-cause mortality than DBP.20-22

The clinical advantages of achieving high rates of BP treatment goals with Coveram in a broad range of patients, such as those with newly diagnosed, untreated, or uncontrolled hypertension (the STRONG study), are obvious, as well as additional BP reduction and BP control in patients previously unsuccessfully treated with multiple antihypertensive therapies (the SYMBIO study). Of note, the rates of guideline-recommended BP goals (<140/90 mm Hg and <130/80 mm Hg in patients with diabetes) reported with Coveram (66% to 74%) seem to be the most effective, since results published for other combinations often include add-on therapy with a diuretic as a 3rd antihypertensive agent (Table I). 18,19,23-27

**Effective reduction of central aortic blood pressure**

The Conduit Artery Function Evaluation (CAFE) substudy examined the effect of the two treatment strategies on central aortic BP and hemodynamics,31 suggesting that the differential effect of amloidipine/perindopril on central aortic pulse pressure may be a factor in the protective efficacy of the treatment strategy.

The CAFE study recruited 2199 patients in 5 ASCOT centers. Most patients received combination therapy throughout the study. Radial artery applanation tonometry and pulse wave analysis were used to determine central aortic blood pressure and hemodynamic indices in repeated clinic visits for up to 4 years. Despite similar brachial SBPs between treatment groups (-0.7 mm Hg; \(P=0.2\)), there were substantial reductions in central BP with the amlodipine-Coversyl regimen (central aortic SBP, –4.3 mm Hg; \(P=0.0001\); central aortic pulse pressure, –3.0 mm Hg; \(P=0.0001\)) (Figure 3, page 286).

Additionally, it was observed that central pulse pressure was significantly associated with total cardiovascular events/procedures and development of renal impairment in the CAFE cohort (unadjusted \(P=0.0001\); adjusted for baseline variables, \(P=0.05\)), suggesting that a differential effect of amloidipine/perindopril on central aortic pulse pressure may be a factor in the protective efficacy of the treatment strategy. The investigators concluded that differences in central aortic pressures might be a potential mechanism to explain the different clinical outcomes between the 2 BP treatment arms in ASCOT.

<table>
<thead>
<tr>
<th>Agent(s) and dosages (mg)</th>
<th>Study</th>
<th>Patients (n); Type; Study duration (wk)</th>
<th>HCTZ (%)</th>
<th>BP at inclusion (mm Hg)</th>
<th>BP at end of study (mm Hg)</th>
<th>Patients achieving BP goals (%) &lt;140/90 mm Hg</th>
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<tr>
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<td>-16/10</td>
<td>44</td>
</tr>
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</table>

*Study dosage was perindopril arginine 5 mg/amlodipine 5 mg.

**Study acronyms:** see selected abbreviations and acronyms box (page 282).

**Abbreviations:** Aml, amloidipine; BP, blood pressure; Fel, felodipine; HCTZ, hydrochlorothiazide; Olim, olmesartan; Val, valsartan.

Table I. Clinical evidence of superior blood pressure–lowering efficacy and achievement of blood pressure goals with Coveram.

**Antihypertensive efficacy beyond brachial BP lowering: evidence for Coveram**

A large body of clinical evidence suggests that central blood pressure (ie, the pressure exerted at the level of the heart, brain, and kidneys) provides additional information regarding cardiovascular risk beyond that provided by peripheral blood pressure.28 Central aortic BP more accurately reflects the contribution of stiffness of the conduit arteries and peripheral resistance to pulse wave morphology and central hemodynamics.28,30
Effective reduction in central carotid blood pressure

Central carotid blood pressure provides information about the arterial pressure in the cerebral arteries. A recent substudy of the ASCOT trial investigated whether directly measured carotid SBP differed between subjects randomized to amiodipine/Coversyl or atenolol/bendroflumethiazide therapies and whether this is accounted for by differences in wave reflection patterns. Between-treatment differences in the left ventricular mass index were also evaluated. Blood pressure was measured in the right carotid artery of 259 patients. Wave intensity analysis was used to separate and quantify forward and backward waves. All of the measurements were performed between 12 and 18 months after randomization, when study drugs had been fully uptitrated and combined and the brachial BP target had been achieved and was stable.

Carotid SBP was significantly lower in subjects randomized to amiodipine/perindopril (127 vs 133 mm Hg; \(P=0.001\)) compared with atenolol/bendroflumethiazide, despite there being no significant difference in brachial BP. This difference is attributable to a lesser magnitude of wave reflection in patients randomized to the amiodipine/Coversyl regimen. The ratio of backward/forward pressure (0.48 versus 0.53; \(P=0.01\)), and wave reflection index (19.8% versus 23.3%; \(P=0.02\)) were significantly lower in patients randomized to amiodipine/perindopril. Similarly, the left ventricular mass index was lower in this group (Figure 4). This study demonstrated that directly measured carotid SBP is lower with an amiodipine/perindopril strategy and determined that the differences in central SBP were attributable to a difference in the magnitude of wave reflection, rather than difference in heart rate. The mechanism underlying a better central carotid BP decrease, as suggested by the investigators, is related to the better decrease in peripheral resistance (vasodilatation and antiremodeling effects) with amiodipine/perindopril than with atenolol/bendroflumethiazide.

24-hour blood pressure control and reduction in nighttime hypertension

The importance of effective 24-h BP management has been established since ambulatory blood pressure monitoring (ABPM) demonstrated that blood pressure behavior over 24 hours is individual to each patient. Nighttime ambulatory BP is known to be superior to daytime ambulatory blood pressure as a predictor of cardiovascular outcomes or stroke.
tory blood pressure monitoring (Figure 5), which demonstrated early and effective reduction in nocturnal BP, was observed across all the study follow-up with a mean difference of 2.2 mm Hg in nighttime SBP in favor of the amlodipine/Coversyl regimen. Nighttime DBP was preserved, which is important in light of renewed interest in the J-curve phenomenon for DBP. In summary, the study showed that amlodipine/perindopril and atenolol/thiazide regimens had different effects on daytime and nighttime ambulatory blood pressure, which may have contributed to the lower rates of events in patients treated with amlodipine/Coversyl.

**Reduction in blood pressure variability**

In healthy individuals, physiological adaptation to physical or emotional stimulus results in changes in blood pressure. However, in hypertensive patients the variability (fluctuation with time) of BP values is associated with a higher risk of stroke and cardiovascular events. The recent ASCOT-BPLA sub-study has evaluated the prognostic value of BP variability. It also examined whether the effects of the BP variability of amlodipine/Coversyl versus β-blocker/thiazide could explain the difference in outcomes. SBP variability was measured by three methods:

- **Within-visit variability:** difference in clinic BP values from 3 consecutive BP measurements during the same visit.
- **Visit-to-visit BP variability:** difference in clinic BP values between visits.
- **Intra-ABPM variability:** difference in BP values over a 24-hour period.

**Results**

1. Variability in SBP was found to be a strong predictor of stroke and coronary events in hypertensive patients.
2. BP variability is thought to be linked to arterial stiffness, changes in peripheral vascular resistance, and structural remodeling of arteries.

**Figure 5. Results of the Anglo-Scandinavian Cardiac Outcomes Trial Ambulatory Blood Pressure substudy.**

Findings show the decrease in nocturnal systolic blood pressure with the amlodipine/perindopril regimen.

**Figure 6. Results of the Anglo-Scandinavian Cardiac Outcomes Trial blood pressure variability substudy.**

Results show the greater extent of reduction in blood pressure variability with amlodipine/perindopril vs β-blocker and thiazide.

**Redeeming and improving hypertension management in clinical practice: the added value of Coveram**

Solid clinical evidence suggests that Coveram provides an elegant therapeutic option, tailored to improve the management of hypertension and survival among a broad range of patients:

- Real-world clinical studies in over 3300 patients have confirmed that Coveram is able to achieve effective BP decrease and the highest rates of BP treatment goals, whether in patients with newly diagnosed hypertension or those uncontrolled on other medications.

**Coveram: antihypertensive efficacy for lifesaving benefits – Vandzhura**
On top of its marked brachial BP-lowering effect, Coveram is the only evidence-based combination to improve all components of antihypertensive efficacy (central and nighttime BP and BP variability), leading to consistent reduction in mortality and morbidity, as demonstrated by the ASCOT-BPLA trial:

- An effective reduction in central aortic blood pressure with Coveram is clinically significant for patients at high cardiovascular risk, and especially at coronary risk.31
- Evidence of central carotid BP reduction with Coveram is important for patients at risk of cerebrovascular events,35
- Effective 24-hour BP control and nighttime hypertension normalization is of added value not only for patients with nocturnal hypertension, but for hypertensives, such as those participating in the ASCOT trial.35
- More stable BP values and fewer incidents of BP “jumps” were seen with amlodipine/perindopril in the ASCOT study. BP variability reduction leads to a lower risk of developing stroke or coronary events in patients with arterial hypertension.35

The evidence for morbidity and mortality risk reduction with Coveram in a broad range of hypertensive patients still free from CAD is provided by the ASCOT-BPLA trial.1 Furthermore, this combination is beneficial in hypertensive coronary patients, as confirmed by the EUROPA trial, with a markedly greater decrease in the risk of cardiovascular mortality and other cardiovascular complications in patients treated with Coversyl together with a CCB.6 Although combinations of RAS- inhibitor/CCB are recommended, one must acknowledge that the level of evidence-based findings differ in terms of real lifesaving benefits. As highlighted by the Reappraisal of European Guidelines on Hypertension, data on morbidity-mortality are lacking for all ARB/CCB combinations.2 Furthermore, clinical evidence suggests that lifesaving benefits for ACE inhibitor/CCB combinations are not class-dependent, but rather drug-dependent, benefits. As demonstrated in the INternational VErapamil trandolapril StuDY (INVEST), a trandolapril/verapamil combination was not different from an atenolol/diuretic combination in terms of mortality reduction in hypertensive patients with CAD.36 In the Avoiding Cardiovascular events through COMBination therapy in Patients Livings with Systolic Hypertension (ACCOMPLISH) trial, more effective reduction in MI did not translate either into reduction of all-cause mortality nor into significant reduction of cardiovascular mortality among patients treated with benazepril/amlodipine compared to those receiving benazepril/hydrochlorothiazide (Table II).30

Coveram is the only treatment among ACE inhibitor/CCB and ARB/CCB combinations that has demonstrated the achievement of the primary objective of antihypertensive therapy, that is, overall reduction of hypertension-related death and morbidity. By effective BP lowering and synergistic action on each criterion of antihypertensive efficacy, Coveram represents a tailored therapeutic option for a broad range of hypertensive patients with their individual profiles of cardiovascular risk.

References
8. Poulter NR, Wieland H, Dahlöf B, et al. Role of blood pressure and other variables in the differential cardiovascular event rates noted in the Anglo-Scandi-

Table II. All-cause mortality and cardiovascular mortality in trials with renin-angiotensin-aldosterone system inhibitor plus calcium channel blocker treatment regimens.

<table>
<thead>
<tr>
<th>Combinations</th>
<th>Trials</th>
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<th>Cardiovascular mortality</th>
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<td>ACE inhibitors/CCB</td>
<td>ASCOT</td>
<td>-11% P=0.02</td>
<td>-24% P=0.001</td>
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<tr>
<td></td>
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<td>NS</td>
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<td>ACCOMPLISH</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>ARB/CCB</td>
<td>No</td>
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<td>No</td>
</tr>
</tbody>
</table>

Acronyms: see selected abbreviations and acronyms box (page 282).

Le traitement antihypertenseur a pour vocation de réduire le risque de morbidité et de mortalité liées à l’hypertension. La réévaluation des recommandations européennes sur l’hypertension a souligné l’importance de la diminution de la pression artérielle (PA) en soi et mis l’accent sur le fait que la pression systolique, le profil de PA en soi et mis l’accent sur le fait que la pression systolique, le profil de PA sur 24 h et la PA centrale sont des facteurs prédictifs forts des événements cardio-vasculaires. Les directives recommandent désormais une prise en charge personnalisée de l’hypertension, adaptée aux besoins individuels du patient, et de débuter le traitement avec une association antihypertensive. Les récents résultats de l’étude ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure-Lowering Arm), ont montré que l’association d’un inhibiteur de l’enzyme de conversion de l’angiotensine (IEC) à un antagoniste calcique (AC) est l’une des options thérapeutiques de premier choix. L’étude ASCOT-BPLA a été une avancée essentielle en ce qu’elle a montré que des stratégies antihypertensives peuvent différer les unes des autres quant à leurs résultats cardio-vasculaires, malgré des diminutions de PA brachiale similaires. L’association amiodépine/péridopril s’est ainsi révélée plus efficace que l’association aténolol/bendrofluméthiazide pour prévenir les décès et les événements cardio-vasculaires majeurs grâce à un contrôle plus précis de la PA centrale et de l’hypertension nocturne. À la suite des résultats de l’étude ASCOT, Coveram a été développé comme association fixe de péridopril et d’amiodépine, et bénéficie déjà de résultats solidement étayés (« médecine fondée sur les preuves » / evidence-based medicine [EBM]). Coveram permet une réduction rapide et efficace de la PA brachiale chez de nombreux patients quel que soit le type d’hypertension en cause et agit en synergie sur chacun et tous les composants de l’efficacité antihypertensive : PA centrale, PA sur 24 h et hypertension nocturne. Coveram, indiqué dans le traitement de l’hypertension et de la maladie coronaire, occupe une place particulière au sein des associations d’IEC et d’AC actuellement disponibles, en diminuant le risque d’événements cardio-vasculaires et de décès.

Keywords: antihypertensive therapy; perindopril/amloïdine fixed combination; arterial hypertension; angiotensin-converting enzyme inhibitor; calcium channel blocker; combination therapy; antihypertensive treatment efficacy; mortality

Coveram: antihypertensive efficacy for lifesaving benefits – Vandzhura
Current guidelines on hypertension management continue to emphasize the importance of hypertension awareness. More effort should be placed on increasing patient education and the willingness of patients to cooperate with physical examinations in order to improve treatment efficacy. Published meta-analyses suggest that improved patient education will bring about a reduction in systolic blood pressure of up to 11 mm Hg; such a reduction in 10 million hypertensives would prevent about 150 000 cardiovascular events over 5 years. Health services struggling to contend with aging populations and rising morbidity need to reduce the toll of cardiovascular disease. This article examines a novel and cost-effective approach to educating patients about hypertension and cardiovascular disease, in which key opinion leaders have collaborated with professional documentary makers. They have produced a viewer-friendly resource modeled on TV documentaries and dramas, which health professionals can give to their patients on DVD to watch at home. In effect, this will be an extension of the traditional consultation, enhancing its messages as well as saving clinicians’ time. A clinical audit has shown that because the DVD has been physically handed to them by a trusted professional, uptake is nearly 100%. As a result, over three quarters of patients improve their lifestyle. This level of engagement is greatly superior to that of the more “fashionable” Internet-based resources. Cardiovascular disease is the world’s biggest killer, accounting for 41% of deaths in the USA, and hypertension is a major cause. Yet even in the UK where primary care is relatively well organized, only 22% of hypertensives are controlled to target. The author and his collaborators have targeted their DVD directly at patients, with the aim of better equipping them to act as partners in their own care.

Medicographia. 2010;32:290-293 (see French abstract on page 293)

As a practicing GP treating hypertensive patients every day, would you say that you and your patients are on the “same side of the barricade” in the fight against high blood pressure?

There is certainly a lot of work to do to persuade patients that the investment of time and effort in lifestyle change and the perceived drawbacks of medication are worth it in the long run. Our job as health professionals is to raise people’s awareness of their future health so that it becomes a daily consideration on a par with other long-term goals, such as financial wellbeing, career, family commitments, and so on.
If we do succeed in persuading them, then the majority will work with us and reduce their risk, but it involves a lot of input. If we only use traditional consulting techniques, we will usually not have sufficient time.

**In your opinion, why do some patients who are motorists readily heed traffic lights yet fail to consider elevated BP as a “red light”**?

High blood pressure (BP) is usually asymptomatic and the hazards are perceived as lying some years in the future, so the danger is not as clear and immediate as more quotidian hazards, such as driving. A driver approaching a red traffic light pays close attention and believes (sometimes wrongly) that he is in control of the outcome. Patients with high BP, on the other hand, sometimes fail to appreciate the extent to which they can take control and reduce their risk of cardiovascular disease either by sustainable lifestyle change or by closer collaboration with their clinician. There is a tendency to regard BP as a matter for their doctor to deal with.

