Hypertension and cardiovascular prevention: where are combinations going?

EDITORIAL

377  Hypertension management: achievements and further needs
    Prise en charge de l’hypertension : acquis et perspectives
    G. Mancia, Italy

THEMED ARTICLES

385  Why do we need antihypertensive combinations?
    R. E. Schmieder, Germany

395  Antihypertensive combinations: what is missing?
    J. Blacher, France

403  When more than two drugs are needed to further decrease blood pressure
    A. Greenstein, K. Khavandi, T. Heagerty, United Kingdom

411  Treating both hypertension and dyslipidemia: a synergistic approach
    N. R. Poulter, United Kingdom

418  Antihypertensive treatment in ischemic heart disease: is there an ideal pill?
    E. V. Shlyakhto, Russia

426  Is fixed-combination antihypertensive therapy needed in post-stroke patients?
    J. Chalmers, H. Arima, Australia

433  Which patients should benefit from ACE inhibitor–β-blocker therapy?
    K. Amosova, Ukraine
CONTROVERSIAL QUESTION

Multiple-drug combinations in hypertension and cardiovascular prevention: should they be used in primary or secondary prevention?

COVERAM

Optimizing combination therapy for cardiovascular protection: evidence from landmark trials
N. Clavreul, France

INTERVIEW

Combinations in hypertension and cardiovascular prevention: are they additive or synergistic?
S. Taddei, Italy

UPDATE

Can genetics influence the choice of antihypertensive combination therapy?
P. Hamet, J. Tremblay, Canada

A TOUCH OF FRANCE

Claude Bernard (1813-1878) and experimental medicine.
“Physiology, physiology, it’s in me…”
C. Régnier, France

The Théâtre des Champs Elysées: the venue that launched a masterpiece
D. Marsh, France
Modern medicine owes much to research on hypertension. To mention a few contributions, studies on hypertension have discovered that elevated blood pressure (BP) is associated with an increased incidence of cardiovascular (CV) and renal morbid or fatal events. These findings cancelled the previous belief that high BP is a compensatory phenomenon that preserves vital organ perfusion against a primitive thickening of the small arteries, and they prompted the start of research on risk factors, which then led to a progressively more accurate quantification of CV risk. Furthermore, in the attempt to discover the cause—or causes—of BP elevation, research on hypertension has substantially contributed to the identification of a variety of systems involved in CV control, among which the neural and renin-angiotensin-aldosterone systems. Finally, through extensive use of randomized controlled trials, hypertension research has been able to prove that the risk associated with BP elevation is not irreversible, which means that when BP is reduced by treatment, so is the incidence of the hypertension-related CV and renal complications, this being the case in both sexes and at virtually all ages, including those above 80 years. However, despite many decades of research and discoveries, several issues related to hypertension have not yet been resolved. This editorial will address some of these unresolved issues.

Residual risk in treated hypertensive patients

As mentioned above, reducing BP by treatment is associated with a reduction in the risk of CV (stroke, coronary heart disease, and heart failure) or renal (end-stage renal disease) morbid or fatal events, the beneficial effects being proportional to the magnitude of the BP reduction to systolic and diastolic BP values below 140 mm Hg and 85 mm Hg, respectively. However, even when BP is effectively reduced, and control achieved, the CV risk remains substantially higher than that of normotensive individuals matched for age, sex, and other demographic and clinical characteristics. This is also the case for renal events, as shown by the observation in patients with diabetic or nondiabetic nephropathy, the rate of renal deterioration remains much greater than in the control population, even when antihypertensive treatment has been optimized.

Several hypotheses have been made to try to understand the reasons for the high residual risk exhibited by well-treated hypertensives. The possibility cannot be excluded that in hypertension, CV and renal risks are at least in part irreversible, perhaps because of a genetic component unrelated to, or independent of, BP values. It is also possible, however, that the treatment of hypertension does not pay suffi-
cient attention to (i) additional risk factors, eg, those generated by alterations in lipid and glucose metabolism, which are much more common in individuals in whom BP is high than in those in whom it is normal; (ii) the failure to consistently reduce BP over time, given the documented relationship between on-treatment visit-to-visit BP variability and CV risk; and/or (iii) the inability to effectively reduce BP values of recognized prognostic importance, such as those measured over 24 hours or at home, which are more difficult to control.

A final attractive hypothesis is that the high residual risk of well-treated hypertensive patients depends on the fact that treatment often starts too late, ie, when organ damage is already present and no longer entirely reversible. This is supported by the observation in the PAMELA population study (Pressioni Arteriose Monitorate E Loro Associazioni) that in treated hypertensive patients, echocardiographic left ventricular hypertrophy (ie, cardiac organ damage)—although less common when BP control was achieved than when it was not achieved—never returned to the prevalence seen in the normotensive control population, this being the case also when presence or absence of BP control was determined by out-of-office BP values (Figure 1). This implies that, in order to reduce residual risk, earlier initiation of antihypertensive treatment may be necessary. It further implies that treatment initiation may have to be guided by detection of asymptomatic organ damage rather than just BP, and that changes in asymptomatic organ damage may also have to be used to measure the effects of treatment.

**Which targets for antihypertensive treatment?**

Antihypertensive treatment aims at reducing BP to values that have been shown to maximize CV and renal protection in randomized controlled trials, currently believed to be between 140 and 130 mm Hg systolic and 90 to 80 mm Hg diastolic. How should CV and renal protection be established is a debated question, however. Several investigators, as well as virtually all regulatory agencies, maintain that the CV benefits of antihypertensive treatment must be established by a reduction in the incidence and risk of the so-called “hard end points,” such as stroke and myocardial infarction, because these events are reliably diagnosed and their clinical significance is obvious. However, this means that only patients capable of generating a sufficient number of events—ie, those at high risk—can be studied, leaving the question of whether, and to what extent, BP-lowering interventions can be beneficial in young or otherwise low-to-moderate risk individuals unaddressed. Expanding the number and type of end points that can be accepted as a measure of benefit is therefore a crucial aspect of future research on antihypertensive treatment. The process was started by including as end points such events as incipient heart failure and revascularization procedures, although diagnosis of incipient heart failure can be difficult and revascularization procedures are variably affected by health care policies in different countries and hospitals. It will have to continue by also considering regression or delayed progression of asymptomatic organ damage as demonstrations of a treatment-dependent benefit. This will, in turn, make it possible to suitably address the following questions of fundamental importance for public health: (i) are BP lowering interventions protective in the most common form of hypertension, ie, in individuals with mild BP elevation who are at relatively low CV risk? (ii) do BP reductions have a beneficial effect in subjects with a BP in the high normal range, in whom the CV risk profile is often suboptimal and the risk of developing hypertension much higher than in the remaining normotensive population? (iii) can basing treatment initiation and targets on initial and subsequent changes in asymptomatic organ damage lead to a more complete CV protection and a lower residual risk than taking only BP as a target?

**Which measures of organ damage?**

In order to be considered as a marker of the beneficial effects of antihypertensive treatment, measures of organ damage should fit a number of requirements. The marker should reflect a type of damage that is frequently associated with BP elevation. Alterations in organ function and/or structure should be reproduced in a sensitive and consistent fashion. Measures should be obtained in a relatively short time, at low cost, and with no need for excessive specialization of the operator. Most importantly, however, there should be evidence that, in hypertension—and possibly also in the general population—a marker has a prognostic value, ie, that it reflects increased incidence and increased risk of clinical events in a proportional manner. This should also be the case for treatment-induced...
changes. At present, many markers of organ damage have been shown to be prognostically relevant; while as far as treatment-induced changes are concerned, a correlation with the incidence and risk of CV mortality and morbidity has only been documented (with few important exceptions, however) for urinary protein excretion, glomerular filtration rate, and echocardiographic or electrocardiographic estimates of left ventricular mass or hypertrophy.\(^{13-16}\) Treatment-induced changes in arterial stiffness have also been related to CV events but in one small study only.\(^{17}\)

Much more validating research thus needs to be done before use of organ damage measures can be safely recommended as a proxy of the protective effect of antihypertensive treatment. Research in this direction is worthwhile, however, because the concept has a strong pathophysiological rationale, which is that clinical events are always preceded by asymptomatic organ damage. Put in a different way, there cannot be a clinically manifest event in a healthy organ perfused by healthy arteries.

**BP control and combination treatment**

One of the major problems faced by antihypertensive treatment is the low rate of BP control in the hypertensive population, with the percentage of hypertensive individuals with BP values less than 140/90 mm Hg rarely exceeding 20%-30% of the patients with BP elevation.\(^{18}\) Given the well-documented high CV risk of patients with uncontrolled BP,\(^{19}\) this low rate of control is responsible for the persistent position of hypertension as the first cause of death worldwide.\(^{20}\)

The reasons why only a limited number of hypertensive patients achieve BP control in real life can be ascribed to deficiencies of the healthcare systems, the failure of physicians to change treatment when BP is not controlled (clinical inertia), and the low adherence of patients to the prescribed treatment regimen. Clinical inertia is common\(^{21}\) and often consists in the failure to move from monotherapy to the combination of two or three antihypertensive drugs when BP is not adequately controlled (Figure 2).\(^{22}\) However, there is overwhelming evidence that (i) as BP is a multiregulated variable, administration of two or more antihypertensive drugs with different and complementary mechanisms of action exerts a much greater antihypertensive effect than monotherapy,\(^{23}\) and that (ii) while a single drug can control BP in no more than 1 out of 4 or 5 patients,\(^{24}\) two drugs can be successful in 60% of hypertensive individuals, and three drugs in 80% to 90%.\(^{25}\) This implies that the goal of achieving BP control in a much greater fraction of the hypertensive population will only be achieved by substantially increasing the currently low use of combination treatment in clinical practice.

Should combination treatment be used as a first step and in a fixed-dose single tablet format? Single tablet fixed-dose combinations are very popular because reducing the number of daily tablets has been shown to improve adherence to treatment\(^{26}\) and promote BP control.\(^{26}\) Furthermore, the recommendation of hypertension guidelines to consider combinations of two drugs for treatment initiation in hypertensive patients with a high CV risk,\(^{1}\) although never addressed by randomized controlled trials, has recently found support from the observation that its adoption in real life is associated with reduced treatment discontinuation rates\(^{27}\) as well as a 25% reduced risk of hospitalization for cerebrovascular and coronary events.\(^{28}\) Thus, a more widespread use of fixed-dose combinations of drugs for treatment initiation may further improve the treatment of hypertension.

![Figure 2. Use of monotherapy and combination therapy to achieve blood pressure (BP) targets (<140/90 mm Hg, or <130/80 mm Hg in diabetics) in patients under GP care.](image)

*In about 37% of the patients, the treatment consisted of monotherapy.


**References**


**Keywords:** blood pressure control; hypertension; marker; organ damage; prognostic value; risk
La médecine moderne doit beaucoup aux recherches sur l'hypertension. Pour ne mentionner que quelques contributions, les études sur l'hypertension ont permis de découvrir qu’une augmentation de la pression artérielle (PA) était associée à une élévation de l’incidence des événements cardio-vasculaires (CV) et rénaux morbides ou mortels. Ces résultats ont démenti la théorie selon laquelle une augmentation de la PA était un phénomène de compensation préservant la perfusion des organes vitaux contre un épaississement primitif des petites artères, et ils ont suscité des recherches sur les facteurs de risque, qui ont conduit à une quantification progressivement plus exacte du risque CV. En outre, les recherches destinées à découvrir la cause – ou les causes – de l’élévation de la PA ont contribué de manière substantielle à l’identification d’un certain nombre de systèmes participant au contrôle CV, parmi lesquels les systèmes neuraux et rénine-angiotensine-aldostérone. Enfin, l’utilisation généralisée des essais randomisés contrôlés a permis à la recherche de démontrer que le risque associé à une élévation de la PA n’était pas irréversible, ce qui signifie que, lorsqu’un traitement permet de réduire les valeurs de la PA, il en va de même de l’incidence des complications CV et rénales liées à l’hypertension, pour les deux sexes et pratiquement pour toutes les tranches d’âge, y compris les patients âgés de plus de 80 ans1,2. Cependant, malgré plusieurs décennies de recherches et de découvertes, un certain nombre de questions liées à l’hypertension n’ont toujours pas trouvé de réponse. Cet éditorial porte sur quelques-uns de ces problèmes non résolus.

**Risque résiduel chez les patients hypertendus traités**

Comme il a été mentionné ci-dessus, la réduction de la PA par traitement est associée à une diminution du risque d’événements CV (accident vasculaire cérébral, coronaropathie et insuffisance cardiaque) ou rénaux (insuffisance rénale de stade terminal) morbides ou mortels, les effets bénéfiques étant proportionnels à l’amplitude de la réduction de la PA aux valeurs systoliques et diastoliques respectivement inférieures à 140 mm Hg et 85 mm Hg1,2. Cependant, même lorsque la PA est efficacement réduite, et qu’un contrôle est obtenu, le risque CV reste substantiellement supérieur à celui des individus normotendus appariés selon l’âge, le sexe et les autres caractéristiques démographiques et cliniques3,4. Cela est également le cas pour le risque d’événements rénaux, comme le montre le fait que, chez les patients atteints de néphropathie diabétique ou non diabétique, le taux de détérioration rénale (ainsi que l’incidence de l’insuffisance rénale et de la dialyse) reste très supérieur à celui de la population témoin, même lorsque le traitement antihypertenseur a été optimisé vis-à-vis des valeurs cibles de la PA et des antihypertenseurs utilisés5.
Plusieurs hypothèses ont été formulées pour tenter de comprendre pourquoi les patients hypertendus traités de manière satisfaisante ont un risque résiduel élevé. Il n’est pas exclu que dans l’hypertension, les risques CV et rénaux soient au moins en partie irréversibles, probablement à cause d’une composante génétique non liée à, ou indépendante des valeurs de la PA. Il est cependant également envisageable que le traitement de l’hypertension ne prenne pas suffisamment en compte (i) les facteurs de risque supplémentaires, par exemple ceux induits par des altérations du métabolisme des lipides et du glucose, qui sont beaucoup plus fréquents chez les personnes présentant une PA élevée que chez celles ayant une PA normale; (ii) l’incapacité de réduire la PA avec le temps, compte tenu de la relation documentée entre les fluctuations de la PA sous traitement et les visite et le risque CV; 7,8 et/ou (iii) l’impossibilité de réduire efficacement les valeurs de la PA présentant une importance pronostique reconnue, notamment en partie irréversibles. Cela est confirmé par l’observation effectuée au cours de l’étude de population PAMELA (Pressioni Arteriose Monitorate E Loro Associazioni) montrant que, chez les patients hypertendus traités, l’hypertrophie ventriculaire gauche (une lésion cardiaque) mise en évidence à l’échocardiographie – bien qu’elle soit moins fréquente avec une PA contrôlée que lorsque celle-ci ne l’est pas – n’est jamais revenue à la prévalence observée dans la population témoin normotendue, cela étant observé également lorsque le contrôle de la PA (ou l’absence de contrôle) a été estimé par des valeurs mesurées en dehors du cabinet médical (Figure 1). 9,10 Par conséquent, pour réduire le risque résiduel, une initiation plus précoce au traitement antihypertenseur peut être nécessaire. Cela conduit également à penser que la mise en place du traitement peut devoir être guidée par la détection de lésions organiques asymptomatiques plutôt que par les seules valeurs de la PA, et que les changements intervenant au niveau des lésions organiques asymptomatiques pourraient également être utilisés pour mesurer les effets du traitement.

**Figure 1.** Prévalence de l’hypertrophie ventriculaire gauche mise en évidence par échocardiographie chez des patients normotendus, des patients hypertendus traités avec une pression artérielle non contrôlée et des patients hypertendus traités avec une pression artérielle contrôlée dans la population de l’étude PAMELA.

Le contrôle de la pression artérielle a été déterminé par des valeurs de la PA mesurées au cabinet médical, à domicile ou sur 24 heures.

**Abréviations:** PA, pression artérielle ; HT, hypertendu ; HVG, hypertrophie ventriculaire gauche ; NT, normotendu ; PAMELA, Pressioni Arteriose Monitorate E Loro Associazioni.


**ÉDITORIAL**

Néanmoins, une dernière hypothèse séduisante suppose que le risque résiduel élevé des patients hypertendus bien traités dépend d’un début trop tardif du traitement, c’est-à-dire lorsque des lésions organiques sont déjà présentes et qu’elles ne sont plus entièrement réversibles. Cela est confirmé par l’observation effectuée au cours de l’étude de population PAMELA (Pressioni Arteriose Monitorate E Loro Associazioni) pour laquelle le traitement antihypertenseur doit être établi par une réduction de l’incidence et du risque de ce qu’il est convenu d’appeler les « critères durs », notamment l’accident vasculaire cérébral et l’infarctus du myocarde, dans la mesure où ces événements peuvent être diagnostiqués de manière fiable et que leur signification clinique est évidente. Cependant, cela signifie que seuls les patients susceptibles de présenter un nombre suffisant d’événements – c’est-à-dire, les patients à haut risque – peuvent être étudiés, en négligeant la question de savoir si, et dans quelle mesure, les mesures antihypertensives peuvent être bénéfiques à des sujets jeunes ou exposés à un risque faible à modéré. Augmenter le nombre et le type de paramètres pouvant être acceptés comme critères d’évaluation du bénéfice constitué par conséquent un aspect essentiel des futures recherches sur les traitements antihypertenseurs. Cette dynamique a commencé en incluant comme critère d’évaluation des événements comme l’insuffisance cardiaque débutante et les procédures de revascularisation, bien que le diagnostic de l’insuffisance cardiaque débutante soit difficile à établir et que les procédures de revascularisation puissent varier selon les politiques de soins de santé dans les différents pays et les différents établissements hospitaliers. Il faudra également prendre en compte la régression ou la progression retardée des lésions organiques asymptomatiques comme preuve d’un bénéfice thérapeutique. Il sera ainsi possible de répondre de manière adéquate aux questions suivantes, fondamentales pour la santé publique : (i) les mesures antihypertensives apportent-elles une protection dans la forme la plus...
fréquente d’hypertension, c’est-à-dire chez les sujets présentant une élévation modérée de la PA et exposés à un risque CV relativement faible ? (ii) La réduction de la PA a-t-elle un effet bénéfique chez les sujets dont la PA se situe à la limite supérieure de l’intervalle normal, chez lesquels le profil de risque CV est souvent sous-optimal et le risque de développer une hypertension plus élevée que dans le reste de la population normotendue ? (iii) Baser le début du traitement et les valeurs cibles sur les changements initiaux et ultérieurs des lésions asymptomatiques des organes, au lieu de se limiter uniquement à la PA comme cible thérapeutique, peut-il conduire à une protection CV plus complète et à une diminution plus importante du risque résiduel ?

Comment mesurer les lésions organiques ?
Pour les considérer comme des marqueurs des effets bénéfiques du traitement antihypertenseur, les mesures des lésions organiques doivent répondre à un certain nombre d’exigences. Le marqueur doit refléter un type de lésion fréquemment associée à une élévation de la PA. Les altérations fonctionnelles et/ou structurelles des organes doivent pouvoir être reproduites de manière sensible et constante. Les mesures doivent être obtenues relativement rapidement, à faible coût et sans nécessité de spécialisation excessive pour l’opérateur. Plus important encore, des preuves doivent montrer que, dans l’hypertension – et le cas échéant également dans la population générale – un marqueur montre une valeur pronostique, c’est-à-dire qu’il reflète l’augmentation de l’incidence et du risque d’événements cliniques de manière proportionnelle. Cela doit également être le cas des changements induits par le traitement. À l’heure actuelle, de nombreux marqueurs des lésions organiques se sont avérés significatifs sur le plan pronostique ; tandis qu’en ce qui concerne les changements induits par le traitement, une corrélation avec l’incidence et le risque de mortalité et de morbidité CV n’a été documentée (avec quelques exceptions importantes, cependant) que pour l’excrétion des protéines urinaires, le taux de filtration glomérulaire et les estimations de la masse ou de l’hypertrophie ventriculaire gauche par échocardiographie ou électrocardiographie. Un rapport a été établi entre les changements induits par le traitement dans la rigidité artérielle et les événements CV, mais seulement dans une petite étude. Un nombre très supérieur d’études de validation doit donc être effectué avant que les mesures des lésions organiques puissent être recommandées de manière sûre comme substitut de l’effet protecteur du traitement antihypertenseur. Les recherches dans cette voie sont néanmoins nécessaires, car le concept repose sur la forte justification physiopathologique suivante : les événements cliniques sont toujours précédés par des lésions organiques asymptomatiques. En d’autres termes, un événement cliniquement manifeste ne peut pas survenir dans un organe sain perfusé par des artères saines.