Our task as health professionals is to gradually raise people’s awareness not only of the risk, but also of the fact that it can be significantly reduced if people become personally involved in their own care. Individuals quite often have a superficial understanding of the issues. For example, they have heard on the radio that “salt is bad,” but they lack a deeper understanding of the science behind it all to either appreciate the extent to which it applies to them or to recognize what practical steps they can take. Part of a primary care clinician’s work is to fill these gaps in patients’ knowledge; I believe that modern media technology will enable us to do that much more effectively if the right resources can be devised and deployed.

**What could be done or are you doing already to encourage patients to take an active part in the management of their hypertension?**

As professionals we need to establish a relationship of trust if we are to persuade patients to focus on their long-term health. That trust will be reinforced by sharing as much of our knowledge as possible.

For any of us to actually alter our diet, go to a gym, or take a tablet every day amounts to a substantial investment. No one will do that unless they are confident that they understand all the facts; and so the key to success is to help people to have as deep an understanding of their condition as possible. If we succeed, they will take their problem seriously without being too frightened to think about it and will realize that better outcomes are possible at minimal cost. Furthermore, we will enable them to make correct decisions on a daily basis.

Traditional consultation is still the cornerstone, but the issues are so complex that they cannot be covered, let alone absorbed, in the 10 to 20 minutes available in primary care. In collaboration with Professor Neil Poulter and Professor Peter Sever of Imperial College London, I have made a DVD for patients that employs a full range of documentary techniques to take the patient through explanations of high BP, its treatment, and its causes and of cardiovascular disease prevention. The principal advantages over Web-based resources are that it is given by a known and trusted health professional as an extension of a consultation and that it can be watched in comfort and in company. The aim of the DVD is to help patients deepen their understanding of their condition so that they can work more effectively with us as partners in their own care. We have completed an independent clinical audit of the DVD in UK general practices that shows that 95% percent of patients watch it after their doctor or nurse has asked them to. All of them said they would recommend the DVD to others. Eighty-one percent reported a change in lifestyle, and we were delighted to find that about a third of the smokers in the group had actually quit after 6 weeks.

The audit supports our own perception that in-depth education in this format really does work, and of course it is very cost-effective when compared to labor-intensive counseling.

**How would you evaluate the impact of lifestyle adaptation in hypertension management?**

Here are several meta-analyses which help us here. In 2003, Boulware et al conducted a meta-analysis of studies comparing patient counseling to ordinary care. Pooled data from 15 studies showed that counseling led to an additional systolic blood pressure (SBP) reduction of 11.1 mm Hg. In 2003, Roumie et al conducted a study in the USA on 1341 patients that evaluated the effect of adding targeted patient education (a letter plus the offer of counseling) to the care package. Patient education resulted in an additional SBP reduction of 8 mm Hg. It seems that if a special (and costly) effort is made, then a reduction of about 10 mm Hg can be achieved. Our intention in making the DVD was to offer first-class patient education and advice at a very low cost.

**Can you tell us how you structured the DVD?**

We realized that the DVD had to cater for the whole population and cover a wide range of knowledge and interests. We deployed the filmmaker’s art not only to save the clinician time, but to convey a depth of understanding that face-to-face consultation simply cannot do.

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**Selected Abbreviations and Acronyms**

- ACE: Angiotensin-Converting Enzyme
- BP: Blood Pressure
- SBP: Systolic Blood Pressure
The first item on the menu is a light-hearted 15-minute drama with a celebrity actor, which covers the key messages in a way that holds the attention of almost everybody. Our “hero” is an unreformed gourmand. We meet him guzzling pork pies (Figure 1) and mocking his more careful neighbor over the garden fence. As the story progresses, he is found to have high BP and has to come to terms with it, accepting treatment and finding the process much easier than he expected. There is a twist to the story; the reason his neighbor turns out to be taking such good care of his diet and lifestyle is because he has a strong family history of heart disease. His problems could have been avoided had he known more and had modern screening and treatments.

Next on the list is a 70-minute documentary, broken into 3 manageable sections of 20 to 25 minutes. These cover the nature and causes of high BP, the other causes of cardiovascular disease (including dyslipidemia, smoking, and type 2 diabetes), the concept of cardiovascular risk, and finally treatment with lifestyle change and medication. In this last section, we talk the audience through a standard approach to a newly diagnosed hypertensive patient, basing treatment on overall cardiovascular risk, employing lifestyle change first and then medication. Animation shows the mode of action of the major drug groups, including angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, diuretics, aspirin, and statins. Our documentary makers were keen to avoid the commonly used format of doctors in white coats “lecturing” patients on what to do. They worked with us to craft a story, using animation, footage from all over the world, patient interviews, and extracts from discussions with the experts to take the viewer on a tour of the subject.

After the documentary is a 15-minute section that covers the particular needs of different ethnic groups and the elderly. Some patients like to know as much as their doctor, or more, and so we finish up with a 30-minute seminar in which we discuss the management guidelines that have been produced by the UK, the USA, Europe, and the World Health Organization. We also cover practical topics, such as home monitoring, when to refer, hypertension in pregnancy, and treatment of resistant hypertension. We have found that this last section, which we call “the doctor’s cut,” is particularly useful for primary care health professionals and can be used as a teaching aid in its own right.

**The role of home BP monitoring is currently being widely discussed. What is your opinion of this type of monitoring?**

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**Figure 1. Depiction of the increase in 10-year risk of heart attack in the United Kingdom as total cholesterol level increases.**

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![Proportion of population vs. total cholesterol level and 10-year risk](image)

- **8+ mmol/L:** Very high risk
- **7 - 8 mmol/L:** High risk
- **6 - 7 mmol/L:** Moderate risk
- **5 - 6 mmol/L:** Low risk
- **4 - 5 mmol/L:** Very low risk
- **3 - 4 mmol/L:** Lowest risk

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**It** is very useful provided that the patient uses a properly validated device (the UK charity the Blood Pressure Association advises patients on which devices to use on their Web site: [www.BPassoc.org](http://www.BPassoc.org)) and that their technique is checked. Taking the readings keeps the patient focused on their management and provides the doctor or nurse with valuable corroborative data. One should take into account the fact that home systolic readings are on average 12 mm Hg less than those obtained in clinic (diastolic readings are 6 mm Hg less).

**Most patients find it very hard to come to terms with the fact that treatment is lifelong and won’t make their hypertension disappear after a few months. What could improve patient adherence to treatment?**

**First and foremost,** we need to foster a good long-term rapport between the patient and their primary care health professional, where management and counseling are tailored to the patient’s individual concerns. Helping them understand the science is a key step in the process of alleviating any misconceptions and motivating the patient to make lifestyle changes. Patients usually take a few weeks to come to terms with the idea of medication, so unless the risk is very high it pays to focus on explanation and lifestyle change initially. Using drugs or drug combinations that minimize side effects is a great help. For example, we know that calcium channel blockers are less likely to cause ankle swelling if administered along with drugs that inhibit the renin-angiotensin system (ACE inhibitors or angiotensin receptor blockers).

**How do you see the role of the medical community and society in general in the fight against hypertension?**

**Health professionals** remain very much at the centre of efforts to focus government policy. We know that collective action, such as a smoking ban, can assist individuals in making lifestyle changes.
The cost effectiveness argument for large-scale, inexpensive public health education about cardiovascular disease is overwhelming. The studies quoted above show that additional patient counseling reduces SBP by 10 mm Hg, and our audit showed a similar effect to that of our DVD. Professor Neil Poulter of Imperial College London estimates that if you achieved that reduction in 10 million hypertensive patients, you would prevent about 150,000 heart attacks and strokes over 5 years. If public health organizations could do it with something as cheap as a DVD for, say, 30 pence per patient, in huge numbers, then they would prevent one event for each £20 spent; that is very attractive when you consider what a stroke costs to treat. Government public health departments work on the basis that £20,000 per event prevented is good value.

Aside from education, various lobbies, including the UK’s Blood Pressure Association and the Scottish High Blood Pressure Foundation, are trying to persuade governments to extend collective action to achieve a reduction in the salt content of processed food (Figure 2). The more support they receive from health professionals and other patient groups, the more likely they are to succeed.

References

Keywords: patient education; treatment compliance; hypertension; DVD; television documentary
Elevated blood pressure is an important cardiovascular risk factor. Achieving control of systolic blood pressure together with further reduction in cardiovascular morbidity and mortality are the current challenges for modern antihypertensive strategies. Hypertension frequently resists control with monotherapy, necessitating combination therapy with two or more antihypertensive agents. Many currently available antihypertensive fixed-dose combinations combine drugs with different, but complementary, mechanisms of action to improve overall efficacy and tolerability. Antihypertensive fixed-dose combinations may provide significant advantages over high-dose monotherapy, such as improved blood pressure-lowering efficacy, reduced adverse event frequency, improved patient compliance, potentially lower treatment costs, and shorter time to blood pressure control. We have reviewed the latest evidence demonstrating the need for better blood pressure control. In addition, results from studies with different combinations strategies are outlined. In specific situations, such as in patients at high risk of experiencing coronary ischemic events, an angiotensin-converting enzyme inhibitor/calcium channel blocker combination has demonstrated beneficial effects on hard end points, reducing cardiovascular morbidity and mortality and inhibiting the development and progression of type 2 diabetes mellitus and the progression of renal disease.
with age. Drugs that have proven to be particularly useful in the treatment of elevated SBP are calcium channel blockers (CCBs), thiazides, and agents that target the renin-angiotensin system (RAS), ie, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), because these agents improve the large artery stiffness and early wave reflection that are major characteristics of this condition.

In spite of the growing recognition that adequate control of SBP is fundamental to reducing cardiovascular risk, a substantial proportion of patients still fail to achieve the target levels defined by current guidelines. For example, data from NHANES (National Health And Nutrition Examination Survey) III show that SBP was controlled to <140 mm Hg in only 34% of hypertensive patients (treated or untreated). In contrast, 73% of patients achieved DBP control (<90 mm Hg). A similar bias was reported in the HYDRA (Hypertension and Diabetes screening and Awareness) study, which analyzed data from 45,125 primary-care patients in Germany. In this study, elevated SBP levels were tolerated by doctors in 51% of affected patients. In contrast, elevated DBP levels were tolerated in 41% of affected patients. These results are confirmed by the results of Mancia and Grassi (2002), who used data from 10 controlled trials to show that far fewer patients achieve the level of SBP recommended by guidelines than the DBP level recommended. Overall, DBP <90 mm Hg and SBP <140 mm Hg were achieved by approximately 90% and 50% of treated patients, respectively. Control of SBP and DBP was even worse in patients with diabetes.

The EUROASPIRE (EUROpean Action on Secondary and Primary prevention by Intervention to Reduce Events) III survey demonstrated that in patients with overt coronary disease, control of elevated BP is still problematic; more than 60% of patients do not achieve BP goals, despite the fact that antihypertensive drugs are being used increasingly.

**Current challenges for modern antihypertensive strategies**

Current guidelines for the management of hypertension emphasize the need to improve long-term cardiovascular outcomes as well as to increase the proportion of patients achieving target BP. Despite the fact that literature shows that SBP is an extremely important target for BP lowering, many physicians remain focused on achieving the DBP target. Thus, hypertension remains poorly controlled. However, there have been changes in the understanding of the necessary treatment algorithm. It is now well recognized that most patients will require combination therapy, initiated first-line or at least early, to achieve guideline BP targets.

Since there is an inverse relationship between regimen complexity and patient adherence, treatment regimens that involve administration of multiple drugs have consistently been associated with reduced compliance and adherence. Fixed-dose combinations (FDCs) represent an alternative approach to multiple drug therapy that has been shown to improve patient adherence. They also offer the possibility of combining agents with different pharmacological profiles to achieve additive effects with enhanced tolerability. In this regard, the 2009 reappraisal of the European guidelines on hypertension management recommends a more individually tailored approach for the management of hypertension. The approaches of using FDCs either as a first-line treatment or earlier in the treatment of patients with comorbidities that require rapid BP reduction are endorsed by current guidelines.

A number of two-drug fixed combinations are available for clinical use. These include ACE inhibitor/thiazide diuretic, ARB/thiazide diuretic, β-blocker/thiazide diuretic, ACE inhibitor/CCB, ARB/CCB, and β-blocker/CCB combinations. However, the most substantial trial evidence of outcome reduction...
has been obtained for combinations of a thiazide diuretic with an ACE inhibitor, ARB with thiazide, and in recent large-scale trials ACE inhibitor with CCB. As a result, these combinations have been recommended for priority use by the recent reappraisal of the European guidelines on hypertension. This also includes a reappraisal of fixed combinations of ARB with ACE inhibitor or direct renin inhibitor, which offer an alternative to classic pharmacological approaches. This strategy needs a large “proof of concept” trial to determine its efficacy as well as its tolerability in unselected hypertensive patients (Figure 1).

Clinical evidence of morbidity and mortality reduction with different antihypertensive combination strategies based on RAS inhibition

The RAS plays a central physiological role in the regulation of cardiovascular, renal, and adrenal function; overactivity of the RAS is implicated in hypertension and other cardiovascular and renal disease states. Inhibitors of the RAS, including ACE inhibitors and ARBs, have demonstrated efficacy in treating hypertension and preventing or reducing cardiovascular morbidity, such as stroke events. For ACE inhibitors, a reduction in myocardial infarction (MI) has also been proven. Thus RAS inhibitor–based combinations have gained increasing support as an initial treatment in recent years.

The combination of a RAS inhibitor and a diuretic, an effective BP-lowering regimen, protects against hypertension-associated complications, such as cardiovascular events and stroke. This has been partly demonstrated in intervention studies, such as PROGRESS (Perindopril PROtection aGainst REcurrent Stroke Study), where the combination of an ACE inhibitor and a diuretic (perindopril plus indapamide) reduced the risk of stroke, MI, and heart failure in patients with previous β-blockers and diuretics.

### Table I. LIFE: effects on primary and secondary trial end points.

<table>
<thead>
<tr>
<th>End point</th>
<th>Losartan (n=4605)</th>
<th>Atenolol (n=4588)</th>
<th>Adjusted hazard ratio (95% CI)</th>
<th>Unadjusted hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite end point†</td>
<td>n = 508 (11%)</td>
<td>n = 588 (13%)</td>
<td>0.87 (0.77-0.98)</td>
<td>0.85 (0.76-0.96)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>204 (4%)</td>
<td>234 (5%)</td>
<td>0.89 (0.73-1.07)</td>
<td>0.87 (0.72-1.05)</td>
</tr>
<tr>
<td>Stroke</td>
<td>232 (5%)</td>
<td>309 (7%)</td>
<td>0.75 (0.63-0.89)</td>
<td>0.74 (0.63-0.88)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>198 (4%)</td>
<td>188 (4%)</td>
<td>1.07 (0.88-1.31)</td>
<td>1.05 (0.86-1.28)</td>
</tr>
<tr>
<td>Other prespecified end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total mortality</td>
<td>383 (8%)</td>
<td>431 (9%)</td>
<td>0.90 (0.78-1.03)</td>
<td>0.88 (0.77-1.01)</td>
</tr>
<tr>
<td>Admitted to hospital for:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>160 (3%)</td>
<td>141 (3%)</td>
<td>1.16 (0.92-1.45)</td>
<td>1.13 (0.90-1.42)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>153 (3%)</td>
<td>161 (4%)</td>
<td>0.97 (0.78-1.21)</td>
<td>0.95 (0.76-1.18)</td>
</tr>
<tr>
<td>Revascularization</td>
<td>261 (6%)</td>
<td>284 (6%)</td>
<td>0.94 (0.79-1.11)</td>
<td>0.91 (0.77-1.08)</td>
</tr>
<tr>
<td>Resuscitated cardiac arrest</td>
<td>9 (0.2%)</td>
<td>5 (0.1%)</td>
<td>1.91 (0.64-5.72)</td>
<td>1.80 (0.60-5.36)</td>
</tr>
<tr>
<td>New-onset diabetes§</td>
<td>241 (6%)</td>
<td>319 (8%)</td>
<td>0.75 (0.63-0.88)</td>
<td>0.75 (0.63-0.88)</td>
</tr>
</tbody>
</table>

† For degree of left ventricular hypertrophy and Framingham risk score at randomization.