Contrôle de la PA et associations thérapeutiques
L’un des problèmes majeurs qui caractérise le traitement antihypertenseur est le faible taux de contrôle de la PA dans la population hypertendue. Le faible taux de contrôle de la PA est donc un facteur majeur de décès à travers le monde.,

Les raisons pour lesquelles, dans la pratique, le contrôle de la PA n’est atteint que chez un nombre limité de patients hypertendus peuvent être imputées aux déficiences des systèmes de soins de santé, au fait que les médecins ne changent pas le traitement lorsque la PA n’est pas contrôlée, ainsi que (i) l’incidence et du risque d’événements cliniques est-t-elle plus importante du risque résiduel ?

La réduction de la PA a-t-elle un effet bénéfique chez les sujets dont la PA se situe à la limite supérieure de l’intervalle normal, chez lesquels le profil de risque CV est souvent sous-optimal et le risque de développer une hypertension plus élevée que dans le reste de la population normotendue ? (iii) Baser le début du traitement et les valeurs cibles sur les changements initiaux et ultérieurs des lésions asymptomatiques des organes, au lieu de se limiter uniquement à la PA comme cible thérapeutique, peut-il conduire à une protection CV plus complète et à une diminution plus importante du risque résiduel ?

Comment mesurer les lésions organiques ?
Pour les considérer comme des marqueurs des effets bénéfiques du traitement antihypertenseur, les mesures des lésions organiques doivent répondre à un certain nombre d’exigences. Le marqueur doit refléter un type de lésion fréquemment associée à une élévation de la PA. Les altérations fonctionnelles et/ou structurelles des organes doivent pouvoir être reproduites de manière sensible et constante. Les mesures doivent être obtenues relativement rapidement, à faible coût et sans nécessité de spécialisation excessive pour l’opérateur. Plus important encore, des preuves doivent montrer que, dans l’hypertension – et le cas échéant également dans la population générale – un marqueur montre une valeur pronostique, c’est-à-dire qu’il reflète l’augmentation de l’incidence et du risque d’événements cliniques de manière proportionnelle. Cela doit également être le cas des changements induits par le traitement. À l’heure actuelle, de nombreux marqueurs des lésions organiques se sont avérés significatifs sur le plan pronostique ; tandis qu’en ce qui concerne les changements induits par le traitement, une corrélation avec l’incidence et le risque de mortalité et de morbidité CV n’a été documentée (avec quelques exceptions importantes, cependant) que pour l’excrétion des protéines urinaires, le taux de filtration glomérulaire et les estimations de la masse ou de l’hypertrophie ventriculaire gauche par échocardiographie ou électrocardiographie. Un rapport a été établi entre les changements induits par le traitement dans la rigidité artérielle et les événements CV, mais seulement dans une petite étude. Un nombre très supérieur d’études de validation doit donc être effectué avant que les mesures des lésions organiques puissent être recommandées de manière sûre comme substitut de l’effet protecteur du traitement antihypertenseur. Les recherches dans cette voie sont néanmoins nécessaires, car le concept repose sur la forte justification physiopathologique suivante : les événements cliniques sont toujours précédés par des lésions organiques. En d’autres termes, un événement cliniquement manifeste ne peut pas survenir dans un organe sain perfusé par des artères saines.

Contrôle de la PA et associations thérapeutiques
L’un des problèmes majeurs qui caractérise le traitement antihypertenseur est le faible taux de contrôle de la PA dans la population hypertendue. Le pourcentage de sujets hypertendus présentant des valeurs de la PA inférieures à 140/90 mm Hg ne dépassant que rarement 20 % à 30 % des patients hypertendus. Compte tenu du risque CV très supérieur et bien documenté auquel sont exposés les patients présentant une PA non contrôlée, ce faible taux de contrôle est à l’origine de la place constante de l’hypertension comme première cause de décès à travers le monde. Les raisons pour lesquelles, dans la pratique, le contrôle de la PA n’est atteint que chez un nombre limité de patients hypertendus peuvent être imputées aux déficiences des systèmes de soins de santé, au fait que les médecins ne changent pas le traitement lorsque la PA n’est pas contrôlée (inertie clinique) et à la faible observance par les patients du traitement pres-
d’atteindre un contrôle de la PA chez un pourcentage très supérieur de la population hypertendue ne pourra être atteint qu’en augmentant de manière substantielle l’utilisation, actuellement insuffisante, des associations thérapeutiques en pratique clinique.

Une association thérapeutique doit-elle être utilisée en première instance et sous forme d’un comprimé unique à dose fixe ? Les associations sous forme de comprimé unique à dose fixe sont très populaires, car il a été montré que la réduction du nombre de comprimés par jour améliorait l’observance du traitement et favorisait le contrôle de la PA. En outre, la recommandation des directives sur l’hypertension préconisant d’envisager une association de deux médicaments comme traitement initial chez des patients hypertendus présentant un risque CV élevé, bien qu’elle n’ait jamais été traitée au cours d’essais randomisés contrôlés, a récemment été étayée par l’observation selon laquelle son application en pratique réelle est associée à une réduction des taux d’interruption du traitement et à une diminution de 25 % du risque d’hospitalisation pour événements vasculaires cérébraux et coronaires. Par conséquent, une utilisation plus large des associations à dose fixe de comprimés en traitement initial permettrait d’améliorer le traitement de l’hypertension.
Why do we need antihypertensive combinations?

by R. E. Schmieder, Germany

Hypertension is a worldwide problem and the leading cause of mortality. Most hypertensive patients have additional cardiovascular risk factors or diseases. In most of these patients, more than one antihypertensive drug is necessary to achieve goal levels of blood pressure. Data from several hypertension management clinical trials have shown that on average two or more antihypertensive agents are needed to reach current blood pressure targets. As physiological and pharmacological synergies result in more effective drug combinations, guidelines recommend adding a drug from another class to the initially prescribed drug. According to the European Society of Hypertension and the European Society of Cardiology guidelines, the most rational antihypertensive combinations are combinations involving angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers (CCBs), angiotensin II receptor blocker (ARBs), and thiazide (-like) diuretics. The combination of an ACE inhibitor with the thiazide-like diuretic indapamide has been shown to be effective in lowering blood pressure and preventing or reducing cardiovascular morbidity in many trials, such as STRATHE (Strategies of Treatment in Hypertension: Evaluation), PROGRESS (Perindopril pROtection aGainst Recurrent Stroke Study), HYVET (HYpertension in the Very Elderly Trial), PICXEL (Perindopril/Indapamide in a Double-Blind Controlled Study versus Enalapril in Left Ventricular Hypertrophy), REASON (PREterax in Regression of Arterial Stiffness in a ContrOlled Double-BliNd study), LIFE (Losartan Intervention For Endpoint reduction in hypertension), and ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation). Likewise, the combination of an ACE-inhibitor and a CCB has been tested in trials like EUROPA (EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease), ASCOT-BLA (Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure–Lowering Arm), or ACCOMPLISH (Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension) and there is evidence of beneficial effects in the prevention of cardiovascular events and new-onset diabetes, or rehabilitation after stroke. Thus, combination therapy should be individualized according to the comorbidities of hypertensive patients.
Hypertension is a worldwide problem and the leading cause of mortality. In 2001, it was estimated that 7.6 million premature deaths and 92 million disability-adjusted life years could be attributed to high blood pressure (BP) worldwide. Most hypertensive patients have additional cardiovascular risk factors or diseases (eg, diabetes). As well as arterial stiffness, endothelial dysfunction, and atherosclerosis, high cholesterol, obesity, smoking, physical inactivity, and oxidative stress also contribute to an increase in systolic BP (SBP) with age, thereby accelerating the aging of the arteries and potentially causing ischemic heart disease and stroke.

Based on extensive prospective observational data, it was shown that both SBP and diastolic BP (DBP) have a strong and linear relationship with adverse cardiovascular events in all age groups. Although the relationship varies with age and sex, a 20-mm Hg difference in SBP or a 10-mm Hg difference in DBP is, on average, associated with a doubling of cardiovascular risk. Therefore, adequate BP control is considered to be essential in reducing this risk. The benefits of more aggressive therapeutic approaches in hypertension are especially pronounced in high-risk groups such as patients with diabetes mellitus or chronic kidney disease (CKD). Drugs that have been proven to be particularly useful in the treatment of elevated BP are calcium channel blockers (CCBs), thiazide(-like) diuretics and agents that target the renin-angiotensin system (RAS), ie, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs).

Management of hypertension

Improvement in cardiovascular outcomes and survival is the ultimate goal of antihypertensive therapy. However, despite the wide range of available antihypertensive drugs, the management of hypertension remains insufficient. About 30% of hypertensive individuals are unaware of their condition and receive no treatment at all. Of the remaining 70% who do, only 34% achieve the recommended target of SBP <140 mm Hg and DBP <90 mm Hg. This is of concern because of the proven benefits of reducing BP, which translate into reductions in the incidence of myocardial infarction (MI) (20%-25%), heart failure (>50%), and stroke (35%-40%).

Large clinical trials have demonstrated that adequate BP control can be achieved and sustained in most patients with hypertension only with the use of multiple antihypertensive drugs. Both the European Guidelines (ESH-ESC 2007 and ESH-ESC 2013) and the American Guidelines (JNC 7) recommend that a significant proportion of hypertensive patients—in fact, the majority of patients—receive treatment with two or more drugs.

The objective of the study of Corrao et al was to assess whether antihypertensive combination therapy provides greater cardiovascular protection in daily clinical practice. This population-based study was carried out in a cohort of 209 650 patients aged 40 to 79 who were newly treated with antihypertensive drugs. Patients who were started on combination therapy had an 11% reduction in cardiovascular risk compared with those who received monotherapy. This was also

**Selected acronyms**

| ACOMPLISH | Avoiding Cardiovascular events in COMbination therapy in Patients Living with Systolic Hypertension (trial) |
| ADVANCE | Action in Diabetes and Vascular disease: PreteAx and DiamicroN MR Controlled Evaluation (trial) |
| ASCOT-BPLA | Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure–Lowering Arm |
| CAFE | Conduit Artery Function Evaluation |
| EUROPA | EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease |
| HYVET | HYPertension in the Very Elderly Trial |
| LIFE | Losartan Intervention For Endpoint reduction in hypertension |
| NHANES | National Health And Nutrition Examination Survey |
| PICXEL | Perindopril/Indapamide in a double-blind Controlled study versus Enalapril in Left ventricular hypertrophy |
| PREMIER | PREterax in albuMinuria rEgResion |
| PROGRESS | Perindopril/pR0tection aGainst Recurrent Stroke Study |
| REASON | PREterax in Regression of Arterial Stiffness in a Controlled Double-Blind study |
| STRATHE | Strategies of Treatment in Hypertension: Evaluation |
| TRINITY | The T RIple therapy with olmesartan medoxomil, amlodipine, and hydrochlorothiazide in hypertensive patients study |

**Selected abbreviations**

- **ACE**: angiotensin-converting enzyme
- **ARB**: angiotensin II receptor blocker
- **BP**: blood pressure
- **CAD**: coronary artery disease
- **CCB**: calcium channel blocker
- **CKD**: chronic kidney disease
- **CV**: cardiovascular
- **DBP**: diastolic blood pressure
- **HCTZ**: hydrochlorothiazide
- **LVH**: left ventricular hypertrophy
- **LVM**: left ventricular mass
- **MI**: myocardial infarction
- **RAS**: renin-angiotensin system
- **SBP**: systolic blood pressure
the case for coronary (-8%) and cerebrovascular (-12%) events, when considered separately. In a study by Neutel et al., combination therapy showed greater efficacy than high doses of the individual agents in increasing arterial compliance and reducing left ventricular mass. Furthermore, a meta-analysis of 42 factorial trials of antihypertensive agents (10,968 patients) showed that combining drugs from two different classes is approximately fivefold more effective than doubling the dose of one drug. Compared with patients who received monotherapy during follow-up, those who were started on combination therapy and remained on it for the entire period of observation had a 26% reduction in cardiovascular risk. As such, the indication for using a combination of BP drugs should be broadened.

Treatment with a two-drug antihypertensive combination is especially recommended in high risk patients to minimize the development or progression of target organ damage or vascular complications, and also in patients with stage 2 hypertension. The JNC 7 guidelines recommend initial combination therapy when BP is >20/10 mm Hg above goal BP. Moreover, results from controlled clinical trials have shown that two or more antihypertensive drugs are required for most hypertensive patients to achieve BP control. The recommendation for a combination of two agents as initial therapy is reflected in current hypertension guidelines, including the consensus statement by the Hypertension in African Americans Working Group (HAAWG), the Guidelines of the Task Force for the Management of Arterial Hypertension, and JNC 7. Antihypertensive combinations offer the possibility of combining agents with different pharmacological profiles to achieve additive effects with enhanced tolerability. The US National Health and Nutrition Examination Survey (NHANES) recommends the use of two or more drug classes to achieve the goal of BP control.

Compliance – the importance of treatment adherence

Compliance represents a major problem in hypertension because of the asymptomatic nature of this chronic disease (at least at the onset), and because in the majority of patients, more than one agent is required to achieve BP targets. Compared with free combinations, fixed-dose combinations offer better treatment adherence because the treatment regimen is simplified. Two meta-analyses reported reductions in noncompliance of 26% and 21%, respectively, with fixed-dose combinations compared with a regimen of the same two agents given separately. A further advantage of combination therapy is the ability to reach BP control more rapidly than with monotherapy or free-combination, due to its expected positive impact on compliance, which should improve long-term clinical outcomes.

### Table 1. Preferred drugs according to clinical conditions in the 2007 ESH/ESC Guidelines.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Preferred Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISH (elderly)</td>
<td>diuretic, CA</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>ACE inhibitor, ARB, CA</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>ACE inhibitor, ARB</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>CA, methyldopa, β-blocker, diuretic, CA</td>
</tr>
<tr>
<td>Blacks</td>
<td></td>
</tr>
<tr>
<td>Subclinical organ damage</td>
<td></td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>ACE inhibitor, CA, ARB</td>
</tr>
<tr>
<td>Asymptomatic atherosclerosis</td>
<td>CA, ACE inhibitor</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>ACE inhibitor, ARB</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>ACE inhibitor, ARB</td>
</tr>
<tr>
<td>Clinical event</td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td>any BP-lowering agent</td>
</tr>
<tr>
<td>Previous MI</td>
<td>β-blocker, ACE inhibitor, ARB</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>β-blocker, CA</td>
</tr>
<tr>
<td>Heart failure</td>
<td>diuretic, β-blocker, ACE inhibitor, ARB, aldosterone agent</td>
</tr>
<tr>
<td>Atrial fibrillation (recurrent)</td>
<td>ARB, ACE inhibitor</td>
</tr>
<tr>
<td>Atrial fibrillation (permanent)</td>
<td>β-blocker, non-dihydropyridine CA</td>
</tr>
<tr>
<td>End-stage renal disease/proteinuria</td>
<td>ACE inhibitor, ARB, loop diuretic</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>CA</td>
</tr>
</tbody>
</table>

Abbreviations: ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor antagonist; CA, calcium antagonist; ISH, isolated systolic hypertension; MI, myocardial infarction.


Which antihypertensive combinations for which patients?

JNC7 is not specific as regards which drug combinations should be used but it does state that “thiazide-type” diuretics are often used as one of the components. According to the European Society of Hypertension and the European Society of Cardiology Guidelines, the most rational antihypertensive combinations are combinations involving ACE inhibitors, CCBs, ARBs, thiazide (-like) diuretics (ie, hydrochlorothiazide [HCTZ], chlorthalidone, or indapamide), depending on clinical conditions (Table I, and Figure 1 [page 388]).

The recently updated British Hypertension Society/National Institute for Health and Clinical Excellence (BHS/NICE) recommendations of 2011 show a simple algorithm. These recommendations are based on the fact that, on average, younger people have higher renin levels and respond better (in terms of BP reduction) to “A” drugs (ACE inhibitors or ARBs), whereas older people or black people of African origin tend to have lower renin levels and respond better in terms of BP reduction.
to “C” drugs (CCBs). When combination is required, “A+C” is recommended but if a diuretic is considered, in patients who are intolerant to CCBs for instance, use of thiazide-like diuretics such as indapamide is advised, as these drugs are safer than older drugs such as HCTZ.

Drug combinations and their studies

◆ RAS inhibition and thiazide-like diuretics

Inhibitors of the RAS, including ACE inhibitors and ARBs, have demonstrated efficacy in treating hypertension and preventing or reducing cardiovascular morbidity, such as strokes (Table II).

In the STRATHE trial (Strategies of Treatment in Hypertension: Evaluation), a randomized, controlled study in patients with uncomplicated essential hypertension, 9 months of treatment with perindopril/indapamide lowered SBP by 26.6 mm Hg and led to normalization of BP in 62% of patients.30 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 demonstrated in interventional studies, such as PROGRESS (Perindopril pROtection aGainst Recurrent Stroke Study), where the combination of the ACE inhibitor perindopril and the thiazide-like diuretic indapamide reduced the risk of stroke, MI, and heart failure in patients with previous stroke or transient ischemic attack (Table II).31

Beneficial effects on mortality have also been noted in elderly patients in the HYVET stroke trial.33 HYVET (Hypertension in the Very Elderly Trial) proved the benefits of effective BP reduc-

### Table II. Different antihypertensive combinations and their effects in cardiovascular and other end points in major clinical trials.

<table>
<thead>
<tr>
<th>Antihypertensive combination</th>
<th>Study</th>
<th>All-cause mortality</th>
<th>RR in diabetic complications</th>
<th>RR in CKD/ micro-albuminuria</th>
<th>RR in stroke/ TIA</th>
<th>RR in MI/ coronary events</th>
<th>RR in LVH/ heart failure</th>
<th>Cardiovascular mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perindopril + Indapamide</td>
<td>PROGRESS31</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>ADVANCE35</td>
<td>✓ (–14%)</td>
<td>✓ (–9%)</td>
<td>✓ (–21%)</td>
<td>NA</td>
<td>✓</td>
<td>✓</td>
<td>✓ (&lt;18%)</td>
</tr>
<tr>
<td></td>
<td>HYVET33</td>
<td>✓ (–21%)</td>
<td>NA</td>
<td>NA</td>
<td>✓ (–30%)</td>
<td>✓ (–64%)</td>
<td>✓ (–23%)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>PICXEL48</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>PREMIER46</td>
<td>NA</td>
<td>NA</td>
<td>✓ (–16%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>REASON49</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Losartan + HCTZ</td>
<td>LIFE51</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>✓</td>
<td>NA</td>
<td>✓</td>
<td>NA</td>
</tr>
<tr>
<td>Perindopril + Amlodipine</td>
<td>ASCOT-BPLA58</td>
<td>✓ (–11%)</td>
<td>✓</td>
<td>✓ (–23%)</td>
<td>✓ (–13%)</td>
<td>NA</td>
<td>✓ (–24%)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>ACCOMPLISH95</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>EUROPA57</td>
<td>✓ (–46%)</td>
<td>NA</td>
<td>NA</td>
<td>✓ (–28%)</td>
<td>✓ (–54%)</td>
<td>✓ (–41%)</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Abbreviations:** ACCOMPLISH, Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension; ADVANCE, Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation; ASCOT-BPLA, Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure–Lowering Arm; CKD, chronic kidney disease; EUROPA, European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease; HCTZ, hydrochlorothiazide, HYVET; Hypertension in the Very Elderly Trial, LIFE, Losartan Intervention For Endpoint reduction in hypertension; LVH, left ventricular hypertrophy; NA, not applicable; PICXEL, Perindopril/Indapamide in a Double-Blind Controlled Study versus Enalapril in Left Ventricular Hypertrophy; PREMIER, PREterax in albuminuria iEgRes1ion; PROGRESS, Perindopril pROtection aGainst Recurrent Stroke Study; REASON, PREterax in Regression of Arterial Stiffness in a Controlled Double-Blind study; RR, relative risk; TIA, transient ischemic attack.

**Figure 1. Recommended combinations of antihypertensive drugs.**

Panel A. Antihypertensive drug combinations recommended as preferred (thick lines) or possible (dash lines) in the 2007 ESH/ESC Guidelines. Panel B. The five combinations retained for priority use in the 2009 reappraisal of the 2007 ESH/ESC Guidelines. **Abbreviations:** ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; CCB, calcium channel blockers; ESC, European Society of Cardiology; ESH, European Society of Hypertension.