§ In patients without diabetes at randomization (losartan, n=4019; atenolol, n=3979).

ous stroke or transient ischemic attack.26 This was also the case for the LIFE (Losartan Intervention For Endpoint reduction in hypertension) study,27 where an ARB (losartan) in combination with hydrochlorothiazide (HCTZ) reduced stroke, but not MI, other cardiovascular outcomes, or mortality in hypertensive patients with confirmed left ventricular hypertrophy (LVH) (Table I).

In ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation),28 the significantly greater antihypertensive effect of perindopril/indapamide given in addition to current therapy in patients with diabetes and hypertension was associated with improvement in morbidity and mortality compared with standard therapy, which included RAS inhibitors, alone. Perindopril/indapamide reduced cardiovascular mortality by 18%, all-cause mortality by 14%, and new microalbuminuria by 21% (Figure 2).29 HYVET (Hypertension in the Very Elderly Trial) provided the first definite demonstration of the benefits of effective BP reduction and reduction in cardiovascular outcomes with indapamide (in combination with perindopril in the majority of patients) in very elderly hypertensive patients.30 The trial demonstrated that even in patients 80 years of age or older, antihypertensive treatment not only prevents cardiovascular events, but contributes to prolonging life.16

The administration of a CCB with a RAS inhibitor (ACE inhibitor or ARB) is another rational approach for the management of hypertension that enhances antihypertensive efficacy compared with equivalent monotherapies.31-32 The largest ever cardiovascular events and procedures ($P<0.001$), a 13% reduction in nonfatal MI (excluding silent) and fatal coronary heart disease ($P=0.0458$), and a 30% reduction in new-onset diabetes ($P<0.0001$). The primary end point (all nonfatal MI plus fatal coronary heart disease) was reduced by 10% with perindopril/amlopidine, although the difference did not reach statistical significance due to early termination, as mentioned (Figure 3, page 298).33 Various substudies of ASCOT have provided further information to support the superior efficacy of an amlopidine/perindopril regimen in patients at moderate risk of experiencing cardiovascular events. In the Conduit Artery Function Evaluation (CAFE) substudy, although brachial SBP was comparable between the groups, the amlopidine/perindopril regimen was associated with substantial reductions in central aortic pressures compared with the atenolol/HCTZ regimen.34 Central aortic BP reflects the effects of conduit artery stiffness on

### Table I

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Number (%) of patients with event</th>
<th>Perindopril/indapamide (n=5569)</th>
<th>Placebo (n=5571)</th>
<th>Hazard ratio</th>
<th>Relative risk reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined macro + micro</td>
<td>861 (15.5)</td>
<td>393 (16.8)</td>
<td>938</td>
<td>9% (0 to 17)</td>
<td></td>
</tr>
<tr>
<td>Macrovascular events</td>
<td>480 (8.6)</td>
<td>520 (9.3)</td>
<td>478</td>
<td>8% (-4 to 19)</td>
<td></td>
</tr>
<tr>
<td>Microvascular events</td>
<td>439 (7.9)</td>
<td>477 (8.6)</td>
<td>439</td>
<td>9% (-4 to 20)</td>
<td></td>
</tr>
<tr>
<td>All deaths</td>
<td>408 (7.3)</td>
<td>471 (8.5)</td>
<td>378</td>
<td>14% (2 to 25)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>211 (3.8)</td>
<td>257 (4.6)</td>
<td>205</td>
<td>18% (2 to 32)</td>
<td></td>
</tr>
<tr>
<td>Noncardiovascular death</td>
<td>197 (3.5)</td>
<td>212 (3.8)</td>
<td>191</td>
<td>8% (-12 to 24)</td>
<td></td>
</tr>
<tr>
<td>Total coronary events</td>
<td>468 (8.4)</td>
<td>535 (9.6)</td>
<td>478</td>
<td>14% (2 to 24)</td>
<td></td>
</tr>
<tr>
<td>Total cerebrovascular events</td>
<td>286 (5.1)</td>
<td>303 (5.4)</td>
<td>273</td>
<td>6% (-10 to 20)</td>
<td></td>
</tr>
<tr>
<td>Total renal events</td>
<td>1243 (22.3)</td>
<td>1500 (26.9)</td>
<td>1207</td>
<td>21% (15 to 27)</td>
<td></td>
</tr>
<tr>
<td>New or worsening nephropathy</td>
<td>181 (3.3)</td>
<td>216 (3.9)</td>
<td>181</td>
<td>18% (-1 to 132)</td>
<td></td>
</tr>
<tr>
<td>New microalbuminuria</td>
<td>1094 (19.6)</td>
<td>1317 (23.6)</td>
<td>1004</td>
<td>21% (14 to 27)</td>
<td></td>
</tr>
</tbody>
</table>

Green squares = point estimates (with area proportional to number of events); horizontal lines = 95% CI.

Diamons = point estimate and 95% CI for overall effects.

### Figure 2

**ADVANCE: effects on primary and selected secondary trial end points.**

Effects of study treatment on deaths, coronary events, cerebrovascular events, and renal events:

*Abbreviations: ADVANCE, Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation; CI, confidence interval.*

pulse wave morphology and central hemodynamics more accurately than brachial BP, which suggests that a differential effect of perindopril/amlodipine on central aortic pulse pressure may be a factor in the protective efficacy of the treatment strategy.

A recent substudy of ASCOT also demonstrated that directly measured central carotid SBP is lower (and associated with a lesser magnitude of wave reflection) with an amlodipine/perindopril regimen than with an atenolol-based regimen. This difference was explained by the investigators as being related to the enhanced improvement in arterial structure and decrease in peripheral arterial resistance seen with amlodipine/perindopril. In addition, clinical confirmation of 24-hour BP control with an amlodipine/perindopril regimen, demonstrated by its superior nighttime SBP reduction, was provided by an ambulatory BP measurement substudy of ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure–Lowering Arm) that examined the impact of the two ASCOT treatment regimens on ambulatory BP.

Finally, recent evidence suggests that in ASCOT, the regimen based on amlodipine that added perindopril as required was more beneficial in reducing BP variability than the β-blocker/diuretic regimen. Authors also found a strong correlation between increased SBP variability and the risk of both stroke and cardiovascular events. From a clinical point of view, this new ASCOT substudy draws attention to patients with sporadically elevated BP who, although not considered hypertensive, are already at high risk of CV complications. For these “hypertensives,” it is prognostically important not only to decrease BP to target level, but also to make sure that antihypertensive treatment works throughout the 24-hour postdosing period and that it also reverses structural arterial changes (such as arterial stiffening and remodeling), which are considered to be responsible for excess BP variability.

The results of the ASCOT trial contrast with those of INVEST (INternational VErapamil-trandolapril STudy), in which stepwise treatment strategies based on trandolapril/verapamil SR and β-blocker (atenolol)/diuretic (HCTZ) were evaluated in
22,576 patients with essential hypertension and documented evidence of coronary artery disease. Although 85% of patients in INVEST were treated with antihypertensive medication at baseline, BP was controlled in only approximately 20%. After two years, BP control was similar in each group (71.7% with the trandolapril/verapamil regimen and 70.7% with the atenolol/HCTZ regimen). After a mean follow-up of 2.7 years, similar rates of primary outcome (first occurrence of all-cause death, nonfatal MI, or nonfatal stroke) were observed with both treatment regimens (9.9% vs 10.2%); overall rates from each component were also similar, and there were no between-strategy differences in secondary outcomes of cardiovascular-related death or hospitalization.\(^4\)

The results of INVEST lead to the hypothesis that the ASCOT findings may not be due to a class effect. This idea is particularly plausible for CCBs, since the pharmacological actions of dihydropyridines and verapamil differ substantially.

Recent results from the ACCOMPLISH (Avoiding Cardiovascular events through COMBination therapy in Patients Living with Systolic Hypertension) trial give an insight into the effectiveness of combinations containing CCB relative to those containing HCTZ. The results demonstrate that therapy with a fixed-dose ACE inhibitor/CCB combination (benazepril/amlo
dipine) was superior to standard ACE inhibitor/diuretic (benazepril/HCTZ) therapy in reducing cardiovascular events, despite similar BP lowering.\(^4\), \(^1\)

ACCOMPLISH enrolled 11,506 hypertensive patients with evidence of cardiovascular or renal disease or target organ damage; 60% of patients had diabetes. The primary end point was a composite of fatal and nonfatal events from cardiovascular causes (individual components are presented in Figure 4).\(^4\) At baseline, 97.2% of patients were being treated for hypertension and 74.7% were being treated with two or more antihypertensive agents, but only 37.3% had BP below 140/90 mm Hg. At the end of the study, BP control (<140/90 mm Hg) had been attained in an average of 75.4% of patients in the benazepril/amlo
dipine group and 72.4% in the benazepril/HCTZ group. After a mean follow-up of 36 months, the relative risk reduction in the combined primary outcome of the benazepril/amlo
dipine strategy versus the conventional therapy strategy was 19.6% (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.72 to 0.90; \(P<0.001\)) (Figure 4).\(^4\) However, ACCOMPLISH does not provide evidence of reduced mortality or improvements in the majority of secondary end points.

There is also established evidence of the antihypertensive efficacy of ARBs and their activity in reversing or inhibiting vaso
constriction, myocardial hypertrophy, vascular hypertrophy, and aldosterone secretion.\(^4\) They also reduce proteinuria in patients with renal impairment, as do ACE inhibitors.\(^4\) Compelling indications for their use include heart failure, diabetes, and chronic kidney disease.\(^3\), \(^4\) The combination of ARBs and CCBs provides better BP control with a more favorable toler-

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard ratio (95% CI)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of death from cardiovascular causes and cardiovascular events</td>
<td>0.80 (0.72-0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Component</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>0.80 (0.62-1.03)</td>
<td>0.08</td>
</tr>
<tr>
<td>Myocardial infarction (fatal or nonfatal)</td>
<td>0.78 (0.62-0.99)</td>
<td>0.04</td>
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<tr>
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<tr>
<td>Hospitalization for unstable angina</td>
<td>0.75 (0.50-1.10)</td>
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<tr>
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<td>0.05</td>
</tr>
<tr>
<td>Resuscitation after sudden cardiac arrest</td>
<td>1.75 (0.73-4.17)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

**Figure 4.** Hazard ratios for the primary outcome and individual components in ACCOMPLISH. Only the first event in an individual patient was counted in the analysis of the primary end point. For subsequent analysis of the component end points, one event per category was counted if a patient had events in more than one category.

**Abbreviations:** ACCOMPLISH, Avoiding Cardiovascular events through COMBination therapy in Patients Living with Systolic Hypertension; CI, confidence interval. Modified from reference 41: Jamerson et al. N Engl J Med. 2008;359:2417-2428. © 2008, Massachusetts Medical Society.

Due mainly to the LIFE study\(^27\) and ASCOT trials, guidelines have recently placed less prominence on \(\beta\)-blocker–based therapy\(^7\) in patients without overt coronary heart disease. It is unclear to what extent these findings relate to other FDCs containing diuretic or CCBs; however, it would seem to support the use of FDC therapy containing an ACE inhibitor and

**Table 1.** Composite of death from cardiovascular causes and cardiovascular events

- **Composite of death from cardiovascular causes and cardiovascular events**
  - Hazard ratio: 0.80 (95% CI: 0.72-0.90)
  - \(P\) value: <0.001

- **Death from cardiovascular causes**
  - Hazard ratio: 0.80 (95% CI: 0.62-1.03)
  - \(P\) value: 0.08

- **Myocardial infarction (fatal or nonfatal)**
  - Hazard ratio: 0.78 (95% CI: 0.62-0.99)
  - \(P\) value: 0.04

- **Stroke (fatal or nonfatal)**
  - Hazard ratio: 0.84 (95% CI: 0.65-1.08)
  - \(P\) value: 0.17

- **Hospitalization for unstable angina**
  - Hazard ratio: 0.75 (95% CI: 0.50-1.10)
  - \(P\) value: 0.14

- **Coronary revascularization procedure**
  - Hazard ratio: 0.86 (95% CI: 0.74-1.00)
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- **Resuscitation after sudden cardiac arrest**
  - Hazard ratio: 1.75 (95% CI: 0.73-4.17)
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- **Hospitalization for unstable angina**
  - Hazard ratio: 0.75 (95% CI: 0.50-1.10)
  - \(P\) value: 0.14

- **Coronary revascularization procedure**
  - Hazard ratio: 0.86 (95% CI: 0.74-1.00)
  - \(P\) value: 0.05

- **Resuscitation after sudden cardiac arrest**
  - Hazard ratio: 1.75 (95% CI: 0.73-4.17)
  - \(P\) value: 0.20
a CCB in hypertensive patients at high risk of experiencing coronary ischemic events. Aliskiren, an oral renin inhibitor, represents another approach to the management of hypertension that has recently become available. Aliskiren is available as monotherapy; an FDC with HCTZ or valsartan is also available in some countries. [4] There is no ongoing trial for aliskiren-based combinations versus any other acknowledged standard combination for hypertensive patients. However, recent results of the ALLAY (ALiskiren Left ventricular Assessment of hypertrophY) study in hypertensive patients with LVH show that the effect on LVH reduction of adding aliskiren 300 mg to losartan 100 mg versus losartan 100 mg alone was neutral. Furthermore, BP values obtained with the combination were not lower than those obtained with either component. [4]

Conclusion
Hypertension frequently resists control with monotherapy, necessitating combination therapy with two or more antihypertensive agents. Many currently available antihypertensive FDCs combine drugs with different, but complementary, mechanisms of action to improve overall efficacy and tolerability. Antihypertensive FDCs may provide significant advantages over high-dose monotherapy, such as improved BP-lowering efficacy, reduced adverse event frequency, improved patient compliance, potentially lower treatment costs, and shorter time to BP control. Combination therapy has been recommended as potential first-line therapy in recent consensus guideline statements, especially for higher-risk patients such as those with stage 2 hypertension. The combination of a renin-angiotensin-aldosterone system–targeting agent, such as an ACE inhibitor or ARB (in the case of ACE inhibitor intolerance), with a diuretic or CCB provides synergy with regard to BP lowering. In specific situations, such as in patients at high risk of experiencing coronary ischemic events, ACE/CCB combinations have demonstrated beneficial effects on hard end points, reducing cardiovascular morbidity and mortality and inhibiting the development and progression of type 2 diabetes mellitus and the progression of renal disease.

References


Keywords: antihypertensive fixed-dose combination; cardiovascular risk factor; BP-lowering efficacy; lower treatment cost

**QUELS SONT LES ARGUMENTS EN FAVEUR DU BÉNÉFICE PRONOSTIQUE DES ASSOCIATIONS FIXES ANTIHYPERTENSIVES ?**

L’élévation de la pression artérielle (PA) est un facteur de risque cardio-vasculaire important. Le défi actuel des stratégies antihypertensives modernes consiste à contrôler la pression artérielle systolique tout en réduisant la morbidité et la mortalité cardio-vasculaires. Les monothérapies ne permettent pas toujours de contrôler l’hypertension, une association de deux antihypertenseurs ou plus s’avérant alors nécessaire. Beaucoup d’associations antihypertensives à dose fixe actuellement disponibles réunissent des produits aux mécanismes d'action différents mais complémentaires pour améliorer l’efficacité et la tolérance globales. Une association antihypertensive à dose fixe permet a priori d'obtenir des avantages supérieurs à ceux d'une monothérapie à forte dose, comme une meilleure efficacité anti-hypertensive, la réduction de la fréquence des événements indésirables, l’amélioration de l’observance, des coûts de traitement éventuellement plus faibles et un raccourcissement du temps d’obtention du contrôle de la PA. Nous avons passé en revue les données les plus récentes qui soulignent la nécessité d’un meilleur contrôle de la PA, et examiné les résultats des études faisant intervenir différentes associations antihypertensives. Dans certaines situations particulières, comme chez les patients à haut risque de développer des événements ischémiques coronaires, l’association d’un inhibiteur de l’enzyme de conversion de l’angiotensine et d’un antagoniste calcique a été bénéfique sur certains objectifs « forts », en réduisant la morbidité et la mortalité cardio-vasculaires et en inhibant le développement et la progression du diabète de type 2 et la progression de la maladie rénale.
Angiotensin-converting enzyme (ACE) inhibitors are among the most commonly used drugs in stable coronary artery disease (CAD), as these agents have been proven effective in reducing the risk of cardiovascular morbidity and mortality. As with other drugs, individual variation in treatment benefit is likely. Such heterogeneity could be used to target ACE inhibitor therapy in those patients most likely to benefit from treatment. However, prior attempts to target ACE inhibitor therapy at the patients most likely to benefit from such prophylactic treatment in secondary prevention based on clinical characteristics or the level of baseline risk have not been satisfactory. A new “tailored-therapy” approach would integrate more patient-specific characteristics, such as genetic information (DNA). Pharmacogenetic research of ACE inhibitors in CAD patients is at a formative stage, and studies are limited. The PERGENE (PERindopril GENEtic association) study is a large pharmacogenetic substudy of the randomized placebo-controlled EUROPA (EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease) trial, which aims to assess the feasibility of pharmacogenetic profiling with the ACE inhibitor perindopril.

We suggest that more comprehensive coverage of genetic variation in multiple renin-angiotensin-aldosterone system (RAAS) genes is needed by using a haplotype approach to study common variations within relevant candidate genes. Combining information from multiple single-nucleotide polymorphisms in the RAAS genes will result in a more comprehensive, in-depth analysis of the RAAS and bradykinin system genes and their relation to angiotensin-converting enzyme inhibitor treatment benefit.”

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme (ACE) inhibitors competitively block the conversion of angiotensin I into angiotensin II. This blockade results in a decrease in circulating and local levels of angiotensin II, thereby inhibiting the main effects of angiotensin II: arteriolar vasoconstriction and water and salt retention. However, ACE inhibitors do not antagonize the AT1 receptor and thus do not inhibit the unfavorable effects of angiotensin II completely. Furthermore, the formation of angiotensin II is restored, at least partially, due to the reactive rise that occurs when renin release is blocked by angiotensin II-induced negative feedback. A second beneficial effect of ACE inhibitors, and a main difference between them and angiotensin receptor antagonists, is the increase in bradykinin levels caused by the decrease in transformation of bradykinin into inactive peptides. The increase in bradykinin levels induced by ACE inhibitors leads to the release of nitric oxide and prostaglandins with vasodilating effects on vessel walls.

The efficacy of ACE inhibitors has been demonstrated by several large clinical trials in patients at high risk of cardiovascular disease, including those with a left ventricular ejection fraction of <40% after myocardial infarction (MI), heart failure (HF), or a
history of cerebrovascular accidents, and in those at a lower risk of cardiovascular events, in particular patients with stable coronary artery disease (CAD) without overt HF.4-10 Nowadays, the use of ACE inhibitors is recommended in guidelines on the management of hypertension, stable CAD, MI, and HF and on the prevention of renal insufficiency progression in diabetes mellitus–related kidney disease.11-13 In particular, ACE inhibitors are recommended as a secondary prevention treatment for the broad group of patients with known CAD.11 This review primarily focuses on patients with stable CAD and the ACE inhibitor perindopril, as studied in EUROPA (EUropean trial On reduction of cardiac events with Perindopril in patients with stable coronary Artery disease).10,14

The EUROPA trial
EUROPA studied the ACE inhibitor perindopril in a population with stable CAD without HF.10 In this trial, 12,218 patients were randomly assigned perindopril 8 mg once daily (n=6110) or matching placebo (n=6108). The primary end point was cardiovascular mortality, MI, or cardiac arrest. The mean age of patients was 60 years, 85% were male, and 92% were taking platelet inhibitors, 62% β-blockers, and 58% statins. During a mean follow-up of 4.2 years, perindopril was associated with a 20% relative reduction in the primary end point, from 9.9% to 8.0%, (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.71 to 0.91; 8% vs 10%) (Figure 1).10 These benefits were consistent in all clinical subgroups across several secondary end points and independent of baseline blood pressure (BP) and use of concomitant medication. Perindopril was safe and well tolerated. To prevent one major cardiovascular event, 50 patients with stable CAD needed to be treated for a period of 4.2 years.10 Several substudies of EUROPA have established that ACE inhibitors exert additional beneficial effects by improving endothelial function and neurohumoral balance and by reducing unfavorable remodeling of the coronary arteries.15-18

<table>
<thead>
<tr>
<th>End Point</th>
<th>Perindopril (n=6110)</th>
<th>Placebo (n=6108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular mortality, MI, cardiac arrest</td>
<td>488 (8.0%)</td>
<td>603 (9.9%)</td>
</tr>
<tr>
<td>Total mortality, MI, UA, cardiac arrest</td>
<td>904 (14.8%)</td>
<td>1043 (17.1%)</td>
</tr>
<tr>
<td>Cardiovascular mortality, MI</td>
<td>484 (7.9%)</td>
<td>596 (19.8%)</td>
</tr>
<tr>
<td>Cardiovascular mortality, MI, UA</td>
<td>753 (12.3%)</td>
<td>885 (14.5%)</td>
</tr>
<tr>
<td>Total mortality</td>
<td>375 (6.11%)</td>
<td>420 (6.9%)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>215 (3.5%)</td>
<td>249 (4.1%)</td>
</tr>
<tr>
<td>MI, fatal and nonfatal</td>
<td>320 (5.2%)</td>
<td>418 (6.8%)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>342 (5.6%)</td>
<td>367 (6.0%)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>6 (0.1%)</td>
<td>11 (0.2%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>98 (1.6%)</td>
<td>102 (1.7%)</td>
</tr>
<tr>
<td>Revascularization</td>
<td>577 (9.94%)</td>
<td>601 (9.8%)</td>
</tr>
<tr>
<td>Heart failure requiring hospital admission</td>
<td>63 (1.0%)</td>
<td>103 (1.7%)</td>
</tr>
</tbody>
</table>

0.5 Favors perindopril 1.0 Favors placebo 2.0 Favors placebo

**Figure 1.**
Treatment benefit of perindopril on primary end point and selected secondary end points in the EUROPA trial.

Size of squares proportional to number of patients in that group. Dashed line indicates overall relative risk.

**Abbreviations:** EUROPA, EUropean trial On reduction Of cardiac events with Perindopril in stable coronary Artery disease; MI, myocardial infarction; UA, unstable angina. Modified from reference 10: Fox and The European Trial on Reduction of Cardiac Events with Perindopril in Patients with Stable Coronary Artery Disease Investigators. Lancet. 2003;362:782-788. © 2003, Elsevier Ltd.

**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>CHD</td>
<td>coronary heart disease</td>
</tr>
<tr>
<td>DBP</td>
<td>diastolic blood pressure</td>
</tr>
<tr>
<td>EUROPA</td>
<td>EUropean trial On reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease</td>
</tr>
<tr>
<td>GENHAT</td>
<td>GENetics of Hypertension-Associated Treatment</td>
</tr>
<tr>
<td>HF</td>
<td>heart failure</td>
</tr>
<tr>
<td>I/D</td>
<td>insertion/deletion</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>PERGENE</td>
<td>PERindopril GENetic association study</td>
</tr>
<tr>
<td>PROGRESS</td>
<td>Perindopril pROtection aGainst REcurrent Stroke Study</td>
</tr>
<tr>
<td>RAAS</td>
<td>renin-angiotensin-aldosterone system</td>
</tr>
<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
</tr>
<tr>
<td>SNP</td>
<td>single-nucleotide polymorphism</td>
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</table>
Prior attempts to direct ACE inhibitor therapy toward those patients most likely to benefit

Several analyses have been performed to test the consistency of the treatment benefit of ACE inhibitors in patient subgroups based on clinical characteristics.\(^{19-23}\) Heterogeneity in the clinical treatment effect of ACE inhibitors could be used to direct ACE inhibitor therapy toward those patients most likely to benefit from such therapy. Tailored ACE inhibitor therapy would improve patient benefits and reduce unnecessary health-care costs and side effects.

Using EUROPA trial data, a risk model based on baseline clinical characteristics was developed.\(^{25}\) The treatment benefit of perindopril was consistent across different risk categories, and therefore not modified by the level of baseline risk (Figure 2).\(^{20}\) Renal insufficiency is an important risk factor for developing cardiovascular disease.\(^{21}\) To study whether patients with normal renal function or impaired renal function experienced different treatment benefit, a subgroup analysis was performed within the EUROPA trial. This analysis showed that treatment benefit was not modified by renal insufficiency.\(^{22}\)

In a recent meta-analysis of the EUROPA, PROGRESS (Perindopril pROtection aGainst REcurrent Stroke Study), and ADVANCE (Action in Diabetics and Vascular disease: 2\(\text{nd}\) PROGress in Reduction of Endpoints in Non-Insulin-dependent Diabetes Mellitus on Vascular Events) trials investigating the same ACE inhibitor perindopril, we demonstrated a consistent treatment effect of ACE inhibitor–based regimens independent of clinical characteristics or baseline BP levels.\(^{23}\) Hence, no heterogeneity of treatment benefit was observed according to clinical characteristics. It did not appear feasible to target ACE inhibitor therapy at stable CAD patients in the specific subgroups most likely to benefit from this type of prolonged prophylactic treatment based on simple clinical characteristics.

Pharmacogenetic approach to individualizing ACE inhibitor therapy

As simple clinical patient characteristics are inadequate for tailoring ACE inhibitor therapy, new approaches that integrate more patient-specific characteristics should be considered, such as pharmacogenetic profiling of drug response. The new field of cardiovascular pharmacogenetics, which is expanding rapidly, involves examining the genetic determinants of patients’ responses to drugs. Pharmacogenetics aims to understand why some drugs work better for some people than others and why some people are more likely than others to experience side effects. Indeed, pharmacogenetic profiling could lead to significant advances in individualized cardiovascular medicine.

A priori, several types of factors are expected to play a role in determining the response of a patient to therapy. Genetic factors causing differences in drug absorption and metabolic clearance are highly relevant; however, this is as yet a relatively unexplored field for ACE inhibitors. Better known are the genetic factors affecting the direct pharmacodynamic pathways that ACE inhibitors act on, the renin-angiotensin-aldosterone system (RAAS) and bradykinin pathways. These are likely to impact the clinical efficacy of ACE inhibitors. In recent years, several genetic polymorphisms in RAAS genes have been associated with high BP levels or increased cardiovascular risk.\(^{3,24,25}\) Nearly all prior studies focused on two polymorphisms, the ACE insertion/deletion (I/D) polymorphism and the M235T polymorphism in the angiotensinogen gene. Because of the limited study sample size and power, results have been inconsistent, and these important topics have not yet been investigated convincingly. With regard to the connection between genetic variation and ACE inhibitor treatment response, results are scarce as clinical data are lacking. No prior research with ACE inhibitors in stable CAD has been performed on a large-scale or in a randomized trial setting.

It has been suggested that the response to drug therapy may be influenced by genetic polymorphisms in different ways. Firstly, pharmacodynamics may be affected by polymorphisms in the genes of all the proteins involved in the RAAS system and related systems, including receptors and signal transduction molecules. Secondly, variations in drug absorption and metabolic clearance may cause interindividual variation in pharmacokinetics. Thirdly, variations within genes of the RAAS system and related systems may influence atherosclerosis (underlying disease process) and inherent differences in the susceptibility to therapeutic agents such as ACE inhibitors.
The concept of using pharmacogenetic research to individualize medicine is emerging rapidly and is clinically highly relevant. Several successes of this approach for different cardiovascular agents have recently been demonstrated, such as the activation of clopidogrel and the risk of rhabdomyolysis associated with statin therapy. Current pharmacogenetic data are often obtained from observational cohort studies or cross-sectional data. Large randomized clinical trials using DNA offer a unique opportunity to study this concept of tailored therapy and to truly test the feasibility of pharmacogenetic profiling of treatment benefit. The objective is to construct a genetic profile that enables doctors to predict the benefit of treatment in a patient in advance. Additionally, pharmacogenetics will teach us more about the individual response mechanism to medications.

**Current literature**

Three studies have performed a pharmacogenetic analysis of ACE inhibitors or of a treatment regimen containing ACE inhibitors. Two of them studied only the ACE I/D polymorphism and found no associations, while one study examined relevant genetic targets within the RAAS and found some interesting results.

The GENetics of Hypertension-Associated Treatment (GEN-HAT) study was the first to assess the concept of pharmacogenetics of antihypertensive drugs. The investigators used a double-blind, active-controlled randomized trial of antihypertensive treatment that included hypertensives >55 years of age with at least 1 risk factor for cardiovascular disease. The ACE I/D genotype was determined in 37,939 participants randomized to chlorthalidone, amlodipine, lisinopril, or doxazosin treatment and followed up for 4 to 8 years. Primary outcomes included fatal coronary heart disease (CHD) and/or nonfatal MI. Fatal and nonfatal CHD occurred in 3096 individuals during follow-up. The hazard rates for fatal and nonfatal CHD were similar across antihypertensive treatments.

The ACE I/D genotype group was not associated with fatal and nonfatal CHD (relative risk of deletion:deletion (DD) versus insertion:deletion (ID) and insertion:insertion (II), 0.99; 95% CI, 0.91 to 1.07). The 6-year hazard rate for fatal and nonfatal CHD in the DD genotype group was not statistically different from the ID and II genotype groups by type of treatment. Therefore, the authors concluded that ACE I/D genotype type was not a predictor of CHD, nor did it modify the response to antihypertensive treatment. The ACE I/D polymorphism is not a useful marker for predicting antihypertensive treatment response. Unfortunately, the authors did not study other relevant candidate genes or multiple genetic polymorphisms within the complex RAAS system.

In PROGRESS, the ACE genotype I/D polymorphism was studied via the effect of a perindopril-based BP-lowering regimen on macrovascular events, dementia, and cognitive decline among hypertensive and nonhypertensive patients with a history of cerebrovascular disease. There were no associations between ACE genotypes and cerebrovascular disease history or cardiovascular risk factors, including baseline BP. ACE genotype was not associated with the long-term risks of stroke, cardiac events, mortality, dementia, or cognitive decline; neither did ACE genotype predict BP reduction associated with the use of the ACE inhibitor perindopril. Similarly, there was no evidence that ACE genotype modified the relative benefits of ACE inhibitor–based therapy versus placebo. ACE genotype is not useful for predicting either the risk of disease or the benefits of perindopril-based BP-lowering treatment.

In the Chinese Community-Based Comprehensive Prevention and Control of Hypertension Project, investigators studied the genetic contribution to variation in BP response to ACE inhibitors. Fourteen single-nucleotide polymorphisms (SNPs) in the angiotensinogen (AGT), angiotensin receptor 1 (AGTR1), and angiotensin receptor 2 (AGTR2) genes were evaluated for their association with BP response to ACE inhibitor in 1447 Chinese patients with hypertension in a 2-stage, 3-year benazepril postmarket survey. The AGT rs7079 (C/T) SNP (3′-untranslated region) was significantly associated with the response of diastolic blood pressure (DBP) to benazepril (DBP response: 7.4 mm Hg for subjects with the CC genotype, 8.9 mm Hg for CA, and 10.1 mm Hg for AA; P<0.001).

Although there was no association of individual SNPs in the AGTR1 gene, there was a graded response between common haplotypes and systolic blood pressure (SBP) reduction. Haplotypes are a combination of alleles at different markers along the same chromosome that are inherited as a unit (linkage disequilibrium pattern). The total variations in response to ACE inhibitor therapy explained by the AGT SNP and AGTR1 haplotype groups were 13% for SBP and 9% to 9.6% for DBP, respectively. These findings will be useful in future studies, providing genetic markers to predict hypertensive response to ACE inhibitor therapy.

An important limitation of prior studies is the investigation of only one or two polymorphisms within one candidate gene, which ignores well-documented feedback mechanisms within the RAAS and also the fact that the two angiotensin II receptors (AT₁ and AT₂) have counteracting effects. Additionally, ACE I/D polymorphism is not a reflection of the entire RAAS. We suggest that more comprehensive coverage of genetic variation in multiple RAAS genes is needed by using a haplotype approach to study common variations within relevant candidate genes. Combining information from multiple SNPs in the RAAS genes will result in a more comprehensive, in-depth analysis of the RAAS and bradykinin system genes and their relation to ACE inhibitor treatment benefit, which is more likely to unravel any existing pharmacogenetic associations.
The PERGENE study: a new substudy of the EUROPA trial

PERGENE (PERindopril GENEtic association study) is a pharmacogenetic substudy of the main EUROPA trial. PERGENE aims to assess the feasibility of pharmacogenetic profiling of the treatment benefit of ACE inhibitors in patients with stable CAD. We hypothesized that genetic polymorphism in the RAAS and kininogen-kallikrein-bradykinin pathways may influence the treatment benefit of ACE inhibitors in patients with stable CAD. Polymorphisms were selected based on haplotype tagging SNPs using the HapMap genome project to comprehensively cover all genetic variation within genes; additional selection was based on functionality, location within the gene (promoter), or relevant literature. The PERGENE study is unique in the field of pharmacogenetic studies because of the large sample size, the randomized placebo-controlled design, and the availability of extensive and accurate phenotypic data. Also, the extensive selection of 52 tagging SNPs in 12 candidate genes in both pathways ensures a new and comprehensive coverage of common genetic variation in candidate genes.