The choice of a combination should be based on systematic effects (ie, ACE-inhibitors/ARBs and thiazide [-like] diuretics) as well as on comorbidities and other cardiovascular risk factors (Table I) as specified by the ESH-ESC 2007 and 2013 guidelines.5,13

More recently, in the ADVANCE trial (Action in Diabetes and Vascular Disease),32 a fixed combination of perindopril/indapamide (4 mg/1.25 mg) was used for 4.3 years on top of standard antihypertensive therapy in both normotensive and hypertensive patients with type 2 diabetes mellitus.42 With a total of 11 140 patients, this was the largest trial ever carried out in this type of population. BP reduction was significantly greater with the perindopril/indapamide combination throughout the study: −15.6 mm Hg for SBP and −2.2 mm Hg for DBP.43 This effect was associated with a reduced incidence (~19%) of diabetes-related complications and a reduction in the incidence of coronary events and cardiovascular and all-cause death.42 Perindopril/indapamide reduced cardiovascular mortality by 18%, all-cause mortality by 14%, and new-onset microalbuminuria by 21% (Figure 2, Table II).32,44-46 With regard to treatment tolerability, this combination appeared well tolerated in more than 80% of patients. This result has important practical implications for health services delivery, since only one follow-up visit is needed to establish a patient’s suitability for long-term treatment with this regimen.32

The echocardiographic substudy of the ADVANCE trial demonstrated that treatment with perindopril and indapamide resulted in a reduction in left ventricular mass (LVM) over 4 years, but did not improve left ventricular diastolic function.43 The results of the ADVANCE study also showed that the reductions in relative cardiovascular risk, and diabetic and renal events achieved with a perindopril/indapamide combination were consistent among subgroups of patients with diabetes defined by CKD stage.42 As a mirror of their substantially increased cardiovascular risk, the aldosterone/renin ratio (ARR) was greater in patients with CKD stage ≥3, underlining the importance of early recognition of CKD in patients with diabetes and the value of this preventive therapy.42

Importantly, the diuretic used in the PROGRESS, ADVANCE, and HYVET trials (ie, indapamide) is a thiazide-like metabolically neutral diuretic compound that differs favorably from the widely used HCTZ in terms of metabolic effects and sustained 24-hour BP lowering. Consequently, it should be considered suitable for first-line therapy in hypertensive patients.47-51 This is further supported by evidence from clinical studies that examined the intermediate end points of hypertensive disease.
The beneficial effects of perindopril/indapamide treatment on renal function were also illustrated in the PREMIER trial (PREterax in albuminuria rEgRession), which enrolled 457 hypertensive patients with diabetes and albuminuria. Treatment with perindopril and indapamide for 1 year led to significant BP-independent reductions in albumin excretion rates compared with treatment with enalapril. Further analysis demonstrated a 16% increase in albuminuria regression.52

The PICXEL study (Perindopril/Indapamide in a double-blind Controlled study versus Enalapril in Left ventricular hypertrophy) compared the efficacy of a strategy based on first-line combination with perindopril and indapamide versus monotherapy with enalapril in reducing left ventricular hypertrophy (LVH) in hypertensive patients.30,34 In this 1-year multicenter study, patients received an increasing dose of perindopril, indapamide, or enalapril.34 SBP and DBP decreased significantly more in the perindopril/indapamide group than in the enalapril group.34 The authors concluded that, in hypertensive patients with LVH, a strategy based on first-line combination with perindopril and indapamide achieved a greater BP decrease with a significantly greater LVH reduction than a strategy based on monotherapy with enalapril.34

Further support for the role of perindopril comes from the REASON study (PREterax in Regression of Arterial Stiffness in a ContriOiled Double-BiINd).30 In this study comparing the antihypertensive effects of the combination of indapamide (0.625 mg)/perindopril (2 mg) with the β-blocking agent atenolol (50 mg), 214 patients with essential hypertension underwent two-dimensional guided M-mode echocardiography.30 Compared with atenolol, treatment with perindopril/indapamide improved arterial structure and stiffness. Patients with LVH showed the greatest LVM regression with a mean regression of 22.5 g after 12 months of treatment with perindopril and indapamide, compared with an 8.9-g regression after treatment with atenolol.53 Last but not least, the SBP reduction was found to be significantly greater with perindopril and indapamide than with atenolol (-21.2 vs -15.3 mm Hg).53

The LIFE study (Losartan Intervention For Endpoint reduction in hypertension) documented the cardiovascular protective effects of using a treatment strategy combining an ARB (losartan) with HCTZ in hypertensive patients with left LVH. In most patients, the combination of losartan with HCTZ was more effective than the combination of atenolol and HCTZ in the prevention of stroke but there were no differences between the two treatments regarding the reduction in coronary outcomes (Table II).

RAS inhibition and calcium channel blockers
There is already solid proof that the ACE inhibitor perindopril and the CCB amlodipine are effective as monotherapy for hypertension,54-58 and they have been available to physicians for many years. They are frequently prescribed in free combination in hypertension and stable coronary artery disease (CAD), particularly since the emergence of large clinical trials, such as EUROPA (EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease) or ASCOT-BPLA ( Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure–Lowering Arm).38

The fixed-combination of perindopril and amlodipine is a credible option in the field of stable CAD.5,10 Its efficacy was established in the EUROPA trial.30,32,60 In this trial, addition of perindopril to CCB significantly reduced total mortality by 46% and reduced the primary end point (a composite of cardiovascular mortality, nonfatal MI, and resuscitated cardiac arrest) by 35%.60 There were 41%, 54%, and 28% reductions in cardiovascular mortality, hospitalization for heart failure, and MI, respectively.61 This effect was independent of BP at baseline.

ASCOT-BPLA was the first clinical trial to demonstrate an effective reduction in mortality among hypertensive patients treated with a CCB in combination with a RAS inhibitor.38,60 ASCOT-BPLA included over 19,267 patients with hypertension and at least three or more prespecified cardiovascular risk factors. The trial compared the effect of a standard antihypertensive regimen (β-blocker/bendroflumethiazide–based regimen) versus a newer regimen of dihydropyridine CCB ± ACE inhibitor, respectively, amlodipine and perindopril. The newer regimen was clearly superior in terms of preventing cardiovascular events. This trial was stopped prematurely after a median of 5.5 years, because of significant beneficial effects on all-cause mortality associated with allocation to the amlodipine/perindopril–based regimen.52 A significant decrease of 11% in deaths from all causes and of 24% in cardiovascular mortality was achieved with the amlodipine/perindopril regimen, despite the reduction in BP being almost comparable to that of the β-blocker/diuretic combination.60 Other secondary end points also favored amlodipine/perindopril, with a 23% reduction in fatal and nonfatal stroke, and a 13% reduction in total coronary events. (Figure 3, Table II).

Various substudies of ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) have provided further information to support the superior efficacy of an amlodipine/perindopril regimen in patients with type 2 diabetes mellitus.36,65 ASCOT included a large subpopulation with type 2 diabetes mellitus (n=5137) in which there was a 14% difference in the end point of major cardiovascular events in favor of the amlodipine/perindopril group.53 This was accompanied by a 25% lower incidence of fatal and nonfatal stroke, 48% less peripheral artery disease, and 57% fewer noncoronary revascularization procedures.53 These results are in line with other studies of ACE inhibitor/ CCB combinations in hypertensive patients with diabetes. In a review article, Ferrari described a study in which 214 patients received either a combination of ACE inhibitor and CCB or ACE inhibitor monotherapy for 3 months.10 The conclusion

---

**HYPERTENSION AND CARDIOVASCULAR PREVENTION: WHERE ARE COMBINATIONS GOING?**
of the study was that the fixed combination was more effective than monotherapy with respect to achieving diabetic BP goals. Fixed-combination perindopril/amlodipine can therefore be predicted to reproduce the positive results of ASCOT in diabetic hypertensives, thereby providing additional reductions in total and cardiovascular mortality.10

A pharmacoeconomic analysis has recently been applied to the results of ASCOT. As might be expected, the actual cost of treatment with the “older” treatment of β-blocker/diuretic was lower than the “newer” combination of perindopril/amlovidine.54 However, for the β-blocker/diuretic combination, these lower costs were rapidly offset by increases in other costs driven by the number of hospitalizations and the cost of procedures, concomitant treatments, and events.50 Moreover, this analysis failed to take into account the costs associated with microvascular complications, excess mortality due to new-onset diabetes, or rehabilitation after stroke.10 These can all be reasonably predicted to be lower in perindopril/amlovidine-treated patients and the authors concluded that the perindopril/amlovidine combination was cost-effective in patients with moderate hypertension and additional risk factors.64

The CAFE study (Conduit Artery Function Evaluation)—a sub-study of ASCOT—examined the impact of the two BP-lowering regimens compared in the ASCOT trial on derived central aortic pressures and hemodynamics in 2199 patients for up to 4 years. The amlodipine/perindopril regimen was associated with substantial reductions in central aortic pressures compared with the atenolol/HCTZ regimen.65 The CAFE population had the same baseline characteristics as the overall ASCOT population, and there were no significant differences between the two groups. However, central aortic SBP was significantly lower in the amlodipine/perindopril group (difference, 4.3 mm Hg). The authors concluded that the differential effects on central BP of the two antihypertensive regimens may be, at least in part, responsible for the differential effects on cardiovascular outcomes.60

In addition, the ACCOMPLISH study (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension)59 provided outcome evidence in favor of the combination of an ACE inhibitor and a CCB. This trial included 11 506 patients with hypertension who were at high risk of cardiovascular events (most patients had type 2 dia-

<table>
<thead>
<tr>
<th>End Point</th>
<th>0.50</th>
<th>0.70</th>
<th>1.00</th>
<th>1.45</th>
<th>2.00</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>0.90 (0.79-1.02)</td>
<td>0.87 (0.76-1.00)</td>
<td>0.87 (0.79-0.96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>0.84 (0.78-0.90)</td>
<td>0.89 (0.81-0.99)</td>
<td>0.76 (0.65-0.90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertiary</td>
<td>0.77 (0.66-0.89)</td>
<td>0.84 (0.66-1.05)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post hoc</td>
<td>0.86 (0.77-0.96)</td>
<td>0.84 (0.76-0.92)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Unadjusted HR (95% CI)

Figure 3. A summary of all end points in ASCOT-BPLA.38

Data from the ASCOT-BPLA trial showing that the newer amlodipine/perindopril regimen was clearly superior in terms of preventing CV events overall—and significantly so—for most of the end points considered.

Abbreviations: ASCOT-BPLA, Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure-Lowering Arm; CHD, coronary heart disease; CV, cardiovascular; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.

betes and/or CAD). BP was reduced very effectively in both treatment arms and to a similar extent, without significantly affecting the rates of postural hypotension. This trial also showed the significant benefit of a benazepril/amlodipine combination on major cardiovascular events compared with a benazepril/HCTZ combination (Figure 4, Table II).

Is there a rationale for a fixed-dose triple combination?
The increased BP-lowering efficacy of the different fixed-dose combinations of either an ACE inhibitor or an ARB and a thiazide-like diuretic, or an ACE inhibitor and a CCB, has been proven.

Furthermore, even though the combination of two drugs may significantly improve efficacy, it is estimated that about 15% to 20% of patients require combination therapy. Recent clinical trials have shown that triple therapy with an ARB, a CCB, and a diuretic significantly reduces BP compared with dual combination therapy. The clinical benefit of triple combination therapy with olmesartan 40 mg, amlopidine 10 mg, and HCTZ 25 mg was compared with that of dual combinations of the individual components in TRINITY (the TRIple therapy with olmesartan medoxomil, amlopidine, and hydrochlorothiazide in hypertensive patientTs studY). This study was conducted on 2492 patients with moderate to severe hypertension. After 12 weeks, reductions in seated DBP and SBP were significantly greater with triple combination therapy than with any of the dual combinations. These results suggest that there are a number of options for a fixed combination of three antihypertensive agents (eg, perindopril/amlodipine/indapamide). Having established the potential of triple combinations, it will now be necessary to assess their long-term efficacy and safety profile.

Conclusion
Antihypertensive 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 or 3 hypertension. The combination of a RAS-targeting agent, such as an ACE inhibitor or an ARB, together with a diuretic, particularly if metabolically neutral (eg, indapamide), or a CCB, or both, provides synergy with regard to the lowering of BP. Furthermore, the dual combination of perindopril/indapamide and perindopril/amlodipine has been documented as improving cardiovascular outcomes and reducing total mortality.

References
Pourquoi avons-nous besoin d’associations antihypertensives ?

L’hypertension est un problème mondial et la cause principale de mortalité. La plupart des patients hypertendus ont des maladies ou des facteurs de risque cardiovasculaires supplémentaires et pour la majorité d’entre eux, plus d’un médicament est nécessaire pour atteindre les valeurs cibles de pression artérielle : deux ou trois en moyenne d’après plusieurs études cliniques sur la prise en charge de l’hypertension. Les associations utilisant les synergies pharmacologiques et physiologiques étant plus efficaces, les recommandations préconisent d’ajouter un médicament d’une autre classe que celle initialement prescrite. D’après les directives de l’European Society of Hypertension et de l’European Society of Cardiology, les associations antihypertensives les plus pertinentes sont celles impliquant inhibiteurs de l’enzyme de conversion (IEC), antagonistes calciques (AC), antagonistes du récepteur de l’angiotensine II (ARA II) et diurétiques thiazidiques. L’association d’un IEC avec le diurétique thiazidique indapamide s’est montrée efficace pour faire baisser la pression artérielle et prévenir ou diminuer la morbidité cardiovasculaire dans de nombreuses études comme STRATHE, PROGRESS, HYVET, REASON, LIFE et ADVANCE. Les études EUROPA, ASCOT ou ACCOMPLISH ont évalué l’association d’un IEC et d’un AC, une association qui s’est montrée efficace dans la prévention des événements cardiovasculaires, la prévention de l’apparition d’un diabète et dans la réadaptation après un accident vasculaire cérébral. L’association médicamenteuse doit donc être personnalisée selon les comorbidités des patients hypertendus.
Antihypertensive combinations: what is missing?

by J. Blacher, France

All the epidemiological studies show that hypertension remains inadequately screened, treated, and controlled. It has been shown that when antihypertensive monotherapy is not sufficient to control blood pressure, the combination of two agents from any two classes of antihypertensive drugs increases the level of blood pressure reduction much more than doubling the dose of one agent. Most of the existing guidelines focus on combinations that use a blocker of the renin-angiotensin-aldosterone system and either a thiazide diuretic or a calcium channel antagonist. Other combinations are underpromoted; specifically, the combination of a thiazide diuretic and a calcium channel antagonist. However, this combination has been used in several therapeutic trials and has shown similar or greater benefits than comparator drugs. In VALUE (Valsartan Antihypertensive Long-Term Use Evaluation), ELSA (European Lacidipine Study on Atherosclerosis), FEVER (Felodipine EVEnt Reduction), and COPE (COMbination therapy of hypertension to Prevent cardiovascular Events), the calcium channel antagonist/thiazide combinations were effective both in terms of systolic blood pressure reduction and prevention of cardiovascular complications. Furthermore, in addition to a well-accepted effect on systolic blood pressure, this combination could also have beneficial effects over and above blood pressure reduction; namely, its effects on central blood pressure and on systolic blood pressure variability. Finally, therapeutic innovation in hypertension will perhaps come more from the combination of older drugs than from the discovery of new drugs.

Address for correspondence:
Prof Jacques Blacher,
Université Paris Descartes, Assistance Publique-Hôpitaux de Paris, Unité HTA, Prévention et Thérapeutique Cardiovasculaires Centre de Diagnostic et de Thérapeutique, Hôtel-Dieu, Place du Parvis Notre-Dame, 75004 Paris, France
(e-mail: jacques.blacher@htd.aphp.fr)

www.medicographia.com

Hypertension is the leading chronic disease worldwide. It is known to increase the risk of stroke, coronary heart disease, heart failure, renal failure, and cognitive disorders, and was responsible for between 7 and 8 million deaths worldwide in 2011. Antihypertensive treatment has been shown to reduce cardiovascular complications. In France, an estimated 12 million patients receive pharmacological treatment for hypertension, most of them receiving combination therapy.

For over 30 years, national and international societies have issued numerous sets of guidelines for the management of hypertension, yet hypertension still remains inadequately screened, treated, and controlled. In France, 20% of patients known to be hypertensive are not treated, and 50% of treated hypertensive patients are not controlled, thus showing that the impact of the guidelines is insufficient at the population level.
To improve the management of hypertension, combination therapies need to be promoted. Most of the existing guidelines focus on combinations using a blocker of the renin-angiotensin-aldosterone system and another drug (thiazide diuretic or calcium channel antagonist), whereas others combinations are underpromoted; namely, the combination of a thiazide diuretic and a calcium channel antagonist. This article will focus on the existing data in favor of such a combination.

**Which strategy after the failure of an initial monotherapy?**

According to the 2007 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines,7 antihypertensive treatment should most of the time start with a single drug, which should initially be administered at a low dose. If blood pressure is not controlled, either a full dose of the initial agent can be given or patients can be switched to an agent of a different class (which should also be administered first at a low dose and then at full dose). Switching to an agent from a different class is mandatory in cases where the first agent had no blood pressure–lowering effect or induced important side effects. This “sequential monotherapy” approach allows one to find the drug to which any individual patient best responds, both in terms of efficacy and tolerability. However, although the so-called “responder rate” for any agent in monotherapy is approximately 50% (response meaning here systolic and diastolic blood pressure reduction of >20 mm Hg and >10 mm Hg, respectively), the ability of any agent used alone to achieve target blood pressure values (<140/90 mm Hg) does not exceed 20%-30% in the overall hypertensive population, except in subjects with grade 1 hypertension. Furthermore, the procedure is laborious and frustrating for both doctors and patients, leading to low compliance.

In its 2009 reappraisal,8 the ESH task force tempered its position, mostly because of the publication of an important meta-analysis.9 This meta-analysis of 42 studies showed that combining two agents from any two classes of antihypertensive drugs increases the blood pressure reduction much more (5 times) than doubling the dose of one agent.2 Admittedly, the advantage of combination therapy over monotherapy may partly be due to the fact that if any agent used in monotherapy is ineffective or scarcely effective in a number of patients, thus its combination with an agent that is effective in these patients must induce a greater response than doubling the dose of an ineffective agent. However, although it is possible that the use of two drugs together implies the administration of one drug that is futile, searching for the most effective monotherapy in every given patient is painstaking, and, as mentioned, may discourage compliance.

It is also important to note that in most trials, a combination of two or more drugs has been the most widely used treatment regimen to effectively reduce blood pressure and reach the predetermined goal. Use of combination therapy has been found to be even more frequently needed in diabetic, renal, and high-risk patients, and in general whenever lower blood pressure targets are pursued.6 For example, in a large-scale trial on high-risk hypertensives, the ASCOT trial (Anglo-Scandinavian Cardiac Outcomes Trial), about 9 out of 10 patients were given two or more antihypertensive drugs in order to reduce blood pressure to <140/90 mm Hg.10

Furthermore, there are physiological and pharmacological synergies that justify the greater effectiveness of drug combinations, and this strategy appears to be that on which the selection of antihypertensive medication may increasingly be based. From a public health perspective, it would seem desirable to see a substantial increase in the use of combination treatment in clinical practice from the relatively low prevalence of today.4,6 This could help attain the goal of substantially improving blood pressure control in the hypertensive population from its present low rate of control worldwide.2

Finally, for all these reasons, in the 2013 French Society of Hypertension guidelines, we have proposed a direct switch to combination therapy when blood pressure is not adequately controlled by initial monotherapy.11

**What is the ideal combination therapy?**

The ideal combination therapy should be: (i) effective in terms of systolic blood pressure reduction, with at least complete (not partial) additive effects of both monotherapies, and at best, synergistic effects; (ii) pertinent in terms of pathophysiological effects: this should be achieved by combining agents that

---

**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCOMPLISH</td>
<td>Avoiding Cardiovascular events in COMbination therapy in Patients Living with Systolic Hypertension (trial)</td>
</tr>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>Action in Diabetes and Vascular disease: Pretax and DiamicroN MR Controlled Evaluation (trial)</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial</td>
</tr>
<tr>
<td>ASCOT</td>
<td>Anglo-Scandinavian Cardiac Outcomes Trial</td>
</tr>
<tr>
<td>ASH</td>
<td>American Society of Hypertension</td>
</tr>
<tr>
<td>CCB</td>
<td>calcium channel blocker</td>
</tr>
<tr>
<td>COPE</td>
<td>COMbination therapy of hypertension to Prevent Cardiovascular Events (trial)</td>
</tr>
<tr>
<td>ELSA</td>
<td>European Lacidipine Study on Atherosclerosis</td>
</tr>
<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
</tr>
<tr>
<td>ESH</td>
<td>European Society of Hypertension</td>
</tr>
<tr>
<td>FEVER</td>
<td>Felodipine EVent Reduction (trial)</td>
</tr>
<tr>
<td>HYVET</td>
<td>HYpertension in the Very Elderly Trial</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
</tr>
<tr>
<td>VALUE</td>
<td>Valsartan Antihypertensive Long-Term Use Evaluation (trial)</td>
</tr>
</tbody>
</table>
either interfere with distinctly different pressor mechanisms or effectively block counterregulatory responses; and (iii) evidence-based; that is to say that this combination should have demonstrated a beneficial effect on cardiovascular morbidity and fatal events in comparison with a monotherapy, or best, another combination treatment.