The main outcome measure of PERGENE was the interaction between genetic factors and treatment effect of ACE inhibitors during follow-up. The secondary end points were the relation between genetic determinants and BP and BP reduction and ACE inhibitor therapy. The size of this pharmacogenetic substudy allowed detection with a statistical power of 98% to detect a difference in hazard ratios (treatment effect) of 20% between genotypes with minor allele frequency of 0.20 (two-sided alpha 0.05).

Genetic analysis within PERGENE

The DNA samples collected in the EUROPA study offer a unique opportunity to investigate the relations between polymorphisms in genes of the RAAS with the treatment benefit of an ACE inhibitor on cardiovascular events in a sufficiently large population and in a randomized double-blind setting. As mentioned, the available studies of this subject have to date been of small size and nonrandomized, so reported relationships may have been due to chance findings. Furthermore, the majority of studies so far include only one RAAS polymorphism or one RAAS gene. In contrast, PERGENE uses a haplotype-tagging selection procedure to comprehensively cover all common genetic variations (>90%) in the relevant genes within the RAAS and bradykinin pathways. We will use the latest information from HapMap Genome Project, SEATTLE, and other up-to-date genetic information platforms as well as sophisticated software packages, such as Haplostats, for these haplotype analyses.

The determination of haplotypes is essential for understanding genetic variation and the inheritance of complex diseases. An analysis based on haplotypes is more advantageous than an analysis based on individual SNPs, especially in the presence of multiple susceptibility alleles and when linkage disequilibria between SNPs are weak. With a single SNP approach, associations may be missed when the causal SNP is not in linkage disequilibrium with the single analyzed SNP. It is more informative to simultaneously analyze multiple markers in a region of interest that identifies genetic variants underlying various human traits; also, these markers should be selected based on tagging principles and linkage disequilibrium.

By combining information from multiple SNPs in the RAAS and bradykinin pathway genes, a more efficient, comprehensive, in-depth analysis of common genetic variation in relation to ACE inhibitor therapy is performed, which is more likely to unearth important pharmacogenetic associations.

Feasibility of pharmacogenetic profiling of ACE inhibitors

Highly developed pharmacogenetic profiling could increase the overall efficacy of ACE inhibitors and reduce the number of patients treated without any benefit. The concept of ACE inhibitor pharmacogenetic profiling should be investigated further and replicated in similar patient populations, but also in patients at higher risk of cardiovascular events, as stable CAD patients are at relatively low risk. With regard to PERGENE, further replication must be sought in other large trials. Additionally, other relevant genetic targets need to be investigated, such as the genes involved in the metabolism of ACE inhibitors, ie, cytochrome P450 genes (pharmacokinetics). However, until now no specific genetic targets for ACE inhibitor metabolism have been discovered. Ultimately, one would wish to perform a genomewide scan on the PERGENE data to elucidate further relevant pharmacogenetic targets in the genome related to the treatment benefit of ACE inhibitors.

When the feasibility of pharmacogenetic profiling of ACE inhibitor therapy is confirmed in other studies, pharmacogenetic analyses of clinical trials will truly offer the prospect of individualizing preventive therapy in patients with cardiovascular disease. Physicians will be able to predict response to treatment (responders and nonresponders) in advance, before starting prescription.

A similar approach could be used for other cardiovascular drugs, such as statins, to optimize patient benefits as strong consistency in treatment benefit has been demonstrated as well. Combining these cardiovascular drug trial results could be used to develop a pharmacogenetic profile for cardiovascular drugs in general. We advocate that future large-scale randomized clinical trials integrate pharmacogenetic analysis in their trial design to prospectively test treatment efficacy in a similar way to that usually done with clinical risk factor assessment of trial patients. “Individualized therapy” using pharmacogenetic profiling will avoid unnecessary treatment of nonresponding patients and considerably reduce healthcare costs.
Summary
In the EUROPA trial, 50 patients with stable CAD needed to be treated with perindopril 8 mg/day for a period of 4.2 years to prevent one major cardiovascular event.10 Several attempts have been made to target ACE inhibitor therapy at specific clinical subgroups to give the most treatment benefit. But until now, treatment benefit of ACE inhibitors in stable CAD has been consistent and clinical characteristics cannot be used to target ACE inhibitor therapy. The field of pharmacogenetics could be a new way to test the consistency of the treatment effect of ACE inhibitors. The PERGENE project is unique not only because of its size, randomized design, accurate phenotypic data, and complete coverage of two pathways (RAAS and bradykinin), but also because of the extensive and comprehensive SNP selection procedure involving multiple SNPs in multiple genes of both pathways, integrating information on the haplotype structure of RAAS and bradykinin genes. At present, attempts to target therapy using simple clinical patient characteristics have been unsuccessful at directing ACE inhibition therapy, and it is not yet possible to tell in advance who to treat.19-21

New and improved approaches that integrate more patient-specific characteristics are needed to better target ACE inhibitor therapy. We will investigate whether specific genetic polymorphisms in RAAS genes modify the treatment effect of ACE inhibitor therapy. Our aim is to develop a pharmacogenetic profile associated with the benefit of ACE inhibitor therapy in patients with stable CAD. If it is possible to construct a pharmacogenetic profile related to treatment benefit, this could lead to a significant reduction in the number of patients needed to treat. A pharmacogenetic profile related to the benefit of perindopril may enable the selection of those patients ahead of treatment. Likewise, targeting therapy in only those patients that are likely to benefit will considerably increase the cost-effectiveness of treatment. Cardiovascular pharmacogenetic research is still in a stage of development, but it has the potential to enhance individualized medicine and tailored therapy in cardiovascular medicine.

Executive summary
ACE inhibitors reduce cardiovascular risk in patients with stable CAD
Assessing the consistency of treatment benefit is crucial for efficacy and cost-effective prescription of ACE inhibitors
Treatment benefit of ACE inhibitors is not modified by clinical characteristics. Thus directing ACE inhibitor therapy does not appear feasible using clinical characteristics
The PERGENE study is a pharmacogenetic analysis of the treatment benefit of ACE inhibitors in a large randomized placebo-controlled clinical trial of patients with stable CAD
Discovery of a pharmacogenetic profile will optimize patient treatment benefits and reduce unnecessary treatment of patients and health-care costs.

The PERGENE study is supported by a grant from the Netherlands Heart Foundation (NHS2005B219), Dr Brugts is supported by a grant from the Netherlands Heart Foundation (NHS2005B219) and a grant from the Netherlands Organization for Health Research and Development (ZonMW).

References
Les inhibiteurs de l’enzyme de conversion de l’angiotensine (IEC) sont parmi les médicaments les plus utilisés dans la maladie coronaire (MC) stable, leur efficacité ayant été prouvée pour la réduction du risque de morbidité et de mortalité cardio-vasculaires. Comme pour les autres médicaments, il existe des variations individuelles quant aux bénéfices du traitement. Cette hétérogénéité de réponse pourrait être utilisée pour cibler le traitement par IEC chez les patients les plus susceptibles d’en bénéficier. Cependant, les tentatives antérieures pour cibler de tels traitements en prévention secondaire basées sur des caractéristiques cliniques ou le niveau de risque initial n’ont pas été satisfaisantes. Une nouvelle approche « sur mesure » devrait inclure des caractéristiques plus spécifiques du patient, comme l’information génétique (ADN). La recherche pharmacogénétique sur les IEC chez les patients coronariens en est à un stade de gestation et les études sont limitées. L’étude PERGENE (PERindopril GENetic association study) est une grande sous-étiude pharmacogénétique de l’étude randomisée contrôlée contre placebo EUROPA (European trial on reduction Of cardiac events with perindopril in stable coronary Artery disease), ayant pour but d’évaluer la faisabilité du profilage pharmacogénétique avec l’IEC perindopril.

**Aspects génétiques de l’efficacité du traitement antihypertenseur**

Les inhibiteurs de l’enzyme de conversion de l’angiotensine (IEC) sont parmi les médicaments les plus utilisés dans la maladie coronaire (MC) stable, leur efficacité ayant été prouvée pour la réduction du risque de morbidité et de mortalité cardio-vasculaires. Comme pour les autres médicaments, il existe des variations individuelles quant aux bénéfices du traitement. Cette hétérogénéité de réponse pourrait être utilisée pour cibler le traitement par IEC chez les patients les plus susceptibles d’en bénéficier. Cependant, les tentatives antérieures pour cibler de tels traitements en prévention secondaire basées sur des caractéristiques cliniques ou le niveau de risque initial n’ont pas été satisfaisantes. Une nouvelle approche « sur mesure » devrait inclure des caractéristiques plus spécifiques du patient, comme l’information génétique (ADN). La recherche pharmacogénétique sur les IEC chez les patients coronariens en est à un stade de gestation et les études sont limitées. L’étude PERGENE (PERindopril GENetic association study) est une grande sous-étiude pharmacogénétique de l’étude randomisée contrôlée contre placebo EUROPA (European trial on reduction Of cardiac events with perindopril in stable coronary Artery disease), ayant pour but d’évaluer la faisabilité du profilage pharmacogénétique avec l’IEC perindopril.
**A TOUCH OF FRANCE**

This issue of *Medicographia* is devoted to France’s largest hospital, the Pitié-Salpêtrière. The first article covers the period from the days of Marie de Médicis and Louis XIV to the 19th century and the birth of modern neurology under Charcot and his illustrious followers. The second article jumps to the (very near) future with the inauguration this fall of the ICM, the Brain and Spine Institute, which is destined to become one of the world’s foremost neuroscience institutes.

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**Gunpowder, madness, and hysteria: the birth of neurology in France**

Vignettes of five great neurologists who made history at the Salpêtrière Hospital in Paris: Jean-Martin Charcot (1825-1893), Pierre Marie (1853-1940), Joseph Babinski (1857-1932), Jean Lhermitte (1877-1959), Paul Castaigne (1916-1988)

C. Régnier, France

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“Hysterical yawnings.”
Three photos in a series showing a hysterical woman screaming.
© Wellcome Library, London.

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**French neuroscience in the vanguard: the ICM is taking off**

Y. Agid, France

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3-D representation of the basal ganglia of a patient with Parkinson’s disease: placement of electrodes in the subthalamic nuclei.
© Luc Mallet/Eric Bardinet/Jérôme Youkni/Inserm/ICM.
Gunpowder, madness, and hysteria: the birth of neurology in France

Vignettes of five great neurologists who made history at the Salpêtrière Hospital in Paris: Jean-Martin Charcot (1825-1893), Pierre Marie (1853-1940), Joseph Babinski (1857-1932), Jean Lhermitte (1877-1959), Paul Castaigne (1916-1988)

by C. Régnier, France

T he early history of the Salpêtrière in Paris was turbulent. Now a major teaching hospital beside the River Seine, it was founded by Louis XIV as the Hospice de la Salpêtrière in the mid-17th century, on the site of a gunpowder factory (whence its name—from saltpeter). By the time of the French Revolution, the Salpêtrière had 10,000 inmates—the mentally disabled, criminally insane, epileptics—as well as paupers and hundreds of prostitutes cleared off the streets of Paris. In September 1792 the revolutionary mob stormed the Salpêtrière, ravished hundreds of girls and women, and slit the throats of 35 among them. For the next two years, in the words of one historian, the doors of the hospital remained open as the Salpêtrière became the largest brothel in Europe. Philippe Pinel initiated humanitarian reforms in the treatment of mental illness in the 1800s, literally unchaining the inmates, and by the close of the century the Salpêtrière was famous worldwide as a psychiatric center and Jean-Martin Charcot and his students had laid the foundations of modern neurology. Using all the scientific resources of his time—laboratory analyses, photographs, electrostimulation, drawings, casts, histological sections—Charcot meticulously described the symptoms observed, sought the corresponding anatomical and histological lesions, and analyzed causes and mechanisms. He attracted hordes of students from France and Europe who were to achieve international renown, such as Sigmund Freud, Eugen Bleuler, Alfred Binet, Georges Gilles de la Tourette, and many others. Charcot also blazed the trail for illustrious followers who in his wake established the fame and reputation of French neurology, such as Joseph Babinski, Pierre Marie, Jean Lhermitte, and Paul Castaigne, and of which the present-day Pitié-Salpêtrière is the worthy successor.

Blanche Wittmann, the “queen of hysterics” at the Salpêtrière, has found posthumous fame of a sort through her depiction in a painting by Pierre-André Brouillet. Une Leçon Clinique du Professeur Charcot à la Salpêtrière [A Clinical Lesson at the Salpêtrière Hospital by Professor Charcot] (1887) shows the neurologist Jean-Martin Charcot (1825-1893) at one of his famous Tuesday demonstrations about to apply an electrode to the swooning Blanche. Among those in attendance were future luminaries in neurology—Gilles de la Tourette, Paul Richer, Pierre Marie, Gilbert Ballet, Maurice Debove, Alfred-Joseph Naquet, Désiré-Magloire Bourneville, Joseph Babinski, Henri Parinaud—as well as other notables, including Théodule Ribot (the director of the Revue Philosophique), Jules Claretie (novelist, ...
playwright, and administrator of the Comédie-Française), Paul Arène (poet, writer, and friend of Alphonse Daudet), and Philippe Burty (art critic and inspector of the French National College of Art and Architecture). Brouillet’s painting symbolizes a certain supremacy of French neurology and was reproduced in a Scientific American supplement in 1887 in the form of an engraving, together with the names of all those present.1-5

The Hospice de la Salpêtrière, the temple of neurology

The emergence of neurology at the Salpêtrière was part of a long history in which Charcot and his students were at one and the same time pioneers and heirs. In 1862, when Charcot started work there, this immense 32-hectare hospital housed some 5000 women suffering from a whole range of ills, which offered vast scope for anatomical and clinical observation in all medical specialties, notably neurology. Yet the staff at the Salpêtrière were hardly numerous: seven doctors, one surgeon, eight interns, fourteen externs, and a pharmacist and his eight interns. From 1804 to 1861, the annual mortality rate was 17.51%, slightly below the average for the public hospitals of Paris.6,7

Between 1823 and 1860, the Salpêtrière was called the Hospice de la Vieillesse-Femmes, a name that masked its psychiatric vocation: it was both an asylum for the insane and a hospice for women young and old deemed “incurable.” While the asylum had acquired a certain prestige since Philippe Pinel’s early 19th-century invention of “moral treatment,” the hospice had been neglected. The women of the Salpêtrière were divided into four large sections: former staff members, women in their seventies, those in their eighties, and those treated in the infirmary (400 beds). Each woman was allowed and had a straw mattress, but the regulations were still very strict.6,8,9,10

In 1852-1853, Charcot completed his internship at the Salpêtrière, after which he compared the hospital to a living museum of pathology with considerable resources, adding that he was determined to return and to stay, unlike many of his contemporaries who moved on to more prestigious institutions.7,11

View of Salpêtrière Hospital, with the River Seine in the foreground. Lithography by Perelle; 1680. © Leonard de Selva/CORBIS.