Unfortunately, the blood pressure effects of combination therapies in hypertension are frequently underadditive, pathophysiological considerations are frequently contradicted by different clinical trials, and there are very few therapeutically trials comparing two different bitherapies with clinical events outcomes. Thus, preferences should take into account a combination of the previous criteria and a large degree of uncertainty.

In their 2009 guidelines, the ESH/ESC reported that (Table I): Trial evidence of outcome reduction has been obtained particularly for the combination of a diuretic with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor antagonist or a calcium antagonist, and in recent large-scale trials for the ACE inhibitor/calcium antagonist combination. In a recent position paper, Gradman et al, on behalf of the American Society of Hypertension (ASH), differentiatized the possible drug combinations in hypertension into three groups: the preferred, the acceptable, and the less-effective combinations (Table II). It is important to note that the calcium channel blocker (CCB)/diuretic combination was considered as “preferred” by the European guidelines and just “acceptable” by the ASH. It will be interesting to see if such discrepancy still exists in the forthcoming European and American guidelines.

Focus on an “acceptable bitherapy”: the calcium channel blocker/diuretic combination

Despite the fact that small pharmacological studies have raised doubts about the synergistic effects of adding a diuretic to a calcium channel antagonist (for review see reference 8), this combination was included in the meta-analysis by Wald et al and did not detract from the demonstration of

◆ Evidence has continued to grow that in the vast majority of hypertensive patients, effective blood pressure control can only be achieved by combination of at least two antihypertensive drugs.

◆ Addition of a drug from another class to the initially prescribed one should thus be regarded as a recommendable treatment strategy, unless the initial drug needs to be withdrawn because of the appearance of side effects or the absence of any blood pressure-lowering effect.

◆ The combination of two antihypertensive drugs may offer advantages also for treatment initiation, particularly in patients at high cardiovascular risk in which early blood pressure control may be desirable.

◆ Whenever possible, use of fixed dose (or single pill) combinations should be preferred, because simplification of treatment carries advantages for compliance to treatment.

◆ As mentioned in the 2007 European Society of Hypertension/European Society of Cardiology guidelines, several two-drug combinations are suitable for clinical use. However, trial evidence of outcome reduction has been obtained particularly for the combination of a diuretic with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor antagonist or a calcium antagonist, and in recent large-scale trials for the ACE inhibitor/calcium antagonist combination. The angiotensin receptor antagonist/calcium antagonist combination also appears to be rational and effective. These combinations can thus be recommended for priority use.

◆ Despite trial evidence of outcome reduction, the β-blocker/diuretic combination favors the development of diabetes and should thus be avoided, unless required for other reasons, in predisposed patients. Use of an ACE inhibitor–angiotensin receptor antagonist combination presents a dubious potentialization of benefits with a consistent increase of serious side effects. Specific benefits in nephropathic patients with proteinuria (because of a superior antiproteinuric effect) expect confirmation in event-based trials.

◆ In no less than 15%-20% of hypertensive patients, blood pressure control cannot be achieved by a two-drug combination. When three drugs are required, the most rational combination appears to be a blocker of the renin–angiotensin system, a calcium antagonist, and a diuretic at effective doses.

Table I. 2009 European Society of Hypertension position concerning combination therapy.


<table>
<thead>
<tr>
<th>Preferred</th>
<th>Acceptable</th>
<th>Less effective</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor/diuretic</td>
<td>ARB/diuretic</td>
<td>ACE inhibitor/ARB</td>
</tr>
<tr>
<td>ACE inhibitor/CCB</td>
<td>CCB/diuretic</td>
<td>Renin inhibitor/ARB</td>
</tr>
<tr>
<td>Renin inhibitor/diuretic</td>
<td>Thiazide diuretics/K+-sparing diuretics</td>
<td></td>
</tr>
</tbody>
</table>

Table II. 2011 American Society of Hypertension position concerning combination therapy.

Abbreviations: ARB, angiotensin receptor blocker; ACE, angiotensin-converting enzyme; CCB, calcium channel blocker.

western topper.23

The FEVER trial (Felodipine EVEnt Reduction) was a multicen-

scriber of calcium channel antagonists with other drugs compared with
doubling the calcium channel antagonist dose in monothera-
py. Even more importantly, the association of a calcium chan-
nel antagonist with a diuretic has been used in several therapeu-
tic trials, where it has shown similar or greater benefits than
the comparators. These trials are detailed hereafter and sum-
marized in Table III.

◆ The VALUE trial
The VALUE trial (Valsartan Antihypertensive Long-Term Use Evaluation) included patients with high-risk hypertension, most with previous histories of coronary disease, stroke, or diabetes. Patients were randomized to either a valsartan-based or am-

The calcium
channel blocker/diuretic combination is at least as effec-
tive as or superior to
other antihypertensive strategies.

The ELSA study
The ELSA trial (European Lacidipine Study on Atherosclerosis) was a randomized, double-blind trial in 2334 patients with hy-
pertension that compared the effects of 4 years of treatment
based on either lacidipine or atenolol on an index of carotid
atherosclerosis: the mean of the maximum intima-media thick-
ess in far walls of common carotids and bifurcations (CB-
Mmax). This index has been shown by epidemiological stud-
es to be predictive of cardiovascular events. If blood pressure
was not at goal, after increasing the study drug dose in each
group, 12.5 mg hydrochlorothiazide was added. Although
clinical blood pressure reductions were identical in both groups,
the primary end point (fatal and nonfatal stroke) was reduced by 27% (P<0.001). Among the second-
ary end points, all cardiovascular events were reduced by 27%
(P<0.001), all cardiac events by 35% (P=0.006), coronary events by 32% (P=0.024),
heart failure by 30% (P=0.239), and cardiovascular death by
33% (P=0.019) in the felodipine group.14

◆ The FEVER trial
The FEVER trial (Felodipine EVEnt Reduction) was a multicen-
ter, double-blind, randomized, placebo-controlled, parallel-
group trial. It enrolled 9800 Chinese patients, of either sex, aged
50 to 79 years, with one or two additional cardiovascular risk
factors or disease, whose blood pressure was in the range of
140-180 mm Hg (systolic) or 90-100 mm Hg (diastolic) 6
weeks after switching from their previous antihypertensive ther-
apy to low-dose (12.5 mg a day) hydrochlorothiazide. These
patients were randomly assigned to either low-dose felodip-
line extended release or placebo, and followed at 3-month
intervals for an average of 40 months. The intention-to-treat
analysis included 9711 patients. Add-on therapy was given
to 33.9% of the hydrochlorothiazide + felodipine patients and
do 42.3% of the hydrochlorothiazide + placebo patients. In
the felodipine group, systolic blood pressure/diastolic blood pressure
decreased (from randomization to study end) from 154.2/
91.0 mm Hg to 137.3/82.5 mm Hg, and in the placebo group
from 154.4/91.3 mm Hg to 142.5/85.0 mm Hg, with an aver-
age difference throughout the trial of 4.2/2.1 mm Hg. In the
felodipine group, the primary end point (fatal and nonfatal
stroke) was reduced by 27% (P<0.001). Among the second-
ary end points, all cardiovascular events were reduced by 27%
(P<0.001), all cardiac events by 35% (P=0.012), death by any
cause by 31% (P=0.006), coronary events by 32% (P=0.024),
heart failure by 30% (P=0.239), and cardiovascular death by
33% (P=0.019) in the felodipine group.14

HYPERTENSION AND CARDIOVASCULAR PREVENTION:
WHERE ARE COMBINATIONS GOING?

<table>
<thead>
<tr>
<th>ELSA13</th>
<th>VALUE13</th>
<th>FEVER14</th>
<th>COPE15</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>2004</td>
<td>2005</td>
<td>2011</td>
</tr>
<tr>
<td>CCB/BB</td>
<td>DIU</td>
<td>CCB/BB</td>
<td>ARB/CCB</td>
</tr>
<tr>
<td>CCB/BB</td>
<td>ARB/CCB</td>
<td>CCB/BB</td>
<td>CCB/BB</td>
</tr>
<tr>
<td>Untreated or treated</td>
<td>Treated</td>
<td>Uncontrolled on DIU</td>
<td>Uncontrolled on CCB</td>
</tr>
<tr>
<td>Baseline: 163/101 mm Hg</td>
<td>Baseline: 154/87 mm Hg</td>
<td>Baseline: 154/91 mm Hg</td>
<td>Baseline: 154/89 mm Hg</td>
</tr>
<tr>
<td>End: 141/86 mm Hg</td>
<td>End: 137/78 mm Hg</td>
<td>End: 141/84 mm Hg</td>
<td>End: 134/77 mm Hg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>↓Strokes</th>
<th>PEP: similar effect</th>
<th>↓Strokes</th>
<th>PEP: tendency in favor of CCB/DIU</th>
<th>↓Strokes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mancia (Italy)</td>
<td>Julius (USA)</td>
<td>Liu (China)</td>
<td>Zhang (China)</td>
<td>Matsuzaki (Japan)</td>
<td></td>
</tr>
</tbody>
</table>

Table III. The calcium
channel blocker/diuretic combination is at least as effec-
tive as or superior to
other antihypertensive strategies.

Abbreviations: ARB, angiotensin
receptor blocker; BB, β-blocker;
CCB, calcium channel blocker;
COPE, Combination therapy of
hypertension to Prevent cardio-
vascular Events (trial); CV, cardio-
vascular; DIU, diuretic; ELSA,
European Lacidipine Study on
Atherosclerosis; FEVER, Felodip-
ine EVEnt Reduction (trial); MI,
myocardial infarction; PEP, primary
end point; VALUE, Valsartan An-

Tensive Long-Term Use
Evaluation (trial).
between treatments was found for any cardiovascular events, although the relative risk for stroke, major cardiovascular events, and mortality showed a trend favoring lacidipine (plus hydrochlorothiazide).  

**The COPE study**

In COPE (COmbination therapy of hypertension to Prevent cardiovascular Events), a randomized, open-label, blinded end point trial, 3501 hypertensive outpatients aged between 40 and 85 years who did not achieve target blood pressure (<140/90 mm Hg) with the CCB benidipine 4 mg/day were randomly equally assigned to receive an angiotensin receptor blocker, a β-blocker, or a thiazide diuretic in addition to benidipine. Median follow-up was 3.61 years. At the end of the treatment, 64.1%, 66.9%, and 66.0% of patients in the benidipine + angiotensin receptor blocker, benidipine + β-blocker, and benidipine + thiazide groups, respectively, achieved target blood pressure. The cardiovascular composite end point trial, 3501 hypertensive outpatients aged between 40 and 85 years who did not achieve target blood pressure (<140/90 mm Hg) with the CCB benidipine 4 mg/day were randomly equally assigned to receive an angiotensin receptor blocker, a β-blocker, or a thiazide diuretic in addition to benidipine. Median follow-up was 3.61 years. At the end of the treatment, 64.1%, 66.9%, and 66.0% of patients in the benidipine + angiotensin receptor blocker, benidipine + β-blocker, and benidipine + thiazide groups, respectively, achieved target blood pressure. The cardiovascular composite end point occurred in 41 (3.7%), 48 (4.4%), and 32 (2.9%) patients, respectively; the hazard ratio was 1.26 in the benidipine + angiotensin receptor blocker group, 1.54 in the benidipine + β-blocker group, and 1.54 in the benidipine + thiazide group compared with benidipine + thiazide group. The secondary analyses revealed that benidipine + thiazide diuretic significantly reduced the incidence of fatal or nonfatal strokes (P=0.0109) and benidipine + angiotensin receptor blocker significantly reduced new-onset diabetes (P=0.0240) compared with benidipine + β-blocker. Finally, there was a trend toward a superior net benefit in the benidipine + thiazide group.  

**Beneficial effects of calcium channel blocker/ diuretic combination over and above blood pressure reduction**

The main benefits of antihypertensive treatment are due to lowering of blood pressure per se, and are largely independent of the drugs employed. Nevertheless, several therapeutic trials have shown differences in the rate of cardiovascular complications between groups without any significant blood pressure difference. Thus, some strategies are undoubtedly associated with a cardiovascular benefit that goes above and beyond blood pressure reduction. The two best candidates to explain part of this benefit are the concepts of central hemodynamics and blood pressure variability.  

**Central blood pressure**

The blood pressure waveform varies substantially between the peripheral conduit (brachial) and the central elastic (aorta) arteries, mainly due to a gradual increase in systolic blood pressure as the wave propagates distally. This phenomenon is called blood pressure amplification and is principally generated by the presence of an arterial stiffness gradient and wave reflections along the arterial bed (Figure 1). More and more clinical studies suggest that central blood pressure may provide additional information regarding cardiovascular risk beyond peripheral blood pressure. Recent evidence suggests, beyond any doubt, that antihypertensive drugs affect peripheral and central blood pressure differentially and alters pressure amplification. We previously published a review paper showing that: (i) it is clear that there are important differences between the classes of antihypertensive drugs regarding their effects on blood pressure amplification; (ii) it seems that the newer antihypertensive drugs (ACE inhibitors, angiotensin receptor blockers, and dihydropyridine CCBs), as well as nitrates, have a more beneficial effect on blood pressure amplification than the older drugs (diuretics and β-blockers); and (iii) there is compelling evidence regarding the detrimental effect of β-blockers (mainly atenolol) on central blood pressure. Nevertheless, very few comparative studies have been performed that focus on central blood pressure parameters. In a double-blind crossover study, the effects on central aortic pressure of the four major drug classes were measured and compared with placebo. Central aortic pressure and various indices were determined using the SphygmoCor® apparatus. The study was undertaken in patients aged 65 to 85 years with systolic blood pressure of >150 mm Hg at study entry.
Results were reported for 32 patients who had satisfactory applanation tonometry in all five periods. This study revealed that CCBs and diuretics caused a greater fall in brachial artery systolic blood pressure than ACE inhibitors or β-blocker drugs. On placebo, central aorta augmentation pressure and index were 23 mm Hg and 33.3%; on ACE inhibitors the values were 18 mm Hg and 30%; on β-blockers, 26 mm Hg and 38.5%; on CCBs, 16 mm Hg and 28%; and on diuretics, 17 mm Hg and 28.8%. The augmentation pressure on β-blocking drugs was greater than on the other three drug classes (P<0.05), and augmentation pressures on ACE inhibitors, CCBs, and diuretics were less than on placebo (P<0.05). The lowest central aortic pressures were achieved with CCBs and diuretics.19

To my knowledge, the effects of combination therapies on central hemodynamics have never been assessed.

◆ Blood pressure variability

Unexplained differences between classes of antihypertensive drugs in their effectiveness in terms of cardiovascular prevention might be due to class effects on intra-individual variability in blood pressure. In order to test this hypothesis, Webb et al performed a systematic review to assess any such effects in randomized controlled trials.20 In their meta-analysis, blood pressure variability was expressed as the ratio of the variances or as coefficient of variation. Compared with other drugs, inter-individual variation in systolic blood pressure was reduced by CCBs (variance ratio 0.81; 95% confidence interval, 0.76-0.86; P<0.0001) and nonloop diuretic drugs (variance ratio 0.87; 95% confidence interval, 0.79-0.96; P=0.007), and increased by ACE inhibitors (variance ratio 1.08; 95% confidence interval, 1.02-1.15; P=0.008), angiotensin receptor blockers (variance ratio 1.16; 95% confidence interval, 1.07-1.25; P=0.0002), and β-blockers (variance ratio 1.17, 95% confidence interval, 1.07-1.28, P=0.0007). CCBs followed by thiazide diuretics could thus be considered as the two best drugs in terms of reduction of blood pressure variability (Figure 2).

As with central hemodynamics, to my knowledge, the effects of combination therapies on blood pressure variability have never been assessed.

Which calcium channel blocker, which diuretic?

In the absence of therapeutic trials comparing drugs within a single antihypertensive class, preferences have to take into account indirect comparisons, level of proof for every single drug, and a large degree of uncertainty.

With regard to thiazide or thiazide-like diuretics, among the four previously described therapeutic trials,13-16 three used hydrochlorothiazide. We could thus believe that hydrochlorothiazide should be the primary recommended thiazide diuretic. However, some data are at odds with such a statement. First, with regard to calcium channel antagonists, amiodipine undoubtedly has the highest level of proof, with the results of four major therapeutic trials in the field of hypertension: VALUE, described previously;15 ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial), which did not find any difference in the composite of fatal coronary heart disease plus nonfatal myocardial infarction compared with lisinopril (primary end point) and also found a decrease in

Figure 2. Changes in systolic blood pressure group variation at follow-up compared with baseline as variance ratio (A) and percentage increase in coefficient of variation (B) in clinical trials of various antihypertensive drugs.

Error bars represent the 95% confidence intervals. (A) is plotted on a logarithmic scale. The apparent increase in variance ratio and coefficient of variation (CV) from follow-up to baseline was mainly as a consequence of the requirement in many trials for narrow ranges of blood pressure at randomization, which tended to lead to an increase in group standard deviation on follow-up; however, this effect applied almost equally to all drug classes.

Abbreviations: AB, α1-blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; CCB, calcium channel blocker; CCBND, non-dihydropyridine calcium channel blocker; DLI, nonloop diuretic drug.


recently reviewed old data are in favor of a superiority of chlortalidone over hydrochlorothiazide.21 Second, indapamide has been tested in two major therapeutic trials, HYVET (Hypertension in the Very Elderly Trial)22 and ADVANCE (Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation),23 and was associated with both a net benefit in terms of cardiovascular end points and also in terms of total mortality. Finally, the most recent National Institute for Health and Care Excellence (NICE) guidelines recommend favoring chlortalidone and indapamide over hydrochlorothiazide.24

With regard to calcium channel antagonists, amlodipine undoubtedly has the highest level of proof, with the results of four major therapeutic trials in the field of hypertension: VALUE, described previously;15 ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial), which did not find any difference in the composite of fatal coronary heart disease plus nonfatal myocardial infarction compared with lisinopril (primary end point) and also found a decrease in
stroke of 23% (secondary end point)\textsuperscript{25}, ASCOT, with a significant decrease in all end points including all-cause mortality in the amlodipine/perindopril group compared with the significant decrease in all end points including all-cause mortality in the amlodipine/perindopril group compared with the final, the ACCOMPLISH trial (Avoiding Cardiovascular events in COMbination therapy in Patients Living with Systolic Hypertension), which found that amlo in combination with benazepril was superior to the combination of benazepril plus hydrochlorothiazide in a high-risk population.\textsuperscript{26}

**Conclusion**

Poor blood pressure control at the population level motivates promotion of new therapeutic strategies. Since the vast majority of hypertensive patients need more than one drug to control their blood pressure, the emphasis should be on combina-
tion therapy evaluation rather than duplication of conventional therapeutic trials evaluating monotherapies. Among the different possible combination therapies, there is one that has been insufficiently evaluated and promoted: the CCB/thiazide diuretic combination. This combination is considered as "preferred" by the ESH but just as "acceptable" by the ASH. Nevertheless, several therapeutic trials have shown that this combination is at least as effective as comparators, and sometimes superior. Furthermore, in addition to a well-accepted systolic blood pressure–lowering effect, this combination could also have beneficial effects over and above blood pressure reduction; namely, its effects on central blood pressure and systolic blood pressure variability. Finally, therapeutic innovation in hypertension will perhaps come more from the combination of older drugs than from the discovery of new ones. ■

**References**


**Keywords:** blood pressure variability; calcium channel blocker; central hemodynamics; combination therapy; thiazide diuretic
ASSOCIATIONS ANTIHYPERTENSIVES : QUE MANQUE-T-IL ?