Entrance to the 17th- and 18th-century buildings of the Salpêtrière hospital, with dome of the Saint-Louis church. © Vaughan.
Jean-Martin Charcot (1825-1893)

Charcot and neurology: a prepared mind

Charcot’s arrival at the Salpêtrière coincided with the emergence of neurology as a medical specialty. “Neurology” was coined in 1664 by the great English neuroanatomist Thomas Willis. The first work exclusively devoted to neurology was the three-volume *A Manual of the Nervous Diseases of Man* published in Berlin between 1840 and 1846 by Moritz Heinrich Romberg. Charcot was an acute observer of clinical signs and excelled in performing autopsies. His methodology was based solely on observation of facts. He didn’t hypothesize and was little interested in experimentation.\(^7,\)\(^12\)

While still an intern and a member of the Biology Society, Charcot studied a 20-year-old epileptic woman with partial atrophy of the left hemisphere. He later attributed the patient’s clinical manifestations with the brain lesions he had observed when conducting an autopsy. This type of so-called localizationist observation was quite common in the mid-19th century. Charcot considered the brain an assembly of regions—modules of sorts—that functioned autonomously. Each zone controlled a very precise nervous function. He started by studying motor cortex areas and used his findings to hypothesize on aphasia, poliomyelitis, and cerebral hemorrhages. Charcot soon admitted that the localizationist theory was too restrictive to explain certain cognitive phenomena, notably hysteria.\(^3,\)\(^13,\)\(^14\)

After joining the Salpêtrière in 1862, Charcot worked with his friend the anatomist and physiologist Alfred Vulpian (1826-1887). Vulpian ran a small department of general medicine at the Salpêtrière and helped Charcot perfect his techniques of microscopy and the preparation and staining of cells, which were essential for deepening histological understanding of nerves and brain structures. The two men had various affinities, as Vulpian recalled in his oration at Charcot’s funeral in 1887: “We were soon brought together by a perfect sharing of feelings, ideas, leanings, and even existential difficulties; and this was lifelong.” Vulpian was one of the first to enunciate the principle of the degeneration and regeneration of nerves and to explain the action of strychnine, nicotine, and anesthetics on the nervous system.\(^2,\)\(^7,\)\(^13,\)\(^15,\)\(^16\)

Charcot read both German and English and was familiar with Charles Bell’s *Exposition of the Natural System of the Nerves of the Human Body* (1824), Romberg’s *Lehrbuch der Nerven-Krankheiten des Menschen* [Textbook of Nervous Diseases in Humans] (1853), as well as Rudolf Virchow’s 1858 work *Die Cellularpathologie in ihrer Begründung auf physiologische und pathologische Gewebelehre* [Cell Pathology Founded on Physiological and Pathological Findings in Tissues]. Through a combination of theoretical knowledge and mastery of tissue preparation, Charcot possessed a solid grounding in pathology, and in 1872 was appointed Professor of Pathology at the Paris Faculty of Medicine.\(^14,\)\(^16,\)\(^17\)

The Salpêtrière School of Neurology and its director

Unlike most French hospital physicians at the time, Charcot did not attend his patients in the wards, but rather had them brought to his consulting room. The patient was undressed, while the intern read the latest findings. Charcot listened, drumming his fingers on the table. Meanwhile, the assistants...
would stand close together, waiting for a word from the master. Charcot would tell the patient to perform a movement and to speak. He asked his assistants to test the patient’s reflexes. Silence again. Another patient was brought in and examined as before. And a third, still without an utterance from Charcot, who would then compare the patients. He noted everything and sketched what he observed, a skill he’d cultivated since childhood.7,11

The confines of the consulting room contrasted sharply with the breadth of his ambition for the Salpêtrière. Charcot set up a pathology laboratory, an outpatient department, a room for ophthalmology, a psychology laboratory, workshops for drawings and casts, a biology laboratory, and a museum. Charcot had an amphitheater built in which the first electrical equipment for the projection of photographic plates to illustrate lectures given to students was installed. Charcot also called upon his “master” Guillaume-Benjamin-Amand Duchenne, who had overseen Charcot as an intern, to set up an electrotherapy laboratory and a photography workshop.2,4,7 Duchenne’s Mécanisme de la Physionomie Humaine [Mechanism of Human Physiognomy] was the first text on the neurophysiology of emotion and a landmark in clinical medical photography, but he is best remembered for his pioneering work on myopathies, including what are now called Duchenne muscular dystrophy, Duchenne-Aran spinal muscular atrophy, and Duchenne-Erb paralysis.

Between 1860 and 1866, Charcot and Vulpian studied the anatomical and clinical forms of multiple sclerosis and defined what has since become known as Charcot’s neurological triad, which although not pathognomonic of multiple sclerosis is associated with it, to wit: nystagmus, an involuntary eye movement; intention tremor of the arms; and staccato speech. They also described the histological characteristics of multiple sclerosis: a thinning or loss of the myelin sheaths and a build-up of scar-like plaque around axons.18,19

On January 25, 1865, Charcot gave a lecture at the Société Médicale des Hôpitaux de Paris on a case of primary sclerosis of the lateral columns of the spinal cord in a hysterical woman admitted in September 1856, who died in January 1862. He detailed the history, the clinical observation, and the disease course, reviewed the medical literature, read his autopsy report, reported his histological findings, and concluded: “I am inclined to believe that there is a distinct anatom-
A T O U C H O F F R A N C E

JEAN-MARTIN CHARCOT’S STUDENTS\(^{2,7,11,13,16,17}\)

Before losing his way in the complexities of hysterical neuroses (around 1880), Jean-Martin Charcot, the “Emperor of the Salpêtrière,” trained or influenced a whole generation of neurologists, psychiatrists, and psychologists. Here are some of them.

- Benjamin Ball (1833-1893) attended Charcot’s lessons on diseases of the elderly and chronic illnesses. He was the first holder of the Chair of Mental Pathology and Illness at the Sainte Anne Hospital in Paris (1875). Ball and Jules Luys (1828-1897) founded the journal L’Encéphale in 1881.

- Leopold Ordenstein (1835-1902), German by birth, was an intern in Charcot’s department in 1867, and the following year while in Paris wrote a thesis in French on the clinical differentiation between Parkinson’s disease and multiple sclerosis.

- Désiré-Magloire Bourneville (1840-1909) was particularly interested in the education of mentally retarded children. He also studied epilepsy, described tuberculous sclerosis, which is still sometimes described as Bourneville’s disease, and founded the journal Progrès Médical.

- Fulgence Raymond (1844-1910) succeeded Charcot as Chair of Neurology in 1894. He studied neuritis, syringomyelia, and tabes dorsalis, and with Charcot was the first to report cases of postpolio syndrome.

- Albert Pitres (1848-1928) was first an intern in Charcot’s department and then his assistant, from 1872 to 1880. He studied lesions of the centrum ovale and did research on peripheral neuritis. The Pitres sign is hypoesthesia of the scrotum and testes in tabes dorsalis.

- Paul Richer (1849-1933) was a physician, anatomical artist, and sculptor who headed the workshop that prepared drawings and casts in Charcot’s department.

- Paul Regnard (1850-1927) was in charge of the photography studio in Charcot’s department. From 1877 to 1880, he published with Bourneville the three-volume Iconographie Photographique de la Salpêtrière [Photographic Iconography of the Salpêtrière].

- Charles Féré (1852-1907) was an intern and demonstrator in the department of Charcot and then his private secretary, before becoming chief physician of the medical laboratory at the Bicêtre Hospital in 1887. With his friend Alfred Binet, he published work on experimental psychology, sexuality, and criminality.

- Gilbert Ballet (1853-1916) was senior resident under Charcot and set up the Department of Psychiatry at the Hôtel-Dieu de Paris. In 1909, he was appointed to the Chair of Clinical Psychiatry and Brain Disorders at the Saint Anne Hospital in Paris. He wrote his thesis on sensitivity disorders in brain lesions, studied hallucinatory chronic psychosis, and was the author of the first major treatise on psychiatry of the 20th century.

- Eugen Bleuler (1857-1939) attended Charcot’s courses on nervous diseases before returning to his native Switzerland to pursue his career as a psychiatrist. He recognized that the condition known as dementia praecox was in fact neither a dementia nor of early onset, and coined the term “schizophrenia” to replace it. Bleuler also familiarized the Latin word “autismus”—autism in English.

- Alfred Binet (1857-1911) joined Charcot at the Salpêtrière in 1884 to study hysteria and was the creator of the first psychometric tests (the Binet-Simon intelligence scale). He set up an experimental psychology laboratory and founded the journal L’Année psychologique.

- Georges Gilles de la Tourette (1857-1904) was an intern and later senior resident at the Salpêtrière under Charcot, whose work on hypnosis and hysteria fascinated him. He studied syphilitic myelitis and in 1885 described the tic disorder which today is known as Tourette syndrome.

- Pierre Janet (1859-1947) was the founder of 19th century French clinical psychology and was a pioneer of psychoanalysis and psychotherapy. In 1889, Charcot made him head of the Psychology Laboratory at the Salpêtrière. He founded the Journal de Psychologie Normale et Pathologique and the Société de Psychologie [Psychology Society].

- Nicolas Dahl (1860-1939), a Russian neuropsychiatrist, attended Charcot’s classes at the Salpêtrière in 1881 and specialized in neurology, psychiatry, and psychology. In 1900, he treated the composer Sergei Rachmaninoff for a nervous breakdown following the poor critical reception of his Symphony No. 1. After his recovery, Rachmaninoff dedicated his Second Piano Concerto to Dahl.

- Achille Souques (1860-1944), one of Charcot’s interns in 1886, was a pioneer of neurosurgery in France at the Salpêtrière. He was a founding member of the Société de Neurologie de Paris [Neurological Society of Paris] and is remembered also for his work on what has become known as Souques-Charcot geroderma (a variant of progeria), as well as Souques’ sign.

- Gheorghe Marinescu (1863-1938), a Romanian neurologist, did postgraduate studies with Charcot in 1885. His work on a case of tremor caused by a tumor in the substantia nigra was a major advance in the understanding of Parkinson’s disease. He made the first science films in the world in his clinic in Bucharest, and is also remembered for his work on Marinesco (sic)-Sjögren syndrome.
ical and pathological entity which will become less and less rare as careful autopsies grow in number.”

Charcot’s merit was that he clarified the hazy nosology of “chronic myelitis” by distinguishing multiple sclerosis from the progressive locomotor ataxia, or tabes dorsalis (linked to sclerosis of the dorsal columns), described by Duchenne. In all, Charcot conducted 34 anatomical and histological observations of multiple sclerosis and published his findings in 1868, the year in which he started classes on the disease.

Between 1867 and 1878, Charcot continued his work on neuropathology in a quest to disentangle the etiologies of tremors in the elderly: cerebellar tremor, Huntington’s chorea, posthemiplegic chorea, hysterical chorea, athetosis, and spasms. In 1870, Charcot gathered the mentally disturbed, epileptics, and hysterics together in a new department of “simple epilepsies.” In the second half of the 19th century, the greatest confusion shrouded understanding of those subject to seizures. Charcot sought to differentiate hysterics from epileptics using anatomical and clinical rules. Thus it was that he entered the world of hysteria, never to leave it until his death.

Drawing on his own work and on the findings of Duchenne, whom he referred to as “mon maître,” and of the anatomist Jean Cruveilhier, Charcot established the anatomical and clinical characteristics of amyotrophic lateral sclerosis (also known in English-speaking countries as Lou Gehrig’s disease, after the New York Yankees baseball player), a motor neuron disorder which in France is still sometimes called Charcot’s disease:

This disease starts with muscle weakness which progressively spreads to all four limbs, and soon gives way to stiffness or more or less pronounced permanent contraction which is more marked in the lower than upper limbs.

For several years, Charcot organized courses in neurology on Tuesdays, where observations on nervous diseases made at the hospital were reported before an audience of attendant students as well as French and foreign physicians.

His career ended in honor: the Chair in Diseases of the Nervous System was created in 1882 for Charcot, the crowning achievement to a lifetime’s work.

In 1900, seven years after his death, the Salpêtrière was divided into three parts: the back housed madwomen, the more agitated among them isolated in individual “chalets”; a large Louis XIII building for elderly women with common rooms 60 meters in length abutted the main thoroughfare (the boulevard de l’Hôpital); and between the two was Charcot’s domain, with its laboratories, maintenance department, museum, and amphitheater.

Many more changes have occurred over the intervening years, but today’s modern Pitié-Salpêtrière Hospital is a living testament to the best of French neurology, thanks to the pioneering vision of Jean-Martin Charcot.

Pierre Marie (1853–1940)

Pierre Marie, one of Charcot’s most outstanding students, first studied law to comply with his father’s wishes, but then entered medical school, qualifying in 1878. He received his medical doctorate in 1883 with a dissertation on Basedow’s disease (also known as Graves’ disease), in which he described tremors of the outstretched arms and fingers, which he had studied while a medical student.

The same year, while the neurologist Howard Henry Tooth (1856–1925) was conducting similar studies in England, Charcot worked with Pierre Marie on what is now known as Charcot-Marie-Tooth disease. This motor neuron disease is one of the most common inherited (usually autosomal dominant) neurological disorders and is characterized by demyelination of the peripheral nerves. Marie was one of the first to study and describe acromegaly and, through his work on this pituitary gland disorder, made a major contribution to the nascent discipline of endocrinology. He published extensively on aphasia, rejecting the views of Pierre Paul Broca (1824–1880) and Karl Wernicke (1848–1905) on the localization of the speech cen-
ter, notably in a paper entitled, *The third left frontal convolution has no special role in the function of language*. Marie’s studies in neurology also concerned spinal cord diseases, spinocerebellar ataxia, pulmonary hypertrophic osteoarthropathy, cerebellar heredotaxia, cleidocranial dysostosis, and rhizomelic spondylisis, and he distinguished rheumatology from neurology, with which it had long been conflated.

In 1897, Marie founded a school of neurology at the *Hospice de Bicêtre*, which soon acquired a worldwide reputation and over the years produced many distinguished pupils guided by his rigorous approach to the practice and study of neurology. Ten years later, Marie was appointed to the Chair of Pathological Anatomy at the Salpêtrière Neurological Clinic. He established a museum and laboratories and modernized the teaching of the subject together with his successor Gustave Roussy, with whom he wrote *Les Psychonévroses de Guerre*, an early work on what we would now call posttraumatic stress disorder.

Pierre Marie cofounded the *Revue Neurologique* with Édouard Brissaud, served as the first General Secretary of the Société Française de Neurologie, and from 1911 was a member of the Académie de Médecine. Towards the end of the Great War, during which he studied and treated the traumatic brain injuries of the wounded, Marie was appointed to the chair that had been created for Charcot. This was a position he held until 1925, when he resigned at the age of seventy-two.

**Joseph Babinski (1857-1932)**

Charcot’s favorite student was Joseph Babinski, the son of a Polish engineer and famous gastronome, whose book *Gastronome Pratique* ran to over one thousand pages by the time of its 1928 edition.

Babinski’s motto of “observation is the highest principle” served him well throughout his rich and varied medical career, which ranged from a treatise on typhoid fever in 1882 and an 1885 thesis on multiple sclerosis to a study of hysteria in 1930. Babinski cofounded the Société de Neurologie de Paris and made major contributions to the development of psychiatry and neuropsychology in France. In 1903, he described his conclusions following years of studying fanning of the toes, the abnormal response to plantar stimulation that signals upper motor neuron damage to the thoracic or lumbar region or brain disease, which is now termed Babinski’s sign.

Babinski foresaw the rise of neurology in France and later said of two of his favorite students—Thierry de Martel and Clovis Vincent—“I showed them the way to found French neurosurgery.” Another of his famous pupils was Egas Moniz, the Portuguese neurologist who developed cerebral angiography and introduced prefrontal lobotomy, for which he won the 1949 Nobel Prize in Medicine. Controversial from its inception, this psychosurgical procedure was used widely in the 1940s and 1950s to treat various psychiatric disorders, but has since fallen into disfavor and is now rarely performed.

Whereas Charcot had relied mainly on medical history taking and observation, Babinski broke with the tradition of his former mentor and developed and emphasized the importance of bedside neurological examination, paving the way for mod-
ern neurology. The *Lancet* concluded Joseph Babinski’s obituary with the following words: “None of Charcot’s pupils is surer to be remembered for his achievements in the field of neurology.”

Jean Lhermitte (1877-1959)

Jean Lhermitte was the son of the French realist painter Léon Augustin Lhermitte, of one of whose works Vincent van Gogh wrote: “…for years I have not seen anything as beautiful as this scene by Lhermitte.” Lhermitte “fils” graduated in medicine in 1907 and specialized in neurology. During the Great War, he studied spinal injuries, and is above all known for Lhermitte’s sign (strictly speaking a symptom, since it is experienced and reported by the patient): an electrical sensation that runs down the spine and into the limbs, which is generated by bending the neck backward or forward. Lhermitte’s sign is most frequently seen in multiple sclerosis, but can also be caused by other conditions, including Behçet’s disease (a form of vasculitis), compression of the spinal cord in the neck, radiation myelopathy, and vitamin B₁₂ deficiency.

A variety of eponyms bear witness to the scope of Lhermitte’s work as a clinical neurologist, including Lhermitte-Cornil-Quesnel syndrome (progressive pyramidal-pallidal degeneration), Lhermitte-McAlpine syndrome (combined pyramidal and extrapyramidal tract syndrome in the middle-aged and elderly), Lhermitte-Trelles syndrome (lymphoblastic infiltrations of the peripheral nervous system associated with paresis and amyotrophy), and Lhermitte-Lévy syndrome (slowly progressive poststroke paralysis). In 1922, he published a work entitled *L’Encéphalite Léthargique*, which describes encephalitis lethargica or von Economo disease, an epidemic of which killed hundreds of thousands around the world and left many more in a state of living death—catatonic, speechless, and motionless—between 1915 and 1926. Theories as to its etiology are not lacking, and recent research suggests that an immune reaction may be involved, but its cause remains unclear.

Lhermitte took intense interest in neuropsychiatry and explored the common ground between alleged religious manifestations and medicine, conducting studies on demoniacal possession and stigmatization. In neuropsychology, he made contributions to the understanding of phantom limbs, visual hallucinations (such as the unreal, abnormal phenomena of Lhermitte’s peduncular hallucinosis), spatial thinking, constructive apraxia, and disorders of consciousness.

Paul Castaigne (1916-1988)

Paul Castaigne became an “intern” (house physician) just as World War II broke out and saw active duty at the front with the Army Medical Corps. Back at the hospital he entered the French Resistance alongside Jacques Chaban-Delmas, starting a lifelong friendship. He embarked on a brilliant hospital career becoming, in the 1960s, Dean of the Medical School, when the Salpétrière merged with its neighbor *La Pitié* hospital, creating the new Pitié-Salpétrière Faculty of Medicine. As Dean of the Medical School, Castaigne oversaw the development of a multidisciplinary university hospital where bench-to-bedside research covered many fields, while staying true to the Salpétrière’s historical vocation of neurology, epitomized today by the work done at the Federative Institute of Neuroscience Research.

In 1951, he became a household name for generations of French medical students and doctors as one of the founding fathers, then director, of a new medical journal destined for general practitioners, *La Revue du Praticien*. *La Revue*, started by Dr André Roux-Dessars–Baillière, gained instant fame and endures to this very day. When Castaigne retired in 1985 after a quarter of a century as its longest holder, Charcot’s chair at the Salpétrière was abolished in university reforms over one hundred years after its creation. And with Castaigne went the last direct link to Charcot. In 1891, Charcot examined 12-year-old Elisabeth H., who suffered from a particular type of progressive muscular atrophy, which later became known as Charcot-Marie-Tooth disease. Four years later, Elisabeth entered the Salpétrière and long afterwards, shortly before her death, she was examined by Paul Castaigne, newly appointed to the chair created for the man who started it all, Jean-Martin Charcot.
Conclusion
Jean-Martin Charcot and his illustrious aforementioned followers at the Pitié-Salpêtrière Hospital: Joseph Babinski, Pierre Marie, Jean Lhermitte, and Paul Castaigne—but there were many others—were the trailblazers of French neurology. They all assisted the present-day Pitié-Salpêtrière Hospital in gaining the top international reputation it enjoys today as one of the world’s leading centers of neurology and neuroscience.

It is perhaps fitting to leave the last word on Jean-Martin Charcot to his students. A decade after his mentor’s death, Charles-Joseph Bouchard (he of the Charcot-Bouchard aneurysm) wrote:

It was Charcot who shaped our intellects; it was he who opened the gates to scientific work, it was he who took my hand and led me to the highest academic position I could reach. Confronted with his memory, I shall always feel the deepest gratitude.

And the young Sigmund Freud, who attended some of Charcot’s Tuesday neurology classes, wrote in a letter to his fiancée Martha Bernays, later his wife and the mother of their six children, how he would leave Charcot’s courses full of new ideas, his mind abuzz as after a good evening at the theater. “Will the seed produce fruit?”, Freud wondered. “I know not, but this I do know: no other man has ever had as much influence on me.”

References
The aim of the Brain and Spine Institute (ICM) is to increase the efficiency of neuroscience research through translational research integrating the fields of molecular and cellular biology, neurophysiology, and cognitive science... so as to relieve, cure, prevent, and repair the disorders of the brain and spinal cord that are affecting a rapidly increasing number of persons to the point that they are reaching epidemic proportions, not only in France and Europe, but throughout the world.”

The Brain and Spine Institute (ICM) is a state-approved private nonprofit neuroscience research foundation, scheduled to start operating in the fall of 2010. Founded by two internationally renowned French neurologists, Yves Agid—also a neuroscientist—and Olivier Lyon-Caen, and an orthopedic and trauma surgery specialist, Gérard Saillant, it is an ambitious and innovative pilot project, located within the Pitié-Salpêtrière Hospital complex in Paris, France’s largest hospital and one of the world’s foremost centers for nervous system diseases. The ICM will provide state-of-the-art facilities for more than 600 researchers and technicians from all over the world. It aims to increase the efficiency of neuroscience research through translational research integrating the fields of molecular and cellular biology, neurophysiology, and cognitive science, to find practical answers in terms of basic knowledge and treatment, so as to relieve, cure, prevent, and repair the disorders of the brain and spinal cord. The ICM will closely interact with the Pitié-Salpêtrière Hospital, and benefit from its huge reservoir of patients and clinical, biological, and tissue databases. It will also establish close relationships with institutional and industrial partners, and interact with society at large through various scientific and cultural programs and activities. Nervous system diseases currently affect 1 in 8 persons in Europe, and their incidence is increasing. Among the ICM’s chief priorities will be to find treatments to halt the progression of, and cure, neurodegenerative diseases such as Alzheimer’s disease, Parkinson’s disease, and amyotrophic lateral sclerosis, and help sufferers of spinal cord trauma recover motor function.

Professor Yves Agid is a busy man and a man with a mission; catching him in between a flight from New York to Geneva and on to Tokyo is no mean feat, yet despite the jet lag and an overburdened agenda he is fresh and more than eager to start an early morning two-hour interview. He is an enthralling and fascinating speaker, with a Bill Bryson—like knack for explaining complicated things in layman’s terms.

Agid is also a happy man. As one of the founding fathers of the ICM (Institut du Cerveau et de la Moelle Épinière—Brain and Spine Institute) he is about, this fall, to cut the ribbon of his life’s project, an institute that probably does not possess its like in the world, slated to gain name recognition on a par with Harvard, MIT, the Karolinska Institute, or the Weizmann Institute. The building housing this ambitious

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French neuroscience in the vanguard: the ICM is taking off

An interview with Y. Agid, France

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project is nearly completed. Its “H” shape is fittingly—Agid claims this was the spontaneous result of the most efficient functional design—reminiscent of that of a brain, with its two all-glass-and-light “hemispheres” linked by a central “corpus callosum” that serves to ensure the “traffic” between the two halves of the building. It is now one of the most imposing structures in the sprawling complex of the Pitié-Salpêtrière, France’s largest hospital, which occupies more than 80 acres of prime real estate in the 13th arrondissement of Paris, a city within the city. Agid, after a career spanning more than 35 years as a neurologist and neuroscientist, will probably never again wield a reflex hammer nor peer into a test tube, deliberately choosing instead to give his full time to gathering around him some 600 of the savviest brains from around the world.

La Pitié-Salpêtrière got off to a start in 1613 with the construction by the Regent Marie de Médicis of the Notre-Dame de la Pitié (Our Lady of Mercy) hospice for the destitute. In 1653, the Sun King Louis XIV had the old buildings of a neighboring ammunition dump called La Salpêtrière (named after the saltpeter used to manufacture gunpowder) refurbished to accommodate the “General Hospital,” which, far from being a place of care, was destined to get the tens of thousands of beggars, cripple, and abandoned children off the streets of Paris. In 1684, a prison for prostitutes and other “wayward” women was added, while insane women were locked away under the most squalid conditions, thereby unwittingly laying the ground for the future psychiatric calling of the Pitié-Salpêtrière. Only gradually did the Pitié-Salpêtrière turn into a genuine hospital, in 1748, thanks in particular to Tenon, a surgeon who sought to humanize the hospice, and under Louis XVI, in 1783, with the addition of a General Infirmary. After the Revolution, Pinel, in 1794, literally freed the insane from their chains and started trying to treat them. Finally, in 1801, La Pitié-Salpêtrière was officially granted the status of full-fledged hospital. The hospital saw the birth of French neurology in 1882, when Charcot founded the first Chair for diseases of the nervous system (one of his students was Sigmund Freud), and where luminaries such as Vulpian, Dejerine, Babinski, Pierre Marie, and Lhermitte made the groundbreaking discoveries that turned them forever into household names in neurology. La Pitié-Salpêtrière is now one of the world’s foremost neuropsychiatric university hospital centers, a 2000-bed hospital treating more than half-a-million patients every year, among which 100 000 patients with diseases of the nervous system, and where a big chunk of France’s neurosciences research is carried out.
The concept of the ICM—whose founding fathers are Gérard Saillant (President), Olivier Lyon-Caen, and Yves Agid—has benefited from the support of a group of personalities from all walks of life who constituted the Founding Members, some of whom are now, alongside institutional partners, members of the Board of Directors:

- Luc Besson, Film director
- Louis Camilleri, Chairman of Altria
- Jean Glavany, Former Minister
- Maurice Lévy, Chairman of the Publicis Group Board
- Michael Schumacher, Formula One racing driver
- Jean-Pierre Martel, Lawyer
- Max Mosley, Former President of the FIA (International Federation of Automobile Sports)
- Sir Lindsay Owen-Jones, President of L’Oréal
- Jean Todt, President of the FIA
- Serge Weinberg, President Weinberg Capital Partners

Actors Jean Reno and Michelle Yeoh are providing high-visibility support as goodwill ambassadors. In 2008, the Presidency of the ICM Research Project fundraising campaign was assumed jointly by David de Rothschild and Sir Lindsay Owen-Jones, with Jean Todt as Honorary President.

How was the ICM founded, and how did you choose the name of the Institute?

I was reminded, a couple of years ago, by a nurse who was leaving on retirement, that all the way back in 1973, as a young senior registrar in neurology, I’d told her: “One day, you’ll see, we’ll need to coordinate all neurology, psychiatry, and related departments into a single structure, and have a big neuroscience research institute just a stone’s throw away…” In 1997, when I was head assistant to Professor Claude Griscelli, the then General Director of the National Institute of Health and Medical Research (INSERM), who was actively planning his own genetics institute, due to open any time now, we often talked about the necessity of a neuroscience institute. The actual decision to create the Institute came in 2002, when Gérard Saillant, a professor of orthopedic and trauma surgery, who initially had wanted to start a bone institute, began playing with the idea that rather than busying himself with bone, a more urgent priority was what lay under the (skull)-bone, ie, the brain. He then told me “I know that Olivier Lyon-Caen (a neurologist) and you want to create a neuroscience institute: why don’t we all do this together? The project really got jump-started when Gérard introduced me to Jean Todt,” who was at the time Team Principal of the Scuderia F1 Team, before becoming CEO of Ferrari. Todt organized a dinner attended by a select group of personalities who immediately warmed to the idea and vowed to sponsor the Institute, and became its Founding Members. From then onward the project snowballed, and we got the support we needed from health, governmental, and regional and local authorities, including the Ministry of Research, the Île-de-France Region, Paris City Hall, and others. Funds and donations started trick-
What we wanted to do was increase the efficiency of neuroscience research through translational research integrating the fields of molecular and cellular biology, neurophysiology, and cognitive science. Our aim is to bring practical answers both in terms of knowledge and treatment, so as to relieve, cure, prevent, and repair the disorders of the brain and spinal cord that are affecting a rapidly increasing number of persons to the point that they are reaching epidemic proportions, not only in France and Europe, but throughout the world.

What is the current situation of neurological diseases in France and Europe today, and what is so special about them?

Neurological disorders affect over 1 billion persons throughout the world, according to WHO. In Europe, the figure is upwards of 94 million. Stroke is the main cause of motor handicap in Europe, affecting 3 million persons; Alzheimer’s disease affects some 4 million persons; Parkinson’s disease 700 000; epilepsy 2.5 million; multiple sclerosis 300 000. Brain and spinal cord trauma claim over 60 000 deaths every year while 1.5 million subjects lose their autonomy as a consequence of their injuries. If we look at psychiatric diseases, the picture is a gloomy one: 3.6 million people suffer from psychoses with delirium and are dangerous to themselves or others; manic-depressive disorder again has 3.6 million sufferers and a high risk of suicide. As for depression and anxiety, both affect some 36 million people, ie, a staggering total of more than 72 million, for a total population of 450 million, ie, more than 15% of Europe’s population. In France alone, 3.5 million persons (out of a total of 60 million) are disabled due to neurological disorders, including 850 000 with motor disabilities (370 000 in wheelchairs); and 650 000 with perception disabilities, of which are 60 000 blind persons. A simple figure says it all: in Europe, more than 1 person in 8 today suffers from some form of disease of the nervous system.

As you can well imagine, much care was put into coming up with an adequate name. The “Brain and Spine Institute” is in essence a neuroscience research institute. We could easily have stressed that aspect, or found a catchy one-word name, but what we wanted to highlight above all was the patient- and general-public–oriented specificity of the ICM. The ICM will of course carry out basic neuroscience research, but what we want is for it to come up with answers, and above all, practical answers: new treatments and new cures. Gérard Saillant played a decisive role in finding a name that would really mean something to the general public by specifically citing spinal cord disorders, chief among which are naturally the high number of victims of automobile and other accidents who are paralyzed after spinal cord injuries. We want these patients and their families to know that we are trying to do something very concrete about this.
Why is that?

Today it so happens that the ICM, which will be inaugurated this fall, comes at an ideal juncture, and this for three reasons.

First of all, the time is just right in regard to the spectacular advances in our knowledge of how the brain works, thanks to neuroscience research over the past two to three decades. Before that, the brain was a black box for us: we knew that information entered, and that behaviors issued, but what actually took place within the brain itself remained a sealed book. Recent technological achievements have changed all that, and we are beginning to understand what is going on. Our imaging capacity is now simply unbelievable. Just think about it: thanks to high-field MRI imaging, the degree of precision is such that we are able to distinguish cellular layers in the brain! There have also been momentous advances in molecular biology, neurophysiology, and genetics, as well as in a field in which France is an uncontested leader—good old clinical symptomatology. I prefer the word “semeiology”—the science of interpreting signs and symptoms, to come to a diagnosis. It is important to realize that cerebral symptomatology has become nearly entirely behavioral: increasingly better-described subtle changes in behavior can now be pinpointed to specific neurological lesions. At first glance, this seems unexciting in comparison to technological wizardry, but make no mistake, this truly represents a cutting-edge field.

Second, the ICM also comes at the right time in view of the rising incidence of many of the diseases that the ICM will be studying, due to the aging of our Western societies (the typical example being Alzheimer’s disease, with, in France, 860,000 persons affected, with an incidence of 225,000 new cases per year, projected to reach 2.1 million in 2040). Not only the number of elderly affected is increasing, but that of younger persons as well—one need only mention traumas due to car accidents or sports—as well as that of the very young, and here I’m talking about rare genetic diseases, associated with motor and intellectual deficiencies, of which there are many kinds. All these diseases are a source of great misery for the patients and their families. The ICM will be putting its full power to work to understand, relieve, cure, prevent, repair: this really could be our motto! Finally, and in this we are truly precursors, the ICM comes at a time when successive governments in France have started to realize how important it is to create “competitive clusters” not only for industry in general, but for medical research as well. Research in France is of very high quality, but has been stagnating somewhat over the past couple of decades, and France was losing its competitive edge, lagging behind other countries in terms of discoveries, patents, publications, and Nobel prize awards. All of this impacts strongly on health economics and even just plain economics. This situation is largely due to structural complexity, regulatory constraints, and the smothering embrace of bureaucracy. Recent governments have begun to see the light, and a radical change is at last under way to put France on a par with the USA and other European countries that have long understood that staying at the top requires cutting down on administrative red tape and uniting individual efforts into larger wholes to increase the efficiency of research. This is the idea behind the so-called competitive clusters or “technopoles” or “poles of excellence and competitiveness” as they are dubbed in France. This is exactly what the ICM is intended to do and what makes it a “pilot project,” expected to have profound economic implications in terms of efficiency, savings, and industrial spin-offs.
So what exactly are the goals of the ICM and what makes it unique?