Toutes les études épidémiologiques montrent que l'hypertension reste insuffisamment dépistée, traitée et contrôlée. Il a été montré que lorsqu'une monothérapie antihypertensive ne suffit pas à contrôler la pression artérielle, il est plus efficace d'associer deux produits de deux classes différentes, quelles qu'elles soient, que de doubler la dose d'un seul produit. La plupart des recommandations actuelles privilégient l'association d'un inhibiteur du système rénine-angiotensine-aldostérone et d'un diurétique thiazidique ou d'un inhibiteur calcique. Les autres associations sont moins encouragées, en particulier celle d'un diurétique thiazidique et d'un inhibiteur calcique, qui a été néanmoins utilisée dans plusieurs essais thérapeutiques avec des bénéfices supérieurs ou equivalents à ceux des médicaments utilisés comme comparateurs. Dans les études VALUE (Valsartan Antihypertensive Long-Term Use Evaluation), ELSA (European Lacidipine Study on Atherosclerosis), FEVER (Felodipine EVEnt Reduction) et COPE (COMbination therapy of hypertension to Prevent cardiovascular Events), les associations inhibiteur calcique / diurétique thiazidique se sont montrées efficaces à la fois pour diminuer la pression artérielle systolique et pour prévenir les complications cardiovasculaires. Outre son efficacité reconnue sur la pression systolique, cette association pourrait également se montrer bénéfique au-delà de la diminution de la pression artérielle, par son action sur la pression artérielle centrale et sur la variabilité de la pression artérielle systolique. Finalement, l’innovation thérapeutique dans l’hypertension viendra peut-être plus de l’association de médicaments plus anciens que de la découverte de nouvelles molécules.
When more than two drugs are needed to further decrease blood pressure

by A. Greenstein, K. Khavandi, and T. Heagerty, United Kingdom

The risk conferred by high blood pressure is continuous, and follows a linear association with all adverse cardiovascular events. Epidemiological studies inform us that hypertension is on the rise, driven by an increasingly unhealthy society and a pandemic of obesity. Unfortunately, a substantial number of individuals will be unaware of their condition, and therefore left unprotected against multiple target organ insults. More frustrating still, a very significant proportion of those being treated for high blood pressure fail to achieve adequate control, and thereby remain subject to an unacceptably high risk of cardiovascular morbidity and mortality. National and international guidelines have consistently emphasized the importance of prompt and effective intervention to reduce blood pressure to recommended levels. Following trial data, combination therapies with multiple antihypertensive agents have been advocated, and conscious efforts made to alert clinicians to the dangers of untreated hypertension, while simultaneously reducing prescriber anxiety when administering multiple antihypertensives. Sadly, we remain conservative in our approach to blood pressure management, and although a fraction of individuals has genuine resistant hypertension, physician inertia and patient nonadherence is responsible for the majority of cases of suboptimal control. Herein, we discuss these contributing factors in more detail, and summarize society recommendations, the scientific rationale, and trial data to support and guide clinicians in managing patients who require more than two antihypertensive agents to control their blood pressure.

Hypertension is now the world’s leading cause of death. Although the pharmacological tools to treat blood pressure successfully have been available for many years, most patients are not well controlled. Evidence shows that above a certain threshold (140/90 mm Hg), the risk of cardiovascular disease is clear and merits treatment. However, despite vigorously published and publicized guidelines, the majority of published studies show that only half of treated patients achieve satisfactory control. Reasons underlying this phenomenon are multiple and complex, but it is undeniable that a large proportion of patients have difficulty taking their medication due to side effects. This article briefly reviews the reasons underlying poor compliance and outlines some of the innovative new ideas for early treatment with a single pill containing a triple combination of drugs. Evidence is now emerging that this is a safe and effective way to treat hypertension which merits further consideration as guidelines evolve.
Resistant or “resisting” hypertension?
It is an unfortunate reality for clinicians who treat hypertension that one of the major obstacles to achieving satisfactory control of blood pressure in patients is compliance with medication. Hypertension is a very different disease to most other chronic medical conditions. In heart failure, for example, treatment often rapidly improves debilitating symptoms such as breathlessness. By contrast, hypertension is asymptomatic for the majority of patients. Elevated blood pressure is usually detected at a health-screening visit to a primary care or occupational physician and therapy is then started on the basis of guidelines promoting primary prevention of cardiovascular disease. Thus, hypertensive patients move quickly from self-perceived health to a position where they are worried about their health and are taking a daily medicine for the first time in their life. Based on current guidelines, the initial therapy is likely to be either an angiotensin-converting enzyme (ACE) inhibitor or a calcium channel blocker (CCB). The previously asymptomatic patient may then variably experience cough, swollen ankles, skin rashes, flushing, or chest pain while acclimatizing to a new therapy. Within the space of six months or so, this patient is likely to be informed by their clinician that their blood pressure is “not controlled” or is even “out of control.” A new medication will be added, and over the subsequent three to four years there will be changes and modifications to doses and regimens. Successful treatment is judged by prevention of disease rather than amelioration of symptoms. It is no wonder, then, that patients are often less enthusiastic about their treatment than we would like.

Although perhaps overly bleak, this picture of routine hypertension care is strongly supported by study evidence. First, and most importantly, there is overwhelming data to show that higher blood pressure is associated with increased incidence of cardiovascular disease and that treatment can reverse this. Thus, a 20-mm Hg difference in systolic blood pressure is associated with a two-fold increase in cardiovascular risk. Conversely, it is only necessary to achieve a 10-mm Hg reduction in systolic blood pressure in 11 hypertensive patients to prevent one cardiovascular death. The initiative for the motivated clinician is therefore both clear and compelling. Furthermore, there are now clear guidelines from national bodies which consistently indicate that, in at risk individuals, blood pressure should be reduced to below 140/90 mm Hg. Despite the availability of both medications and guidance, blood pressure is still very poorly controlled in treated patients. In the USA, data from NHANES (National Health And Nutrition Examination Survey) show that only around 50% of treated patients have blood pressures below 140/90 mm Hg.

There are several reasons why blood pressure tends to be poorly controlled in treated patients. Drugs may be ineffective or the patient may have resistant hypertension. However, poor control is more likely to have resulted from drug side effects, which lead to poor compliance, or—as is increasingly recognized—inadequate control of blood pressure is due to a phenomenon known as “physician inertia.” Physician inertia is recognized but understudied, and is certainly under-addressed. It represents the apparent reluctance of a doctor...
needed to achieve satisfactory control.10,11 patients either two or three antihypertensive agents will be potential combination therapy.4 JNC 7 also recommended that dual from the outset. This has since been supported by trial data antihypertensive therapy was appropriate in some patients pressure to less than 140 mm Hg in only 15% of patients.9 In- deed, available evidence indicates that for the majority of hypertension, monotherapy will control systolic blood pressure. For example, in elderly patients with previously un- treated hypertension, a one drug is unlikely to achieve effective control of blood pressure than those patients under the care of clinicians with high levels of therapeutic inertia.8 A further important point, which may not always be appreciated by the treating clinician, is that treatment with only one drug is unlikely to achieve control of blood pressure. For example, in elderly patients with previously un- treated hypertension, monotherapy will control systolic blood pressure to less than 140 mm Hg in only 15% of patients.9 Indeed, available evidence indicates that for the majority of patients either two or three antihypertensive agents will be needed to achieve satisfactory control.10,11

Guideline recommendations Hypertension guidelines vary in their recommendations for first- line antihypertensive agents, and, therefore, combination ther- apies differ also. The 7th report of the JNC (JNC7 [The Sev- enth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure]) did not provide definitive recommendations for combination therapy, but did suggest that thiazide diuretics were appro- priate first-line agents and should form a component of ini- tial combination therapy.4 JNC 7 also recommended that dual antihypertensive therapy was appropriate in some patients from the outset. This has since been supported by trial data from ACCELERATE (Aliskiren and the Calcium ChannEL block- ER Amlodipine combination as an initial treatment strategy for hypertension),12 although a combination of aliskiren and a CCB was used in this study. The European Society of Hypertension (ESH) and European Society of Cardiology (ESC) guidelines were published in 2007,5 and reappraised in 2009.13 There was again no clear preference for a specific class of antihyperten- sive agent; instead, the recommendation was to select optimal agents based on the individual, taking into consideration factors such as cardiovascular risk profile, target organ dam- age, and concomitant disease. Again, there was a strong em- phasis on the use of multidrug combinations to achieve blood pressure control, and five potential combinations were pro- posed for priority use, as illustrated in Figure 1.

Guidelines from the British Hypertension Society (BHS) and National Institute for Health and Clinical Excellence (NICE) were released in 2011, and form the most recent evidence- based recommendations available.14 The guideline was struc- tured in a similar format to its predecessor, with a stepped approach to achieving blood pressure control, and recom- mendations for specific agents determined by age and eth- nicity of the individual (Figure 2). In those <55 years of age, an ACE inhibitor is the preferred choice, or a low-cost angioten- sin II receptor 1 blocker (ARB) if intolerant of ACE inhibitors (eg, due to cough). Those ≥55 years of age or black people

![Figure 1. Recommended potential combinations proposed in the ESH/ESC Guidelines. Combinations recommended in the general hypertensive population are represented as thick lines. The frames indicate classes of agents proven to be beneficial in controlled intervention trials. Abbreviations: ACE, angiotensin-converting enzyme; ESC, European Society of Cardiology; ESH, European Society of Hypertension. After reference S: Mancia G et al. J Hypertens. 2007;25(6):1105-1187. © 2007, Lippincott Williams & Wilkins, Inc.](image1)

![Figure 2. Algorithm from the NICE/BHS guidelines in 2011, recommen- ding calcium channel blocker + angiotensin blocking agent as the only preferred combination, with sequential addition of a thiazide-like diuretic, further diuretic (spironolactone), and/or β- or α-blockade. Abbreviations: BHS, British Hypertension Society; NICE, National Institute for Health and Clinical Excellence. A = angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker; C = calcium channel blocker; D = thiazide-like diuretic. After reference 14: NICE Clinical Guideline 127. © 2011, National Institute for Health and Clinical Excellence.)](image2)
of African or Caribbean decent of any age should commence treatment with a CCB, or if not suitable, a thiazide-like diuretic such as chlorthalidone or indapamide. This is based on the fact that younger patients (excluding black people) have higher renin levels, and therefore receive greater benefit from angiotensin blocking agents, whereas older people and people of African and Caribbean origin tend to have lower renin levels and respond better to CCBs and diuretics. If blood pressure remains elevated, step 2 involves addition of a second agent to give the combination of an ACE inhibitor (or ARB if intolerant) and a CCB (or thiazide-like diuretic if intolerant, or in heart failure). If a third agent is required, a thiazide-like diuretic should be added. If clinic blood pressure remains >140/90 mm Hg after treatment with optimal or best-tolerated doses of a CCB, angiotensin blocker, and thiazide-like diuretic, the disorder is classified as resistant hypertension, and a fourth antihypertensive agent should be considered and expert opinion sought. If potassium is not elevated, further diuretic therapy with low-dose spironolactone can be considered, or if contraindicated/ineffective, an α- or β-blocker.

Scientific rationale
Combination therapies should be based on complementary physiological mechanisms of action. The pathophysiology of blood pressure is multifactorial, but the predominant factors are an increased peripheral vascular resistance and elevated cardiac output. A combination regimen should therefore, aim to target these pathways, for example with an angiotensin blocker to reduce peripheral vascular resistance, a diuretic to reduce excess fluid volume, and β-blockers to reduce the heart rate. However, as peripheral vascular resistance is the primary driver of increased blood pressure, additional benefit may be conferred by vasoconstricting dihydropyridine CCBs over β-blockers. Mechanistically, therefore, a rational choice might be a renin-angiotensin system (RAS) blocker and a CCB. Third- and fourth-line add-on agents should overcome any potential compensatory changes caused by previous medications, which can trigger reflex elevations in blood pressure. For example, the RAS can be activated as a counter-regulatory response to diuretics or CCBs, as a maladaptive response to restore the elevated blood pressure. An angiotensin blocking agent, with a CCB and a thiazide diuretic may, therefore, provide synergistic benefits. Further, when blood pressure control is not achieved with two antihypertensive agents, subjects are likely to have fluid retention, and treatment with diuretics is often necessary for that reason. Aldosterone excess may also contribute to the development of resistant hypertension, and spironolactone blocks the action of aldosterone at the mineralocorticoid receptor, stimulating natriuresis and alleviating fluid overload. This can also address aldosterone rebound, which is seen with long-term angiotensin blockade, where aldosterone escapes blockade and levels return to baseline.

Deriving rational pharmacological combinations from such principles has, unsurprisingly, lead to discrepancies in practice—for example with some promoting the combination of dihydropyridine and nondihydropyridine CCBs, while others support the use of high-dose nitrates and direct vasodilators or α-agonists. It is therefore necessary to evaluate trial evidence to confirm which combinations carry the best evidence.

Current evidence
High blood pressure investigation is one of the most evidence-rich areas in medical research, and patients have benefited significantly from application of evidence-based recommendations. However, when taken collectively, the literature concerning combination therapies (with more than two drugs) is not structured, with comparator trials including a mix of monotherapy and placebo, with a variety of different add-on agents, and no definitive head-to-head comparisons for combination regimens with two or more drugs. Data has, therefore, been extrapolated from the efficacy of agents as monotherapy, or as dual combinations.

Diuretics were prominent in early guideline recommendations. This was based on evidence of their efficacy as monotherapy in trials such as SHEP18 (Systolic Hypertension in the Elderly Program) and Syst-Eur19 (Systolic Hypertension in Europe), but primarily driven by their low cost. More recent comparator trials such as ACCOMPLISH20 (Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension), ASCOT-BPLA21 (Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm), and ANBP22 (second Australian National Blood Pressure Study), have shown thiazide diuretics as inferior to their comparators in preventing adverse cardiovascular endpoints. Consequently, there has been a decline in the use of diuretic prescriptions for the treatment of hypertension in recent years. If used, thiazide-like diuretics are preferred over true thiazides. Data from ADVANCE22 (Action in Diabetes and Vascular disease: Preterax and DiamicroN MR Controlled Evaluation) and HYVET24 (Hypertension in the Very Elderly Trial) support the use of perindopril/indapamide combinations in high-risk diabetic patients and hypertensive individuals over 80 years of age, respectively.

The LIFE trial (Losartan Intervention For Endpoint reduction in hypertension)25 supported the use of an ARB over a β-blocker in combination with a thiazide diuretic, with a reduced composite cardiovascular end point (driven by improvement in rates of stroke). Now that ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) has unequivocally showed that perindopril plus amlodipine was superior toatenolol and thiazide diuretic in normalizing blood pressure parameters and preventing cardiovascular events, β-blockers have fallen out of favor, which is reflected by their exclusion as preferred agents in the recent NICE guidance. The ASCOT and ACCOMPLISH26 trials (Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension) support the use of an angiotensin-blocking agent in combination with
a CCB as superior in preventing cardiovascular end points. There is some debate about class benefits independent of blood pressure lowering, with some evidence that CCBs are preferential in stroke, and ACE inhibitors in coronary heart disease,\textsuperscript{25} above and beyond blood pressure lowering. However, the general focus over recent years has been to prioritize blood pressure lowering, which ultimately remains the absolute priority.\textsuperscript{26} A number of important secondary analyses of ASCOT have, however, provided evidence of additional benefits for this combination, above and beyond greater blood pressure control,\textsuperscript{27} including reduced incidence of diabetes,\textsuperscript{28} reduced blood pressure variability,\textsuperscript{29} superior reduction in central blood pressure,\textsuperscript{30} and indirect measures of improved arterial remodeling and peripheral vascular resistance.\textsuperscript{31} Additional RAS blockade achieved by combining an ACE inhibitor with an ARB did not confer any additional cardiovascular benefit in ONGTARGET (ONGOing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial), and produced increased adverse renal outcomes;\textsuperscript{32} despite a slight reduction in blood pressure.\textsuperscript{33} There is limited evidence for direct renin inhibition, although a recent trial of type 2 diabetic patients failed to show any benefit from the addition of aliskiren to either an ARB or ACE inhibitor, for cardiac or renal end points.\textsuperscript{34}

There is no robust evidence to guide the selection of a third antihypertensive agent.\textsuperscript{34,35} Chlorthalidone (ALLHAT [Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial] and SHEP) and spironolactone have particular efficacy in lowering blood pressure in resistant hypertension,\textsuperscript{36,37} although indapamide has a more favorable metabolic profile and has demonstrated strong mortality reduction. In ASCOT-BPLA, spironolactone\textsuperscript{38} was used as a fourth-line add-on agent in resistant hypertension, which was well tolerated at low doses and produced significant additive blood pressure–lowering benefits. If side effects such as gynecomastia and breast tenderness are experienced, consideration can be made for the more selective mineralocorticoid receptor blocker eplerenone. Amiloride is another suitable substitute, although it would require increased doses.\textsuperscript{34} Side effects with spironolactone are related to duration/dose, and are normally reversible upon discontinuation of treatment. Electrolytes and renal function must be monitored within two weeks of initiating these agents, and with subsequent follow-up depending on baseline values and dosage. If potassium is elevated, the dose of the thiazide-like diuretic can be increased. In ASCOT-BPLA, doxazosin gastrointestinal therapeutic system was used as the third-line agent for both of the blood pressure–lowering treatment regimens,\textsuperscript{39} and afforded sustained blood pressure–lowering effects without adverse effects on heart failure (in contrast to ALLHAT) or lipids. The recent concept of sequential nephron blockade was proposed as a strategy in resistant hypertension.\textsuperscript{40} It is centered on countering intrarenal compensatory sodium reabsorption at unblocked nephron sites through stepped addition of low doses of four different diuretics, working at different sites. In those individuals unable to achieve blood pressure control on triple therapy with an ARB, thiazide, and CCB, sequential nephron blockade achieved blood pressure control in 58% of patients, compared with 20% in patients treated with sequential RAS blockade.

**Nonadherence**

When taken together, what is clear from the above data is that a number of antihypertensive agents are available and have proven efficacy in decreasing blood pressure and reducing cardiovascular risk. Even accounting for physician inertia, it seems surprising that quite so many “treated” individuals have uncontrolled hypertension. Of course, the bulk of responsibility for control of blood pressure lies with the patient. If they are compliant with their medication, then it is far more likely that they will achieve a satisfactory blood pressure. However, published studies indicate that compliance with prescribed antihypertensive medication may be as low as 25% to 50%.\textsuperscript{41} Reasons for noncompliance are complex, but can be divided into intentional and unintentional reasons. Intentional nonadherence is usually due to the side effects of medications and compounded by lack of communication between the doctor and patient regarding the importance of good blood pressure control. Unintentional nonadherence is more common in elderly patients, who are more likely to be on complex medication regimens or may forget to take their tablets.

It is for all of these reasons that single-pill combination treatments (also known as fixed drug combinations) are increasingly used in patients with hypertension. Thiazide diuretics are the most common components, usually combined with ACE Inhibitors, ARBs, or \(\beta\)-blockers. Combinations including dihydropyridine CCBs are also available and increasingly popular. These single-pill combination regimens are used much more sparingly for hypertension management in the UK (2% of all antihypertensive prescriptions) compared with the rest of Europe (40%-50% of prescriptions).\textsuperscript{42} Despite evidence that their use is associated with improved adherence and blood pressure control, it is often due to indications regarding cost. However, a retrospective analysis of a UK primary care database of over 25 000 patients treated for hypertension has shown that patients on single-pill combination treatments attain significantly better blood pressure control than those on individual drug regimens.\textsuperscript{43} Subsequently, although prescription costs were higher in the group taking the single-pill combination treatments, cardiovascular event rates (and thus, overall management cost per patient) were higher for those on individual drug regimens.

The use of single-pill combination treatments for initial therapy in hypertension therefore confers a number of important advantages over starting treatment with a single drug. First, it is a reality that most patients will need at least two drugs to control their blood pressure. Thus, initiation with a combination treatment is more likely to achieve a rapid and effective re-
duction in blood pressure compared with monotherapy. Second, judicious combination of therapies may actually reduce side effects. For example, the side effect that most commonly limits the use of CCBs is ankle edema. However, when CCBs are used in combination with an ACE inhibitor or an ARB, the incidence of ankle edema is significantly reduced.\(^{45,46,47}\) Therefore, when used appropriately, the single-pill combination approach has the potential to fundamentally alter the initial management of hypertension. It is interesting to reflect on the Veterans Affairs Cooperative Study from the 1960s, which was the first clinical trial to show prevention of adverse cardiovascular events with effective pharmacological treatment of hypertension. The study adopted a triple-drug combination consisting of reserpine, hydralazine, and hydrochlorothiazide,\(^{48}\) which was highly effective but associated with significant side effects. This prompted the paradigm change to the now familiar stepped therapy approach, where practitioners start with a single therapy and then titrate this up to the maximum tolerated dose. However, using the single-pill combination approach, multiple drugs can be initiated at lower doses than those which might be expected to have an effect individually, and there is evidence that this is associated with more effective blood pressure control.\(^{49}\) Furthermore, because lower doses of the individual components of the combination pill can be used, side effects are less likely to occur than when titrating a single agent up to a maximum.

More recently, commercially available single-pill combination treatments have included three drugs: an ARB, a CCB, and a thiazide diuretic. The use of these three drug classes reflects the evidence from a number of clinical studies. STITCH (Simplified Therapeutic Intervention To Control Hypertension) compared a treat-to-goal protocol starting with an ARB or ACE inhibitor combined with a thiazide diuretic, with subsequent addition of a CCB against conventional care based on national guidelines. The study demonstrated that the triple combination therapy was well tolerated and achieved a greater degree of blood pressure control compared with a guideline-based approach within the study period of six months (intervention group, 64.7% vs control group, 52.4%; \(P=0.026\)).\(^{50}\)

In the TRINITY study by Oparil and colleagues (TRiple therapy with olmesartan, amlodipine, and hydrochlorothiazide in adult patients with hypertension), initial triple therapy with olmesartan, amlodipine, and hydrochlorothiazide was compared with dual combination or placebo in hypertensive patients. After three months, 69% of patients on triple combination therapy had achieved target blood pressures of ≤140/90 mm Hg compared with only 41%-53% of patients on dual combination therapy.\(^{51}\) Of the 2400 patients treated, only 52 patients discontinued therapy due to adverse effects (4% drop-out rate in the triple combination group vs 1%-2% in the dual combination group). In a study in a cohort with diastolic hypertension, the fixed-dose combination of valsartan, amlodipine, and hydrochlorothiazide was shown to reduce blood pressure to a greater extent than any of the dual therapy combinations of the same drugs, with a significantly higher rate of blood pressure control (71% vs 45%-54%).\(^{52}\) A number of new fixed-dose combinations including triple therapies have been approved for the treatment of hypertension. Aliskiren has been approved in combination with hydrochlorothiazide, amlodipine, or as a fixed-dose combination of the three.

Conclusions
Reducing blood pressure has become an international priority. Hypertension is now the biggest killer in the world, and its incidence is growing as a result of overweight and obesity. Among those individuals with known hypertension who are receiving treatment, a significant number have uncontrolled hypertension and are left unprotected from adverse cardiovascular events. Ultimately, many of these individuals will succumb to premature cardiovascular death as a direct consequence of this. National and international guidelines encourage aggressive blood pressure control and, in keeping with trial data, support combination regimens to achieve this. Current evidence supports the use of a CCB and an angiotensin-blocking agent for dual therapy. The evidence is less robust for the choice of further agents, but a thiazide-like diuretic, followed by spironolactone and then doxazosin represent rational add-on agents with some supporting evidence. The BHS Collaborative Research Working Party has initiated the PATHWAY studies (Prevention And Treatment of resistant Hypertension with Algorithm guided therapy) to investigate the best approach to the treatment of resistant hypertension.\(^{34}\) Although it is interesting (and important) to dissect the data and determine precise combination regimens with the most evidence, in reality it is unlikely that there will be an optimal three- to four-drug combination to suit everyone. Conversely, it is probable that if patients were prescribed, and adhered to, current recommended combination therapies based on complimentary pharmacology, the majority would achieve satisfactory blood pressure control. At the prescribers’ end, the promotion of the recent national guidelines issued by NICE/BHS will encourage practitioners to comply with evidence-based recommendations and the frequent need to adopt multi-combination therapies. As hypertension is a stealth condition, public health campaigns to raise awareness of the risks of high blood pressure will increase adherence. Fixed-dose combinations will likely improve things at both ends of the stethoscope. These interventions should be combined with diet and lifestyle campaigns, which will ultimately prevent hypertension in most cases. We cannot afford to take a casual approach to high blood pressure treatment, and the “conservative” approach, which is so often adopted, equates to delayed or failed control, and a number of avoidable cardiovascular deaths.
References


When more than two drugs are needed to further decrease blood pressure – Greenstein and others

Quand plus de deux médicaments sont nécessaires pour obtenir une réduction supplémentaire de la pression artérielle

Il existe une relation linéaire et continue entre une pression artérielle élevée et la survenue d’événements cardiovasculaires. D’après les études épidémiologiques, l’hypertension est en progression, notamment à cause de la pandémie d’obésité et de l’hygiène de vie de moins en moins bonne de nos sociétés actuelles. Malheureusement, de nombreuses personnes ne sont pas conscientes de leur pathologie et ne sont donc pas protégées contre les nombreuses agressions qui subissent les organes cibles. Encore plus frustrant, une proportion très significative d’hypertendus sous traitement n’est pas contrôlée correctement et reste donc soumise à un risque inacceptable de morbidité cardiovasculaire. Les recommandations nationales et internationales soulignent régulièrement l’importance d’une prise en charge rapide et efficace pour réduire la pression artérielle aux niveaux souhaités. Suivant les données des études, des associations de plusieurs antihypertenseurs ont été préconisées et des efforts délibérés ont été faits pour alerter les médecins des dangers d’une hypertension non traitée, tout en les rassurant sur la prescription de plusieurs antihypertenseurs. Malheureusement, notre approche de la prise en charge de la pression artérielle reste frileuse. Même si une partie des patients souffre véritablement d’hypertension résistante, c’est bien l’inertie des médecins et la mauvaise observance des patients qui sont responsables de la majorité des cas de contrôle insuffisant. Nous analysons ici plus en détail certains de ces facteurs et nous résumons les recommandations des sociétés, les arguments scientifiques et les données des études afin d’aider et de guider les médecins dans la prise en charge des patients nécessitant plus de deux antihypertenseurs pour contrôler leur pression artérielle.
T\text{reating both hypertension and dyslipidemia: a synergistic approach}

by N. R. Poulter, \textit{United Kingdom}

The cardiovascular benefits of lowering blood pressure have been clearly established for decades. More recently, the cardiovascular benefits of lipid lowering with statins among subgroups of hypertensive patients and in specific trials of hypertensive patients have also become clear. Because raised blood pressure and dyslipidemia coexist more frequently than chance would predict, a combined approach to improve both blood pressure and lipid levels in patients with hypertension appears logical. ASCOT-LLA, the lipid-lowering arm of the ASCOT trial (Anglo-Scandinavian Cardiac Outcomes Trial) confirmed the logic of such an approach by showing not only the independent and superior benefits of the “A + C” (angiotensin-converting enzyme inhibitor plus calcium channel blocker) combination of antihypertensive agents over the then-standard β-blocker +/- thiazide (“B + D”) combination in terms of cardiovascular prevention, but also the benefits of atorvastatin versus placebo. The combined effects of amlodipine +/- perindopril plus atorvastatin in ASCOT-LLA were large and compelling with some suggestion of a real synergy between these two regimens in preventing coronary events. Meanwhile, guidelines for hypertension management based on best current trial data increasingly recommend an “A + C” regimen for optimizing cardiovascular prevention among hypertensive patients and the use of statins for a significant proportion of the hypertensive population. Urgent steps must be taken to implement best practice before the anticipated global increase in the prevalence and absolute numbers affected by hypertension translates into an ever greater cardiovascular burden than that which currently prevails.

Trials of lipid lowering in hypertensive patients

With that background, two trials were designed to incorporate an evaluation of lipid lowering specifically among hypertensive patients. Unfortunately, the first trial—ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial)—was designed to compare the effects of pravastatin (a relatively ineffective statin) with usual care, which in the context of the ALLHAT trial population involved significant use of other, and possibly stronger, statins. The net effect was a limited differential effect on low-density lipoprotein (LDL)–cholesterol with a consequently limited effect on CV events between treatment groups.

In contrast, the ASCOT trial (Anglo-Scandinavian Cardiac Outcomes Trial) included as part of a 2 × 2 factorial design, a placebo-controlled evaluation of atorvastatin 10 mg once daily on major CV events. Figure 1 shows the benefits of atorvastatin on primary and secondary end points in this hypertensive population of 10 305 patients who had a baseline total cholesterol of ≥5.6 mmol/L. This lipid-lowering component of the trial (ASCOT-LLA) was stopped prematurely after a median follow-up period of 3.3 years due to a highly significant reduction (36%; \( P=0.0005 \)) in the primary endpoint of non-fatal myocardial infarction (MI) and fatal coronary heart disease (CHD).

The ASCOT trial: combining lipid lowering and blood pressure lowering

The blood pressure (BP)–lowering arm of the trial (ASCOT-BPLA), which included 19 257 hypertensive patients at baseline, continued for a further 2 years after the end of ASCOT-LLA. This arm of the trial was also stopped prematurely because of the significantly reduced rates of all-cause mortality and other CV events (notably stroke) among those randomized to receive amlodipine with perindopril added as required compared with those randomized to receive atenolol with bendroflumethiazide added as required.

**Table I. Cardiovascular end point reduction by hypertension status in statin trials.**

<table>
<thead>
<tr>
<th>Trial</th>
<th>1°/2°</th>
<th>&quot;Hypertensive&quot;</th>
<th>Total population</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>% reduction*</td>
<td>n</td>
<td>% reduction*</td>
</tr>
<tr>
<td>4S</td>
<td>2°</td>
<td>1154 37</td>
<td>4444 34</td>
</tr>
<tr>
<td>CARE</td>
<td>2°</td>
<td>1774 23</td>
<td>4159 24</td>
</tr>
<tr>
<td>LIPID</td>
<td>2°</td>
<td>3758 15</td>
<td>9014 24</td>
</tr>
<tr>
<td>GREACE</td>
<td>2°</td>
<td>686 48</td>
<td>1600 51</td>
</tr>
<tr>
<td>HPST</td>
<td>1° + 2°</td>
<td>10594 20</td>
<td>20536 24</td>
</tr>
<tr>
<td>PROSPER</td>
<td>1° + 2°</td>
<td>2212 15</td>
<td>5804 15</td>
</tr>
<tr>
<td>AF/TexCAPS</td>
<td>1°</td>
<td>1445 39</td>
<td>6605 37</td>
</tr>
</tbody>
</table>

*All CHD except (†) - CHD + stroke

---

**Figure 1. Effects of atorvastatin and placebo on primary and secondary end points in ASCOT-LLA.**

**Abbreviations:** ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm; CHD, coronary heart disease; CV, cardiovascular; MI, myocardial infarction.


**Table 1.** Cardiovascular end point reduction by hypertension status in statin trials.

**Abbreviations:** 4S, Scandinavian Simvastatin Survival Study; AF/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; CARE, Cholesterol And Recurrent Events trial; CHD, coronary heart disease; LIPID, Long-term Intervention with Pravastatin in Ischemic heart disease; GREACE, GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study; HPS, Heart Protection Study; PROSPER, Pravastatin in elderly individuals at risk of vascular disease study.

---

**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLHAT</td>
<td>Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial</td>
</tr>
<tr>
<td>ASCOT</td>
<td>Anglo-Scandinavian Cardiac Outcomes Trial</td>
</tr>
<tr>
<td>ASCOT-BPLA</td>
<td>Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm</td>
</tr>
<tr>
<td>ASCOT-LLA</td>
<td>Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>CCB</td>
<td>calcium channel blocker</td>
</tr>
<tr>
<td>CHD</td>
<td>coronary heart disease</td>
</tr>
<tr>
<td>CV</td>
<td>cardiovascular</td>
</tr>
<tr>
<td>GREACE</td>
<td>GREek Atorvastatin and Coronary-heart-disease Evaluation study</td>
</tr>
<tr>
<td>LDL</td>
<td>low-density lipoprotein</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
</tbody>
</table>
One of the tertiary objectives of the ASCOT trial was to evaluate whether there was any interaction between the BP-lowering and lipid-lowering therapies used in the trial in terms of impact on three specified CV events. Consequently, the relevant and appropriate analyses were carried out to evaluate this question and revealed that there was indeed a statistically significant interaction ($P=0.025$) between the use of atorvastatin in the amlodipine +/- perindopril and atenolol +/- thiazide groups in terms of impact on the primary end point of the trial (nonfatal MI and fatal CHD). As shown in Figure 2, allocation to atorvastatin was associated with a 53% reduction ($P<0.001$) in the primary end point among those also allocated to amlodipine +/- perindopril, whereas the equivalent effect on those randomized to atenolol +/- thiazide was a 16% reduction ($P=0.30$). The other two CV end points that were prespecified for evaluation as to whether the impact of statins and the BP-lowering agents in ASCOT would show any sign of interaction in terms of differential effects were nonfatal or fatal stroke (total stroke) and total CV events and procedures (CV mortality, nonfatal MI [symptomatic and silent], unstable angina, chronic stable angina, life-threatening arrhythmias, nonfatal heart failure, nonfatal stroke, peripheral arterial disease, revascularization procedures, and retinal vascular thrombosis). No such significant effect was observed for either of these two end points ($P=0.728$ and $P=0.253$, respectively) (Table II).

The differential effect of statins on coronary events when stratified by BP-lowering regimen was of modest statistical significance given that this was a tertiary objective of the trial. Furthermore, the difference between BP-lowering regimens was to an extent driven by a less-than-expected impact of atorvastatin among those allocated to atenolol +/- thiazide. The possibility that this difference occurred by chance should

### Table II. The effects of atorvastatin vs placebo for amlodipine-based and atenolol-based treatment for fatal coronary heart disease and nonfatal myocardial infarction, total cardiovascular events and procedures, and fatal and nonfatal stroke.

<table>
<thead>
<tr>
<th>End point and blood pressure regimen</th>
<th>Atorvastatin</th>
<th>Placebo</th>
<th>Unadjusted HR 95% CI</th>
<th>P-value</th>
<th>Interaction P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal myocardial infarction + fatal CHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amlodipine-based</td>
<td>38 (1.5%)</td>
<td>4.6</td>
<td>80 (3.1%) 9.8</td>
<td>0.47 (0.32-0.69)</td>
<td>0.00007</td>
</tr>
<tr>
<td>Atenolol-based</td>
<td>62 (2.4%)</td>
<td>7.5</td>
<td>74 (2.9%) 9.0</td>
<td>0.84 (0.60-1.17)</td>
<td>0.295</td>
</tr>
<tr>
<td>Total cardiovascular events and procedures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amlodipine-based</td>
<td>173 (6.7%)</td>
<td>21.3</td>
<td>233 (9.1%) 29.4</td>
<td>0.73 (0.60-0.88)</td>
<td>0.001</td>
</tr>
<tr>
<td>Atenolol-based</td>
<td>216 (8.4%)</td>
<td>27.0</td>
<td>253 (9.8%) 31.7</td>
<td>0.85 (0.71-1.02)</td>
<td>0.079</td>
</tr>
<tr>
<td>Fatal and nonfatal stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amlodipine-based</td>
<td>35 (1.4%)</td>
<td>4.2</td>
<td>50 (2.0%) 6.1</td>
<td>0.69 (0.45-1.06)</td>
<td>0.088</td>
</tr>
<tr>
<td>Atenolol-based</td>
<td>54 (2.1%)</td>
<td>6.5</td>
<td>71 (2.7%) 8.6</td>
<td>0.76 (0.53-1.08)</td>
<td>0.129</td>
</tr>
</tbody>
</table>

*Per 1000 patient years.
also not be ignored. Nevertheless, the 53% reduction in coronary events (95% confidence interval, 31-68) observed among those allocated to atorvastatin 10 mg daily and amiodipine +/- perindopril compared with those allocated to placebo and amiodipine +/- perindopril was large and greater than might, on average, have been expected with atorvastatin 10 mg daily.

**ASCOT-LLA: impact on guidelines**

The large relative reductions in risk among those randomized to atorvastatin compared with placebo are clear (Figure 1) and argue forcibly for the routine use of statins among the hypertensive population. Indeed, hypertension guidelines\(^ {17,18}\) proposed after the results of ASCOT-LLA were published\(^ {16}\) supported such a position, including the following statement for patients with hypertension in the context of primary prevention:

“With the results of the ASCOT trial and other currently available trial data, it seems reasonable, in the interests of simplicity, to treat with a statin, all those patients at least at the age of 80 years with a total cholesterol >3.5 mmol/L who have an estimated 10-year cardiovascular disease risk of 20% or more. In reality, this would mean considering statin therapy in most hypertensive patients (especially men) over the age of 50 years. As resources allow, a rationale for lowering this threshold could be made on the basis of trial evidence.”\(^ {11,16}\)

Furthermore, support for the use of statins in the context of hypertensive patients arose from cost-effectiveness analyses based on the ASCOT-LLA data.\(^ {11}\) These data showed that the cost per life-year gained using atorvastatin 10 mg daily in hypertensive adults was about €10 000, and based on these findings, it was concluded that the use of atorvastatin in hypertensive patients at modest CV risk but who have not suffered a prior MI was a cost-effective strategy. It is important to add that since these health economic analyses were performed, atorvastatin has become generic and so any residual cost-based reservations regarding the use of atorvastatin in hypertensive patients appear to have no basis. Finally, the CV benefits of lipid lowering with atorvastatin 10 mg in ASCOT-LLA would reasonably be expected to be enhanced by higher doses of atorvastatin and by use among those with more adverse lipid profiles (inclusion in ASCOT-LLA was restricted to those with a total cholesterol of \(\leq 6.5\) mmol/L \(\leq 250\) mg/dL).

Statistical synergy between lipid-lowering and blood pressure lowering in ASCOT: possible mechanisms

The apparently greater preventive effect on coronary events of atorvastatin when used in combination with amiodipine +/- perindopril compared with atenolol +/- thiazide (Figure 2) may have occurred as a result of differential BP-lowering or lipid-lowering effects induced by atorvastatin in the two BP treatment groups. While statins do cause a small BP-lowering effect,\(^ {20}\) no differential effect was noted in ASCOT (unpublished data). Furthermore, the effect of atorvastatin compared with placebo on LDL-cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglycerides was essentially the same once stratified by BP-lowering group,\(^ {16}\) and if anything, what minor differences that did exist favored the atenolol +/- thiazide group.

More generally, angiotensin-converting enzyme (ACE) inhibition has been reported to be associated with reductions in CHD events beyond BP-associated benefits\(^ {21,22}\) and in both experimental\(^ {21}\) and clinical situations,\(^ {24,25}\) dihydropyridine calcium channel blockers (CCBs) have been reported to have antiatherosclerotic actions. Furthermore, a hypothesis based on studies of a cellular and molecular interaction between amiodipine and atorvastatin has been proposed.\(^ {26,27}\) Based on Mason’s report that electrochemical bonding between amiodipine and atorvastatin occurs in the lipid bilayer of vascular smooth muscle membranes,\(^ {27}\) it is hypothesized that, while the functionality of L-type calcium channels in vascular smooth muscle cells is normally lost during the migration of these cells in the atherosclerotic process, the effect of atorvastatin is to induce arrest of growth and differentiation of the smooth muscle cells and restoration of their responsiveness to CCBs.

In addition, it is argued that atherosclerotic plaques are stabilized due to the reduced apoptosis and destruction of vascular smooth muscle cells, a reduction in the release of matrix metalloproteinases, and preservation of the intracellular matrix. The findings of bonding between amiodipine and atorvastatin have not been replicated using other statins and other anti-hypertensive agents and hence makes any such interaction, if true, product-specific.