The first and most important aspect is that all of the ICM’s activities will be centered on the patient, who is the linchpin around which the entire ICM will revolve. And no matter the extent of pure science pursued and produced at the ICM, our immediate and constant concern is the patient, and what tangible benefits we will be able to provide. I’d like to insist again on what I have called our motto: we want to find out more about nervous system diseases in order to come up with better treatments—and we want to work on the full gamut of what “treatment” implies: relieve, cure, prevent, repair. Effective treatments exist to alleviate the manifestations of brain disorders prior to an accident. Second, to achieve its goals, the ICM is going to recruit the very best researchers, from all over the world. I’m sometimes asked whether the ICM will help stem the brain drain of French neuroscientists to the US. Like all French postdocs, they go there because they are better paid and have better working conditions. Let them stay where they are! I certainly don’t want them all to flock back in droves; what I want for the ICM is the best, only the very best, be they French, American, German, or Chinese! These elite researchers will be headhunted according to rigorous requirements and vetted by a completely independent international jury of experts. Of course excellence comes at a price: it requires attractive salaries and quality of life, and a working environment devoid of the vexing problems that beset so much of research in our country, all of which the ICM is pledged to provide.

The third characteristic feature of the ICM is translational research. To this end the ICM will strive to eliminate barriers between clinicians and scientists, and will go from bedside to bench and bench to bedside, and back and forth from the patient to the cellular and even molecular level. Our main fields of research will involve clinical research, state-of-the-art technologies, cell biology, molecular biology, neurophysiology, genetics, cognitive science, etc.

Fourth, these researchers will be free to do just what they want—provided they excel. Of course their research will be carried out within an overarching strategy at the service of public health-oriented concerns, comprising such priorities as neurodegenerative diseases, cerebral and spinal cord trauma sequelae, dementias, and the major psychiatric illnesses. Strategic choices mean that some fields will have to be left out, such as migraine—in spite of the over 6 million migraine sufferers in France—in favor of others, such as mental dysfunctions or neuroplasticity. Emphasis will also be put on topics that have hitherto been traditionally neglected in France, such as the study of consciousness and of emotional and mood disorders in relation to anxiety and depression. Another such neglected field is “brain computer interface” devices, for example to restore motor function by bypassing spinal cord lesions.

A fifth characteristic is the ICM’s location within the hospital complex of La Pitié-Salpêtrière. This is a feature that makes the ICM absolutely unique. Just think of it: this center, dedicated to neuroscience research, is situated right in the middle of the biggest hospital in France, and one of the biggest in all of Europe, where out of the 600 000 patients attending the hospital every year, more than 100 000 receive treatment in the Neurology, Psychiatry, Neurosurgery, or Neurological Rehabilitation Departments. “Bench to bedside—and back to bench” will be immediate, constant, with no loss of time and energy, providing ideal conditions for translational research and clinical trials. Not only will the ICM have onsite access to the patients, but also to the hospital’s biological data, brain tissue, and DNA bank resources, indispensable for research.
A sixth characteristic is that the ICM will interact with society at large, with the community. We want the ICM to be a hotbed of intellectual activity, with a constant stream of seminars and lectures by international leading lights for in-house researchers, as well as for researchers in other fields, industrial leaders, and the pharma industry. We will also offer a variety of programs for the general public, such as lectures, exhibitions, and concerts—we’d even like schoolkids and students to come over to get a first taste of science and a whiff of hospital atmosphere in order to stimulate interest in neuroscience research as a career.

How is the ICM financed, what are your sources of support?
The ICM is a state-approved private nonprofit research Foundation, with mixed public and private funding, similar to the Pasteur or Curie Institutes. Again, this is something that is quite innovative, and not all that common in France. Our initial investment requirements were in the region of 67 million euros. The operating costs are estimated at 55 to 60 million euros per year, which is a lot of money. Most of these costs will be earmarked for salaries, which must be high enough to attract the best researchers available, and the cost of technological equipment. Again, if we want to be in the top league, we can only be satisfied with the most up-to-date cutting-edge equipment. Forty million euros of the running costs will be financed by public funds, but we still need to find more than 15 million euros every year to be in the black. And since we will not be producing any consumer goods, but research and publications, this will be quite a challenge!

We receive funding from sponsors and partners from the public and private sectors. We are grateful to the administrations who authorized the allocation of the ICM’s construction site—INSERM, the Île-de-France Region, the City of Paris, and the Ministry of Research. We are of course very much indebted to the Assistance Publique – Hôpitaux de Paris (AP-HP), which gave the ICM a 4400-m² plot within the Pitié-Salpêtrière hospital grounds—quite an appreciable gift considering the hefty price of real estate in central Paris. We have received support from the Pierre and Marie Curie University (Paris VI); the CNRS; and the Caisse des Dépôts (a public financial institution that granted the ICM an important loan). We are applying for subsidies from the European Union.

Among the private sector partners, there is the pharmaceutical industry, and of course Servier. Special mention should be made of the FIA Foundation (International Federation for Automobile Sports), currently headed by Jean Todt. The FIA is strongly committed to the ICM, consonant with its actions to promote road safety and prevent automobile accidents responsible for so many cases of brain and spinal cord trauma.
We will rely on subsidies, to obtain grants and contracts from the French National Research Agency (ANR), or from European and other international institutions. We will also rely on industrial partnerships, including with people like Servier, who will sponsor and/or carry out research programs under co-patenting and co-licensing agreements with all guarantees of the strictest confidentiality to preserve intellectual property rights.

And last but not least, we are counting very much on donations from private individuals. Whatever their amount, we consider none too trivial and are grateful for all!

**What can you tell us about the architecture of the ICM, and the facilities it will feature?**

We pride ourselves on the choice of architect: Jean-Michel Wilmotte. He is a graduate of the École Camondo, and among his most celebrated achievements are the Incheon International Airport (Korea, 2000); the Palace of Congress of Bordeaux (2003); the Museum of Contemporary Art in Beijing (2007); the Collège des Bernardins, a spearheading catholic cultural institution inaugurated by Pope Benedict XVI in 2008. Wilmotte is currently working on the Korea Art Center in Pusan, a high-rise office building office in Azerbaijan, a hotel in Bahrain, and a Formula One racing track in France. The ICM building is a wonder of glass and light. It’s 8 floors, of which 2 are basement levels, offer a total surface area of 22 000 m² and will provide ideal working conditions for its 600 investigators. The lower ground floor will contain a neuroimaging platform, with a 7-tesla MRI scanner for clinical research, which will produce exquisitely detailed 3-dimensional mapping images of human brain structures. The ICM will also boast two to three 3-tesla MRI scanners for patients and an 11.7-tesla MRI scan-
The first floor will house a Clinical Investigation Center (CIC) with a capacity of 14 inpatients, to conduct research to determine the innermost mechanisms of nervous system diseases and test experimental treatments, under the most stringent ethical and legal constraints.

To the casual, nonspecialist reader, this may seem like precious little for such a big research institute—in fact it is unusually large, as these investigations are not classic clinical trials of study drugs, but special investigations carried out on a case-by-case basis under very specific conditions.

Research laboratories for more than 40 research teams totaling 600 to 700 researchers, technicians, and other personnel will occupy some 11,000 m² on the 4 upper floors, organized into modifiable modules on either side of the central linking section of the building, which will house the technology platforms. This is a very astute concept, aimed at centralizing the bulk of the technical facilities in order to optimize their use and save significant space, time, and money. The modules will allow great flexibility in use, either as labs, offices, or meeting rooms, at a moment’s notice. Communication between teams and individuals will be enhanced thanks to the centralization of the technological equipment and the liberal use of glass walls and partitions and the overall conception of the building.

The ICM will boast a generous offering of teaching and training facilities, with conference rooms, meeting rooms, a 180-seat amphitheater, spaces for industrial partners and startup companies, and even a museum dedicated to French neurology.

**So what will the ICM do exactly?**

First of all, we want to do a lot of research—a massive, multifaceted thrust of basic research in neurosciences and related fields. You just can’t compare our knowledge of the brain with that of any other organ: the brain is so infinitely complex that even though we have made giant strides, our understanding is still in its infancy.

This is particularly the case if you take the higher functions: how do neurons manage to produce thought, consciousness, and what happens when dysfunctional neurons produce dysfunctional thought? What exactly is memory, and what happens in dementias and degenerative diseases when one loses it, when one loses language? Just understanding how two neurons, which are universes unto themselves, manage to “talk,” exchange information, exchange “thoughts” is a conundrum. To record what is going on in a single neuron requires tremendous computational resources, to do this in time and space for groups of neurons is just mind-boggling! But researchers are starting to make some headway, and are even developing a few practical applications, like the “brain computer interface” programs I mentioned a little while ago.

But to get back to how the ICM is going to operate, this is going to be in a “bottom-up” fashion: we are going to have scores of independent teams with a meticulous and rigorous selection of the best people in their respective fields. Of course there will be also a selection of projects to fit in with the overall picture of the major fields that will have been defined by the ICM as our priorities, eg, there will be an overall program for neurodegenerative diseases (ie, Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, etc), epilepsy and related disorders, as well as brain and spinal cord trauma.

But in essence, these teams will come to us already with their own projects and be completely independent, including financially: they will actually “pay rent” for the facilities they use—this will be made possible through their own research grants. Again what characterizes the ICM is that it will provide an ideal setting for translational research, cross-fertilization, and out-of-the-box creativity.
Our research will involve three major fields. First, molecular biology, to identify abnormal genes and assess the role and the consequences of gene mutation in cell and animal models. We will also use gene therapy to protect the nervous system by modifying gene expression and reconstructing lesioned tissue by implanting genetically modified cells. Second, cell biology, to modify abnormal metabolic chains by acting on nerve cell nuclei via receptors at the cell membrane, or through transplanted cells or stem cells. Third, neurophysiology studies, supported by computational or simulation and modeling tools, in vitro or in vivo, to understand how abnormal activity of one or a group of nerve cells can alter a neuronal circuit, and subsequently one of the brain’s functions. Research today is a totally globalized endeavor, and can only function through an international network of teams in close collaboration with each other. One of our aims is to set up strategic alliances with institutions throughout the world. Another goal will be to set up satellite teams or affiliated institutes in France and abroad, like the Pasteur Institute. We’ve already got plans for this...

One of our first priorities will be tackling neurodegenerative diseases, and trying to stop the progression, or even cure, amyotrophic lateral sclerosis—you know, cosmologist Stephen Hawking’s disease—or Parkinson’s disease, or Alzheimer’s disease.

So tell me, when do you expect the first drug to come out of the ICM? What’s the first disease you expect to find a cure for?

We’re looking at finding a treatment for stopping the progression of one of the neurodegenerative diseases within, say, 5 years, and a cure perhaps in 20 years—but figures don’t really mean anything in this context. If you’re talking of tangible results, a box of pills on the patient’s bedside table, your question is more for the pharmaceutical industry than for the ICM!

In fact, our role will be to pave the way for the drug industry to develop effective treatments, ie, to assist in drug discovery, and this in a twofold way. Firstly, by identifying or confirming specific therapeutic targets, and this will be a major help to the industry, which will know where to focus the screening process. Secondly, by providing the setting to rapidly test promising drug candidates, ie, to fast-track a new potential drug within a very small-scale yet genuine clinical pharmacology setting in humans, once its absence of toxicity has been confirmed, in Phase 2a and b–like trials in very small numbers of patients to evaluate the “proof-of-concept.” This will save a lot of money, but above all time, in that only drugs with a proven potential will then be subjected to the gauntlet of standard clinical trials in large numbers of patients.

To conclude, what are your hopes for the ICM?

To answer that, I need to run through a few figures. The brain, all 1350 g of it, is infinitely more complex than any other organ or system in the human body. It is composed of more than 2500 different types of cells. It contains 100 billion (10¹⁴) neurons; each neuron has some 10 glial cells catering to it—so that’s a grand total of 10¹⁵ cells! each neuron establishes between 10 000 and 100 000 contacts with neighboring neurons and emits thousands of signals per second. This means that, right now, your brain is producing billions of billions of signals every single second, dwarfing into complete insignificance the most complex computers designed by humans—now, and probably that ever will be! Just try to imagine what takes place in a single cubic millimeter of brain tissue, which contains more than 10 000 neurons! Blaise Pascal, the 17th-century mathematician and father of the first computer—a calculating machine with a complex ratchet wheel mechanism—and a physicist who discovered the properties of vacuum and pressure, was also a philosopher who was completely awestricken by the infinite. One of his “thoughts,” or “pensées,” which he used to scribble on little slips of paper stowed away in his pockets, states: “For after all, what is man in nature? A nothing in relation to infinity, all in relation to nothing, a central point between nothing and all, and infinitely far from understanding either” (Pensées 72). I feel that way when thinking about the brain, with its infinite cells, signals, biochemical processes, thoughts, emotions. In complexity and beauty, it can only be compared with the Universe itself, with its trillion upon trillions of asteroids, planets, nebulae and galaxies, and mysterious dark matter. Our latest models of the brain involve...
mathematical-computational theories, which only take into account time and space, and are probably already obsolete. Future models will probably need to include a fourth, a fifth, or even more dimensions. What we now need is a paradigm shift, a quantum leap in our understanding of how the brain works. We need a new Claude Bernard, the father of experimental medicine who introduced the revolutionary concept of “milieu intérieur” to explain how the body’s organs communicate with each other to ensure homeostasis. We need a new Einstein, a new Heisenberg, a new Schrödinger, whose relativistic and quantum mechanics theories completely superseded Newtonian physics and transformed our grasp of reality. My dream is that the ICM will one day produce such a person!

La neuroscience française à l’honneur : l’ICM prend son départ

L’Institut du Cerveau et de la Moelle Épinière (ICM) est une Fondation privée reconnue d’utilité publique, dont les activités débuteront à l’automne 2010. Fondé par trois médecins français de réputation mondiale, Yves Agid, Professeur en neurologie et neurosciences ; Olivier Lyon-Caen, Professeur en neurologie ; et Gérard Saillant, Professeur en chirurgie orthopédique et traumatologique, l’ICM est un projet pilote novateur et ambitieux implanté au cœur du CHU Pitié-Salpêtrière à Paris, le plus grand hôpital français et l’un des tout premiers centres mondiaux pour la prise en charge des maladies du système nerveux. L’ICM fournira à plus de 600 chercheurs et techniciens, recrutés dans le monde entier, un cadre et des équipements à la pointe du progrès. L’ICM veut contribuer à améliorer l’efficacité de la recherche en neurosciences en favorisant la recherche translationnelle intégrant des domaines aussi variés que la biologie moléculaire et cellulaire, la neurophysiologie, et les sciences cognitives. Il se fixe comme but d’apporter des réponses concrètes tant sur le plan de la connaissance fondamentale que sur celui de la thérapeutique, afin de soulager, guérir, prévenir et réparer les affections du cerveau et de la moelle épinière. L’ICM fonctionnera en étroite collaboration avec l’Hôpital de la Pitié-Salpêtrière, qui mettra à sa disposition ses richesses inestimables en registres de malades, et ses collections d’échantillons de tissus, de cellules et d’ADN. L’ICM tissera également des liens étroits avec des partenaires institutionnels et industriels, tout en s’ouvrant largement au grand public à travers diverses manifestations scientifiques et culturelles. Les maladies du système nerveux touchent actuellement 1 personne sur 8 en Europe, et leur incidence est en croissance. L’une des priorités de l’ICM sera de trouver des traitements destinés à freiner l’évolution et à guérir des maladies neurodégénératives telles la maladie d’Alzheimer, la maladie de Parkinson et la sclérose latérale amyotrophique ainsi qu’à aider les victimes d’atteintes traumatiques de la moelle épinière à récupérer une fonction motrice adéquate.
Instructions for authors

General instructions

◆ Manuscripts should be provided by e-mail or CD double-spaced, with 2.5-cm margins. Pages must be numbered. Standard typed page = 25 lines of 90 characters (including spaces) double-spaced, 2.5-cm margins = a total of about 320 words per page.

◆ All texts should be submitted in English.

◆ Provide 1 color photograph of main author.

◆ On the title page, provide: a title (concise and informative); full names of authors (first name, middle name initial, and last name); highest academic degrees (in country-of-origin language); affiliations (names of department[s] and institution[s] at the time the work was done); a short running title (no more than 50 letters and spaces); keywords (5-10); corresponding author’s complete mailing address and telephone No., fax No., and e-mail address; acknowledgments (on title page, or at end of main text).

◆ Include an Abstract of 200-230 words for all texts except Editorials and replies to the Controversial Question.

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