**Statin/CCB interaction: supportive data**

\* **Internal consistency from ASCOT**

The possible mechanisms underlying the superiority of amiodipine +/- perindopril over atenolol +/- thiazide in ASCOT-BPLA were evaluated and published along with the main final results.\(^ {26}\) The authors concluded that it was likely that some as-yet-unidentified mechanisms—other than those identified in this publication, and certainly beyond the mean BP differences achieved—might have contributed to the differential CV event rates. One such possibility might involve a positive interaction between atorvastatin and amiodipine among those in the amiodipine +/- perindopril group (half of whom were on atorvastatin). However, more recently, the differential effects of the two BP-lowering regimens on BP variability appear to have explained away most of the CV differences observed.\(^ {29,30}\)

Other examples of synergy between atorvastatin and amiodipine +/- perindopril have also been observed in analyses of two subgroups from among the ASCOT participants. In the first one, Manisty and colleagues described a statistically significant interaction between the lipid-lowering and BP-lowering regimens in terms of their impact on carotid systolic BP in a subgroup of ASCOT patients.\(^ {31}\) Systolic BP was found to be significantly lower among those randomized to atorvastatin

---

Footnotes:

1. Poulter

2. Treating both hypertension and dyslipidemia: a synergistic approach – Poulter

---

**Hypertension and cardiovascular prevention: Where are combinations going?**

**MEDICographia, Vol 35, No. 4, 2013**

414
and the amlodipine +/- perindopril combination than in those treated with atorvastatin and atenolol +/- thiazide. In the second example, analysis of the subgroup of diabetic patients in ASCOT demonstrated a significant interaction favoring the atorvastatin, amlodipine +/- perindopril combination in terms of a beneficial effect on estimated glomerular filtration rate (eGFR), which was not observed between the two BP-lowering groups randomized to placebo.35

*External consistency from other studies*

In the GREACE trial (GREek Atorvastatin and Coronary-heart-disease Evaluation) a synergistic effect between atorvastatin and ACE inhibitors was reported among patients with established CHD.33

**Statin/CCB interaction: conflicting data**

In the Prospective Pravastatin Pooling Project, the impact of pravastatin on CHD events among hypertensive patients was significantly less than among nonhypertensives (14% vs 33%, heterogeneity; *P* =0.003).34 However, the authors were unable to attribute this apparent difference to any specific antihypertensive agents. To be compatible with the ASCOT-BPLA findings, a predominance of β-blocker use and limited CCB use among the hypertensive population of the pooling project would have been required.

In the Heart Protection Study,35 the effect of simvastatin on CHD events did not differ between those receiving or not receiving antihypertensive medication. Furthermore, no differential CCB-specific effect on events was apparent in this large trial.36

In the meta-analysis carried out on behalf of the Cholesterol Treatment Trialists (CTT) collaboration,36 the presence or absence of hypertension at baseline in the 14 trials included did not affect the impact of statins on CHD event rates, or indeed any other event rates.

**Conclusion**

Whether the apparent synergy between atorvastatin and the amlodipine +/- perindopril regimen shown in Figure 2 was the result of chance or not, when the results of ASCOT-BPLA and ASCOT-LLA are viewed together, it is quite clear that of the four possible means of preventing CV events incorporated in the ASCOT trial design (Table III), those allocated to the newer antihypertensive regimen (amlodipine +/- perindopril) and atorvastatin (a) were less likely to suffer any of the major CV end points evaluated in this trial than those allocated to any of the other three possible treatment combinations (b, c, or d). By contrast, those allocated to receive atenolol +/- thiazide and placebo (d) were more likely to suffer any of the major CV end points evaluated than those allocated to any of the other possible treatment combinations (a, b, or c). Those allocated to either of the other two possible combinations (b and c in Table III) were neither ‘best’ nor ‘worst’ in terms of prevention of whatever CV end point was considered.

Table III. ASCOT trial design: blood pressure–lowering arm and lipid-lowering arm combined.

<table>
<thead>
<tr>
<th>End point</th>
<th>Amlodipine ± perindopril</th>
<th>Atenolol ± thiazide</th>
<th>Relative risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal MI and fatal CHD</td>
<td>4.8</td>
<td>9.2</td>
<td>48%</td>
</tr>
<tr>
<td>Fatal and nonfatal stroke</td>
<td>4.6</td>
<td>8.2</td>
<td>44%</td>
</tr>
</tbody>
</table>

Table IV. ASCOT blood pressure–lowering arm and lipid-lowering arm combined: insight into optimal cardiovascular prevention.


The absolute event rates of the primary end point of the trial (nonfatal MI and fatal CHD) and all strokes (fatal and nonfatal) suffered by those allocated to the “best” and “worst” therapy combination (respectively, a and d in Table III) are shown in Table IV.

**Summary**

As recently stated in the most recent NICE guidelines on hypertension management, “The prime motivation for treatment in hypertension, as an asymptomatic condition, is the prevention of mortality and morbidity.”37 Similarly, the purpose of using statins is to reduce the huge burden to global health that CV disease currently causes.

Since raised BP and dyslipidemia frequently coexist to impart a multiplicative impact on CV risk (i.e., if for example, raised BP doubles CV risk and abnormal lipids trebles risk, the combined effect is to increase risk six-fold), a combined approach of lowering BP and improving lipid profiles is a logical one. The best currently available evidence from clinical trials supports the routine use of such an approach, and consequently several sets of guidelines for the management of hypertension also recommend the routine use of statins for a large proportion of hypertensive patients.17,18

Some data suggest that specific combinations of BP-lowering drugs and statins may interact to generate synergistic benefit on CHD events,16 but even without synergy, the ASCOT trial clearly shows large beneficial effects on all CV events as-
associated with the use of amlopidine +/- perindopril with atorvastatin (Table IV). It seems likely that, for patients with hypertension, the routine use of the combination of an “A” drug (ACE-inhibitor or ARB) plus a “C” drug (CCB) as recommended in the NICE guidelines of 2011,2 along with a cost-effect-

stantin (eg, atorvastatin), would result in a dramatic re-
duction in the dreadful CV burden currently caused by raised BP and, on the basis of best currently available evidence, should probably form the cornerstone of standard hypertension management.

References
15. Dahlöf B, Sever PS, Poulter NR, et al. ASCOT investigators. Prevention of cardiovascular events with an angiotensin-receptor blocker of amlopidine adding perin-

tension. 2007;49:792-795.
24. Lichtlen PR, Hugenholtz PG, Flaitenbeul W, Hecker H, Jost S, Deckers JW; INTACT group investigators. Retardation of angiographic progression of coro-
25. Nissen SE, Murat Tuzu E, et al. Effect of antihypertensive agents on cardiovas-
26. Munro E, Patel M, Chan P, et al. Inhibition of human vascular smooth mus-

eral cell proliferation by losartan: the role of isoprenoid intermediates of cho-

27. Preston Mason R, Walter MF, Day CA, Jacob RF. Intermolecular differences of 3-

28. Poulter NR, Wedel H, Dahlöf B, et al; ASCOT investigators. Role of blood pres-
30. Rothwell PM, Howard SC, Dolan E, et al; ASCOT-BPLA and MRC Trial Investi-
31. Manisty C, Mayet J, Tapp RJ, et al; ASCOT investigators. Atenosartan treat-
maint is associated with less augmentation of the carotid pressure waveform in hypertension. A sub-study of the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT), Hypertension. 2008;54:1009-1013.
32. Tiller T. Atenosartan in combination with amlopidine/perindopril retards de-
33. Athyros VG, Milhaidis DP, Papageorgiu AA, Bouloukis VI, Pehivanidis AN, Symeonidis AN; GREACE Study Collaborative Group. Effect of statins and ACE in-
34. Sacks FM, Tonkin AM, Shepherd J, et al. Effect of pravastatin on coronary dis-
36. Baigent C, Kear A, Kearney PM, et al; Cholesterol Treatment Trials (CTT) Col-

416 MEDICOGRAPHIA, Vol 35, No. 4, 2013

Treating both hypertension and dyslipidaemia: a synergistic approach – Poulter
UNE APPROCHE SYNERGIQUE POUR TRAITER À LA FOIS L’HYPERTENSION ET LA DYSLIPIDÉMIE

Les bénéfices sur le plan cardiovasculaire d’une diminution de la pression artérielle sont clairement établis depuis des années. Plus récemment, c’est également devenu le cas pour les bénéfices cardiovasculaires d’une diminution des lipides par les statines dans le cadre d’études spécifiques menées chez des patients hypertendus et dans des sous-groupes de patients hypertendus. Étant donné qu’une pression artérielle élevée et une dyslipidémie sont plus fréquemment concomitantes que ne le voudrait le hasard, il semble logique d’associer chez les patients hypertendus l’amélioration de la pression artérielle à celle des taux de lipides sanguins. L’étude ASCOT-LLA, le bras hypolipémiant de l’étude ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) a confirmé la logique d’une telle approche : non seulement l’association d’antihypertenseurs A+C (inhibiteur de l’enzyme de conversion + inhibiteur calcique) s’est montrée indépendante et supérieure en termes de bénéfices sur la prévention cardiovasculaire à l’association standard B+D (bêta bloquant +/- diurétique thiazidique), mais les effets supérieurs de l’atorvastatine par rapport au placebo ont également été démontrés. Les effets combinés de l’amlodipine +/- périndopril plus atorvastatine dans l’étude ASCOT-LLA sont importants et incontestables et suggèrent une réelle synergie entre ces deux traitements dans la prévention des événements coronaires. Par ailleurs, les recommandations dans la prise en charge de l’hypertension, basées sur les meilleures données actuelles, sont de plus en plus en faveur d’une association A+C, afin d’optimiser la prévention cardiovasculaire chez les hypertendus, et de l’utilisation des statines pour une proportion significative des hypertendus. Il est urgent de prendre des mesures pour mettre en œuvre de meilleures pratiques, avant que l’augmentation globale et attendue de la prévalence et du nombre absolu d’hypertendus ne se traduise par un fardeau cardiovasculaire encore plus lourd qu’il ne l’est actuellement.
Antihypertensive treatment in ischemic heart disease: is there an ideal pill?

by E. V. Shlyakhto, Russia

The coexistence of arterial hypertension and ischemic heart disease results in more than a simple summation of their clinical features. Mutual activation of common pathophysiological mechanisms leads to increased levels of morbidity and mortality in this group of high-risk patients. This is characterized not only by progression of atherosclerosis and stabilization of high blood pressure, but also by the occurrence of a number of concomitant problems such as arrhythmias and heart failure. All of this places additional demands on the choice of treatment for hypertensive patients with ischemic heart disease. When choosing a treatment for these patients the whole complexity of the problem should be considered: atherosclerosis, angina, fibrosis, arrhythmia, dyslipidemia, and other metabolic disorders. Drug therapy should be individualized and take into account the heightened risk for cardiovascular events. Recent data suggest that the use of certain groups of medication raises many questions, but administration of ACE inhibitors, statins, and acetylsalicylic acid seems to have undeniable benefits.

Despite the significant progress made by medical science in the last several decades, ischemic heart disease (IHD) is still the leading cause of death in the majority of countries worldwide. With improvement of technology, the availability of invasive treatment methods, and extension of pharmacological treatment options, the IHD mortality rate has decreased, but the incidence of cardiovascular risk factors—particularly obesity, hypertension, and hyperlipidemia—is rapidly increasing. Statistics from 2010 revealed that hypertension was present in 34% of the adult population, with obesity found in 33%, the metabolic syndrome in 34%, and 59% having no daily physical activity.1

Hypertension as a risk factor for ischemic heart disease

In 2002-2003, Khot et al analyzed the incidence of traditional risk factors (hypertension, diabetes mellitus, hyperlipidemia, and smoking) among 122 458 patients with evident IHD. They reported the absence of risk factors in only 10% to 15% of patients; in all others, at least one of the risk factors was present.2 The presence of hypertension ranged from 21% to 60% across different age groups.2,3 There is no doubt that risk factors significantly affect the course of atherosclerosis, including the state of coronary plaques, and that the risk of complications is increased with the presence of risk factors. Hypertension is known to be not only the major risk factor for stroke and heart failure, but also for IHD. According to the results of the INTER-
HEART study, which involved participants in 52 countries, hypertension is a more significant additional risk factor for myocardial infarction than diabetes. In patients aged 40 to 90 years, for every 20/10-mm Hg elevation in blood pressure, the risk of fatal coronary events doubles. Hypertension accelerates the development and progression of atherosclerosis, and stable blood pressure elevation can lead to destabilization of the coronary plaque and development of acute coronary syndrome. Hypertension can lead to myocardial ischemia even in the absence of coronary atherosclerosis.

Pathophysiological mechanisms in arterial hypertension and ischemic heart disease
The pathophysiological association of hypertension with IHD is probably due to two main mechanisms: endothelial dysfunction, which is an early stage of atherosclerosis, and increased afterload leading to myocardial hypertrophy.

Early atherogenesis is characterized by endothelial damage caused by high arterial pressure leading to impairment of nitric oxide production and release, and simultaneous accumulation of free radicals and mediators of inflammation in the vascular wall. Inflammation and activation of the renin-angiotensin-aldosterone (RAS) system and sympathetic nervous system are common pathophysiological processes for arterial hypertension and IHD. In particular, angiotensin II maintains elevated blood pressure and leads to atherosclerosis progression due to vasconstriction and vascular remodeling. It is also known to stimulate hypertrophy of cardiomyocytes and smooth muscle cells by the direct activation of type 1 receptors, and to increase expression of inflammatory factors and cytokines. Aside from this, RAS activation leads to the accumulation of low-density lipoproteins in the vascular wall.5

The metabolic syndrome
Hypertension is one of the components of the metabolic syndrome, which affects about one-third of the population and is becoming increasingly prevalent. Several studies report a correlation between the metabolic syndrome and atherosclerosis. The clustering of abdominal obesity with other components in the metabolic syndrome results in a significantly higher incidence of elevated carotid intima-media thickness. In addition to increased incidence of IHD, the metabolic syndrome is associated with a more severe disease course, and the presence of a higher number of components from the metabolic syndrome is correlated with worse IHD on coronary angiography. Patients with the metabolic syndrome are approximately four times more likely to die of IHD.6-8

Adiponectin
The increased cardiovascular risk arising from the metabolic syndrome is the result of a complex interaction of individual risk factors that is not completely understood. One of the possible explanations is oxidative stress. Increased oxidative stress is known to be strongly associated with atherosclerosis development and progression. Furthermore, visceral adipose tissue is a source of a large number of biologically active substances, including RAS components, inflammatory factors, interleukins, adiponectin, and others. Obesity is characterized by low serum adiponectin levels (hypoadiponectinemia). The severity of hypoadiponectinemia correlates with coronary lesions, and plasma adiponectin levels can be used to identify patients prone to coronary artery disease. It is of interest that adiponectin can limit the damage from myocardial infarction caused by high arterial pressure leading to impairment of nitric oxide production and release, and simultaneous accumulation of free radicals and mediators of inflammation in the vascular wall. Inflammation and activation of the renin-angiotensin-aldosterone (RAS) system and sympathetic nervous system are common pathophysiological processes for arterial hypertension and IHD. In particular, angiotensin II maintains elevated blood pressure and leads to atherosclerosis progression due to vasconstriction and vascular remodeling. It is also known to stimulate hypertrophy of cardiomyocytes and smooth muscle cells by the direct activation of type 1 receptors, and to increase expression of inflammatory factors and cytokines. Aside from this, RAS activation leads to the accumulation of low-density lipoproteins in the vascular wall.5

One possible role of adiponectin in atherosclerosis may relate to its ability to decrease lipid accumulation in the subendothelial space, which is the earliest step in atherosclerotic plaque formation. In addition, a single nucleotide polymorphism at position +276 in the adiponectin gene is known to be linked with IHD. T/T polymorphism is associated with a lower risk of developing coronary artery disease than G/G or G/T variants of the genes. Adiponectin has been shown to activate the peroxisome proliferator-activated receptor-α pathway and to increase expression of AdipoR1 in IHD. Expression of adiponectin receptors is 30% lower than normal in the subcutaneous fat of obese patients, and expression normalizes

Selected abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
</tr>
<tr>
<td>AF</td>
<td>atrial fibrillation</td>
</tr>
<tr>
<td>ARB</td>
<td>angiotensin receptor blocker</td>
</tr>
<tr>
<td>ASCOT</td>
<td>Anglo-Scandinavian Cardiac Outcomes Trial</td>
</tr>
<tr>
<td>CHARM</td>
<td>Candesartan in Heart failure Assessment of moRtality and Morbidity (trial)</td>
</tr>
<tr>
<td>HOPE</td>
<td>Heart Outcomes Prevention Evaluation</td>
</tr>
<tr>
<td>IHD</td>
<td>ischemic heart disease</td>
</tr>
<tr>
<td>IPC</td>
<td>ischemic preconditioning</td>
</tr>
<tr>
<td>LIFE</td>
<td>Losartan Intervention For Endpoint reduction in hyper-tension (trial)</td>
</tr>
<tr>
<td>LVH</td>
<td>left ventricular hypertrophy</td>
</tr>
<tr>
<td>RAS</td>
<td>renin-angiotensin-aldosterone</td>
</tr>
<tr>
<td>REACH</td>
<td>Reduction of Atherothrombosis for Continued Health (registry)</td>
</tr>
<tr>
<td>SCOPE</td>
<td>Study on COgnition and Prognosis in the Elderly</td>
</tr>
<tr>
<td>VALUE</td>
<td>Valsartan Antihypertensive Long-term Use Evaluation (trial)</td>
</tr>
</tbody>
</table>
following weight loss. It is well established that adiponectin plays an important role in type 2 diabetes, hypertension, multiple sclerosis, and dyslipidemia, the most significant of which is its insulin-sensitizing effect. Adiponectin blood levels are lower in diabetic patients than in nondiabetic individuals, and higher plasma levels of adiponectin minimize the risk of developing type 2 diabetes. Adiponectin is negatively related to blood glucose and insulin levels.\textsuperscript{10,12}

**Left ventricular hypertrophy**

Another important link between hypertension and IHD has been attributed to left ventricular hypertrophy (LVH), one of the forms of myocardial remodeling. Myocardial hypertrophy impairs myocardial relaxation and coronary perfusion during diastole. LVH is known to be an independent strong predictor of adverse cardiovascular events, including death from IHD, congestive heart failure, sudden cardiac death, and stroke.\textsuperscript{13} Data from the Framingham Heart Study showed that males with electrocardiographic signs of LVH had an eightfold increase in cardiovascular mortality and a sixfold increase in the rate of sudden death compared with those who did not have LVH.\textsuperscript{14}

So far, there is no clear opinion as to the reasons for the close association between hypertension, LVH, and IHD. Both experimental and clinical evidence confirms that high blood pressure stimulates the development of atherosclerosis.\textsuperscript{15,16} In addition, LVH is associated with changes in the density, structure, and tone of coronary arteries. Despite the fact that absolute coronary blood flow is elevated in the hypertrophied heart, a decrease in capillary density and coronary reserve is observed, even in the absence of coronary atherosclerosis.\textsuperscript{17,18}

In accordance with experimental data, hypertrophied myocardium is more susceptible to electrical instability during ischemia/reperfusion. During reperfusion after global ischemia, the ability to restore contractility is impaired in hypertrophied hearts, and levels of lactate dehydrogenase and creatine kinase are increased. A number of hypotheses have been put forward to explain the high sensitivity of the hypertrophied myocardium to ischemia/reperfusion injury, which include mitochondrial damage, lactate accumulation, disturbance of glycolysis, as well as oxidative stress and an increase in oxygen free radicals.\textsuperscript{16}

Elevated systemic blood pressure is one reason for the development of endothelial dysfunction and degenerative changes of the peripheral arteries associated with elasticity loss and an increase in vascular stiffness. Such changes lead to elevation of central blood pressure, causing additional strain and further remodeling of the left ventricle. These changes are especially significant in patients with isolated systolic hypertension, as a simultaneous decrease in diastolic blood pressure can worsen perfusion pressure in the coronary arteries. Both structural and functional changes in the peripheral arteries make a significant contribution to the phenomenon of blood pressure variability, which, in turn, leads to further hypertrophy and coronary flow impairment.\textsuperscript{10,20}

LVH is also associated with an increased risk of sudden cardiac death, which is usually due to fatal ventricular arrhythmias. The electrophysiological mechanisms are not fully understood, but experimental data suggest a prolongation of the action potential and changes in the ionic fluxes in hypertrophied cardiomyocytes. The presence of fibrosis foci is typical of LVH in arterial hypertension, and leads to the appearance of zones of impaired conductivity.\textsuperscript{21} Fibrosis also contributes to the dispersion of the duration of action potentials and to the formation of reentry. The frequency and severity of tachyarrhythmia is probably increased in the presence of LVH. Belichard et al demonstrated in 1987 that the duration of ventricular tachycardia paroxysms caused by coronary occlusion was significantly higher in spontaneously hypertensive rats than in control normotensive animals.\textsuperscript{22} This phenomenon was due exclusively to myocardial hypertrophy and not to elevated blood pressure. Similar results confirming the high rate of ventricular fibrillation in ischemia in hypertrophied myocardium were produced by other authors.\textsuperscript{15} Fibrosis of the myocardium and the phenomenon of high blood pressure variability probably contribute to the occurrence of another form of arrhythmia; namely, atrial fibrillation (AF), which is the most prevalent type of rhythm disturbance. At present, hypertension is the most frequent independent modifiable risk factor for AF. The relative risk of AF in hypertension is lower than in other diseases (eg, heart failure or valvular heart diseases), but because of the high worldwide prevalence of arterial hypertension, it is the main risk factor for AF.\textsuperscript{23} Investigations into the pathogenesis of AF have confirmed a strong association between AF and RAS activation.\textsuperscript{24}

**Treatment of arterial hypertension and concomitant ischemic heart disease**

The close association between arterial hypertension and IHD, the presence of common pathophysiological mechanisms, and the widespread prevalence of a number of concomitant problems (systolic and/or diastolic myocardial dysfunction, AF, ventricular arrhythmia) demand special attention with regard to choice of antihypertensive medication. Modern risk stratification criteria refer patients with arterial hypertension and concomitant cardiovascular disease to the very-high-risk group. It is well known that achievement of goal blood pressure levels in this particular category of patients is a serious problem. The debate concerning appropriate blood pressure lowering (“the lower, the better”) in this category of patients has been going on for more than 30 years. At the end of the 1970s, Steward demonstrated a fivefold increase in the relative risk of myocardial infarction in patients with diastolic blood pressure below 90 mm Hg compared with those in whom it remained within the 100-109 mm Hg range.\textsuperscript{25} There is still no definitive explanation for this “J-curve” phenomenon.
It is believed that excessive diastolic blood pressure reduction leads to the worsening of coronary perfusion and thus induces adverse coronary events. Most experts do not recommend diastolic blood pressure lowering to below 60 mm Hg.

According to the majority of the current guidelines, the target blood pressure level in hypertensive patients with concomitant cardiovascular diseases is 130/80 mm Hg; this demands more aggressive treatment and early administration of combination therapy. The presence of coexisting IHD requires medications with the following effects: (i) a decrease in the severity of symptoms (eg, angina pectoris); (ii) prevention of atherosclerosis progression; and (iii) modification of other factors that induce or worsen ischemia.

The general principles of nonpharmacological treatment in patients with arterial hypertension and IHD do not differ significantly from those in the general population of hypertensives. Regular physical activity improves inotropic function, decreases blood pressure, afterload, and arterial stiffness, and leads to an increase in coronary reserve.26

◆ β-Blockers

β-Blockers have been used in cardiology for more than 40 years, and according to many reports, they contribute significantly to blood pressure lowering, decrease cardiovascular morbidity and mortality, and positively affect clinical manifestations in patients with IHD. So at first glance, β-blockers could be an optimal treatment for this particular group of patients. However, it is well known that the use of β-blockers may be limited by a number of adverse events and poor tolerability: fatigue, weakness, sexual dysfunction, cold in the extremities, etc. Moreover, a large pool of data has demonstrated the negative effects of β-blockers on metabolism—first and foremost, on glycemic control. Finally, the results of an analysis of data from the REACH registry (Reduction of Atherothrombosis for Continued Health) published at the end of 2012 produced a strong response.27 Having analyzed data from 44 708 patients (31% with a history of myocardial infarction, and nephroprotection due to vasodilation caused by nitric oxide stimulation, stimulates aldosterone release, enhances cardiomyocyte contractility, hypertrophy, and fibrosis, and increases vascular tone and sodium reabsorption. It is thought that binding of angiotensin II to type 2 receptors promotes cardioprotection and nephroprotection due to vasodilation caused by nitric oxide release and antiproliferative and anti-apoptotic activity mediated by kinins.31 Both ACE inhibitors and ARBs are effective antihypertensive medications. Both classes prevent cardiovascular complications, which makes them the basic drugs for the treatment of high-risk patients. Leading European and American experts recommend these medications for patients with concomitant cardiovascular diseases.

◆ Angiotensin receptor blockers

In 2006, the results of a meta-analysis were published suggesting that ARBs can increase the risk of myocardial infarction. In the LIFE trial (Losartan Intervention For Endpoint reduction in hypertension) involving more than 9000 patients, losartan therapy was associated with a 5% increased rate of myocardial infarction (statistically insignificant) compared with atenolol-based therapy, despite the lower levels of blood pres-

◆ Calcium channel blockers

Another well-studied group of medications is the calcium channel blockers. They appear to be good substitutes for β-blockers in the treatment of angina in hypertensive patients; however, they are not recommended for secondary prevention because of their inability to prevent ventricular dilatation and heart failure. Nondihydropyridine agents should not be used in patients with systolic heart failure, and short-acting dihydropyridine calcium channel blockers should be avoided in patients with acute myocardial infarction, pulmonary edema, or significant left ventricular dysfunction.26

◆ RAS blockade

As mentioned, the RAS system plays a key role in the pathogenesis of arterial hypertension, atherosclerosis, type 2 diabetes, heart failure, and kidney damage. Thus, the groups of drugs that block RAS activity, namely angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), attract much attention. The level of RAS activity is believed to be a strong predictor of cardiovascular complications and death. For example, in untreated hypertensive patients, high plasma renin levels are associated with a more than twofold increase in cardiovascular morbidity, and in patients with severe IHD, they are associated with a high mortality level.28,29 Aside from its potent vasoconstrictor effect, angiotensin II affects cell growth and sodium and water metabolism, and modulates sympathetic activity. It also promotes endothelial dysfunction, inflammation, oxidative stress, and insulin resistance, and decreases the reactivity of pancreatic β-cells.20
sure obtained in the losartan group. In SCOPE (Study on COGnition and Prognosis in the Elderly), compared with the control group, candesartan treatment was associated with a 10% increased incidence of fatal and nonfatal myocardial infarction, which also did not achieve statistical significance. The results of VALUE (Valsartan Antihypertensive Long-term Use Evaluation) in 15 245 patients demonstrated a significant 19% increase (P=0.02) in the rate of myocardial infarction in patients receiving valsartan 160 mg compared with those receiving amlodipine 10 mg.

It should be noted that all of the aforementioned trials included hypertensive patients at very high risk, 80% of whom had evident cardiovascular disease. In total, 9 of the 11 major clinical trials on ARBs reported an increased rate of myocardial infarction, and in 2 of these (VALUE and CHARM [Candesartan in Heart failure Assessment of moRtality and Morbidity]), the difference was statistically significant.

This paradox can be explained by the excessive stimulation and overexpression of angiotensin type 2 receptors. As a result of angiotensin type 1 receptor blockade, ARBs can cause an increase in angiotensin II levels that leads to the excessive stimulation of type 2 receptors. It is thought that such stimulation has adverse effects due to enhanced cell growth, fibrosis, hypertrophy, a proinflammatory effect, and stimulation of atherogenesis. Experimental data report that excessive stimulation of type 2 receptors leads to cardiomyocyte contractile dysfunction, and in humans, this phenomenon is associated with hypertrophy. It was also demonstrated that activation of type 2 receptors inhibits hypoxia-induced neovascularization, which is an important compensatory mechanism in chronic myocardial ischemia. In 2005, Alfakih et al in the UK revealed an association between increased expression of angiotensin type 2 receptors and early development of IHD. These data suggest that ARBs can cause plaque injury and rupture.

ACE inhibitors

ACE inhibitors are not associated with increased levels of angiotensin II. Besides ACE inhibition, the drugs are accompanied by increased levels of some ACE-dependent substrates; eg, bradykinin, substance P, and enkephalins. This phenomenon provides ACE inhibitors with additional physiological and clinical properties: increased vasodilation, decreased thrombogenesis, and the slowing down of atherogenesis and tissue proliferation. Bradykinin suppresses platelet aggregation and decreases the level of plasminogen activator inhibitor-1, which is a potent fibrinolysis inhibitor and can independently predict the mortality rate after myocardial infarction. Thus, long-term use of ACE inhibitors improves peripheral vasodilation mediated by bradykinin and stimulates the release of tissue plasminogen activator to levels achieved during systemic thrombolysis. Bradykinin is also the main mediator of ischemic preconditioning, a unique phenomenon that allows cardiomyocytes to avoid damage during ischemia, decreases the size of infarction, and prevents ventricular arrhythmia. ACE inhibitors have been shown to improve endothelial function in peripheral and coronary arteries. One of the suggested mechanisms for this is their effect on gene expression, which leads to the enhanced activity of cyclo-oxygenase-2, and consequently to prostacyclin and prostaglandin E2 production, without increasing thromboxane A2. In contrast, ARBs have practically no effect on endothelial dysfunction, which is known to be an early marker of atherosclerosis.

Although the beneficial effects of ACE inhibitors on postinfarct left ventricular remodeling have been unequivocally demonstrated in both animal models and clinical trials, the acute infarct-limiting effect of these drugs has been controversial. Recent evidence suggests that a genetically-determined decrease in ACE activity is associated with a significant reduction in infarct size. By contrast, increased ACE activity in mice was found to be associated with a trend toward increased infarct size and blunted preconditioning-mediated infarct limitation. Oral administration of ramiprilat at a dose of 50 μg/kg during 1, 4, and 10 weeks resulted in a significantly reduced infarct size in a rat model of myocardial ischemia-reperfusion. It should be noted, however, that the infarct-limiting effect of ACE inhibitors has been called into question by other investigators. This controversy could stem from the use of different routes of drug administration in different studies and differences in the doses of drugs and their pharmacokinetic profiles.

In our own experiments, we investigated the infarct-limiting and antiarrhythmic effects of captopril and zofenopril in the rat model of myocardial ischemia-reperfusion in vivo. Both ACE inhibitors were administered intravenously and the mean blood pressure and heart rate were monitored throughout the experiments. Baseline blood pressure and heart rate values were no different among the groups. Intravenous administration of ACE inhibitors at a dose of 2.5 mg/kg resulted in a significant blood pressure decrease (by 40% to 45% from baseline). The ACE inhibitor–induced decrease in blood pressure persisted throughout the entire experiment. No changes in heart rate were observed after ACE inhibitor infusion. The anatomical area at risk was no different between the groups. In comparison with controls, infarct size was significantly smaller in the group of animals treated with zofenopril, and there also tended to be a decrease in the captopril group. These data indicate that zofenopril significantly limited the infarct size when administered 30 minutes prior to ischemia. The enhanced infarct-limiting effect could be explained by the presence of an SH group in the chemical structure of zofenopril, as well as by its greater ability to inhibit tissue ACE.

Ischemic preconditioning

Ischemic preconditioning (IPC) is a phenomenon of increased myocardial tolerance to ischemia-reperfusion injury occurring after single or multiple brief episodes of ischemia-reper-
We were interested in investigating whether a subthreshold preconditioning stimulus could be strengthened by the concomitant administration of the ACE inhibitor spirapril. IPC was elicited by a single 5-minute episode of ischemia followed by 5 minutes of reperfusion. IPC significantly reduced infarct size, but spirapril alone failed to limit the infarct size.

However, a combination of the preconditioning stimulus and a nonhypotensive dose of spirapril resulted in significant attenuation of infarct size compared with IPC alone, which is suggestive of a potentiation of the protective effect of IPC by the ACE inhibitor. These data are in agreement with the findings of Miki et al, who showed that captopril could enhance the infarct-limiting effect of a single 2-minute IPC stimulus in rabbits. This effect was abolished by the concomitant administration of the B2-receptor blocker HOE 140, which indicates that ACE inhibitor–induced potentiation of IPC is bradykinin dependent.

**Metabolic effects**

Another important issue with regard to RAS blockade concerns the beneficial metabolic effects of RAS blockers. A number of clinical trials have observed beneficial effects of RAS blockade on cardiovascular morbidity and mortality in both hypertensive and normotensive patients with the metabolic syndrome. RAS blockade is known to have positive effects on insulin resistance, glucose tolerance, lipid profiles, and oxidative state. In an animal model of insulin resistance and RAS overactivity, administration of RAS blockers improved insulin sensitivity, stimulated glucose transport into muscle, and reduced oxidative stress. Similar results were shown in other experimental studies in which RAS blockade was associated with increased numbers of GLUT-4 transporters and increased glucose uptake.

Moreover, analysis of HOPE (Heart Outcomes Prevention Evaluation) demonstrated a 32% reduction in the incidence of new-onset diabetes in patients treated with an ACE inhibitor.

**Statins**

When discussing the treatment of hypertensive patients with IHD, one cannot avoid mentioning the statin group of drugs. The addition of lipid-lowering medications to RAS inhibitors is a widely-accepted treatment strategy in this category of patients. There are several possible interactions between cholesterol and angiotensin II: (i) as they affect endothelial function, they may interact to promote the development and progression of atherosclerosis; (ii) hypercholesterolemia, particularly high levels of low-density lipoprotein, leads to the upregulation of vascular ACE and angiotensin II type 1 receptors; and (iii) angiotensin II promotes oxidation and vascular uptake of low-density lipoprotein cholesterol.

Aside from lowering cholesterol levels, statins are known to modify endothelial function and atherogenesis, stabilize atherosclerotic plaques, and reduce inflammation and thrombus formation. These pleiotropic properties of statins may have important clinical implications in addition to their lowering of serum cholesterol levels.

Important data on statins came from ASCOT-LLA (the lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial, which was a double-blind placebo-controlled trial of atorvastatin in 10,305 hypertensive patients originally enrolled in the blood pressure–lowering arm of ASCOT and with baseline total cholesterol concentrations of below 6.5 mmol/L. ASCOT-LLA was stopped prematurely after a 3.3-year follow-up because of a 36% relative risk reduction in nonfatal myocardial infarction and fatal coronary heart disease (the primary outcome) in favor of atorvastatin and a nonsignificant reduction in cardiovascular death (16%) and all-cause mortality (13%). In the 11 years after initial randomization and 8 years after closure of the lipid-lowering arm, all-cause mortality remained significantly lower in patients assigned to atorvastatin. Cardiovascular deaths were also fewer, although not significantly, and noncardiovascular deaths were significantly lower, which was attributed to a reduction in deaths from infection and respiratory illness. The study authors concluded that the pleiotropic effects of statins may play a role in these protective effects.

Clinical data suggest that hypertensive diabetic patients who experience an acute myocardial infarction have a smaller infarct size, better global systolic function, and less hospital morbidity and mortality if they were receiving combined ACE inhibitor and statin therapy prior to the event. Thus, prior combination therapy with an ACE inhibitor and a statin has cardioprotective effects in hypertensive diabetic patients with acute myocardial infarction.

The combination of an ACE inhibitor and a statin stops proteinuria and protects against renal dysfunction and structure impairment. Statins reduce cholesterol, are antiatherosclerotic, and improve endothelial function. ACE inhibitors are effective in controlling hypertension and cardiovascular disease, not only because of their blood pressure–lowering effect, but also as a result of their ability to block the production of angiotensin II. Further studies are warranted to confirm the beneficial impact of ACE inhibitors and statins and their potentially synergistic mode of action, as this could represent a potent and effective combination in high-risk patient populations.

**Future therapies**

In terms of the development of new drugs and therapeutic approaches, one attractive option is the newly-discovered class of intracellular regulators, microRNAs (miRNAs). Their small size and known conserved sequences make them promising candidates in the development of new drugs. Currently, there are two major approaches in microRNA therapeutics—activation of existing miRNAs (miRNA mimetics) and blockade of miRNAs with the help of complementary oligonucleotides (antimiRs). The latter approach is easier and currently much...
more advanced; however, there are no cardiology clinical trials presently in progress using anti-miRs, despite the development of many approaches and intracellular targets in this area. In the field of arterial hypertension and coronary artery disease, protection of the target organs—in particular, prevention of left ventricular hypertrophy—is an important task. To this end, miR-208a, the only cardiac-specific microRNA encoded in the α-MYH7 gene, is known to block cardiac hypertrophy. At the same time, it has been shown to have a protective effect against development of cardiac fibrosis and cardiac remodeling after ischemia and development of dias- tolic heart failure, as well as the ability to improve tissue and systemic energy metabolism. Other potential options are miR-21 and miR-29, which specifically target cardiac fibrosis.

Conclusion
In general, the choice of treatment for a hypertensive patient with a serious comorbidity such as IHD should take into account the whole complexity of the problem: atherosclerosis, angina, fibrosis, arrhythmia, dyslipidemia, and other metabolic disorders. Drug therapy should be individualized and should take into account the heightened risk for cardiovascular events. Recent data suggest that the use of certain groups of medications raises many questions, but administration of ACE inhibitors, statins, and acetylsalicylic acid seems undeniably beneficial. It is of note that hypertensive patients with concomitant IHD belong to the very-high-risk group, and as such, should all receive combination therapy as a first step in their treatment regimen.

References

424 MEDICOGRAFIA, Vol 35, No. 4, 2013
Antihypertensive treatment in ischemic heart disease: is there an ideal pR? – Shykhto

H Y P E R T E N S I O N A N D C A R D I O V A S C U L A R P R E V E N T I O N:
W H E R E A R E C O M B I N A T I O N S G O I N G?


**Keywords:** cardiovascular risk; ischemic heart disease; hypertension; metabolic syndrome; renin-angiotensin system
Is fixed-combination antihypertensive therapy needed in post-stroke patients?

by J. Chalmers and H. Arima, Australia

Combination antihypertensive therapy is now recommended for the vast majority of patients who need blood pressure–lowering therapy. Patients with previous stroke form a particularly important group for whom combination therapy has been shown to be both beneficial and superior. The best evidence for this comes from the PROGRESS trial (Perindopril pROtection aGainst REcurrent Stroke Study), which clearly demonstrated that a regimen based on the angiotensin-converting enzyme inhibitor perindopril, with additional use of the diuretic indapamide, as required, reduced the incidence of recurrent stroke by around one quarter. In the PROGRESS trial, combination therapy with perindopril and indapamide produced an even larger reduction in the risk of stroke (relative risk reduction, 43%), which is consistent with the larger blood pressure reduction obtained with combination therapy compared with single drug therapy (12.3/5.0 mm Hg vs 4.9/2.8 mm Hg). Similar trends toward greater reductions associated with combination therapy were also observed for all other outcomes including major vascular events, coronary heart events, heart failure, disability, dependency, cognitive decline, and death. Therefore, the combination of perindopril and indapamide can be recommended for the prevention of recurrent stroke and associated cardiovascular events in all patients with cerebrovascular disease.

Medicographia. 2013;35:426-432 (see French abstract on page 432)

Combination antihypertensive therapy is now recommended for the vast majority of patients who need blood pressure–lowering therapy, including those with hypertension (defined as systolic blood pressure ≥140 mm Hg), and also patients with high cardiovascular risk, whether hypertensive or not. Furthermore, in the past 10 years, these recommendations have broadened to cover the use of combination therapy to initiate drug treatment for patients with more severe hypertension (systolic blood pressure ≥160 mm Hg) or patients at high cardiovascular risk. In addition, many guidelines now recommend that fixed-dose (or “single pill”) combinations may be used, as they may facilitate adherence and improve blood pressure control.

Patients with previous stroke form a particularly important group for whom combination therapy has been shown to be both beneficial and superior. The best evidence for this comes from the PROGRESS trial (Perindopril pROtection aGainst REcurrent Stroke Study), which clearly demonstrated that a regimen based on the angiotensin-converting enzyme inhibitor perindopril, with additional use of the di-
uretic indapamide, as required, reduced the incidence of re-
current stroke, major vascular events, coronary heart events,
and heart failure by around one quarter.\textsuperscript{15,16} Even more impor-
tant, the main analysis and all subsequent analyses have
confirmed that the greatest reductions in stroke and all other
major cardiovascular events were obtained in the subgroup
treated with both perindopril and indapamide.\textsuperscript{6,9}

Since then, a number of other studies have reported the ef-
fects of blood pressure–lowering after stroke, using a variety
of other regimens.\textsuperscript{10,11} Some of these studies compared active
treatment with placebo,\textsuperscript{11} while others compared two active
treatments.\textsuperscript{10} None of these studies involved combination ther-
apy either in the trial as a whole, or in a specific subset of pa-
ents. In this article, we examine the results of PROGRESS
and of the more recent trials and present analyses based both
on PROGRESS and on a meta-regression of numerous stud-
ies. The particular focus of this article will be on the evidence
regarding the use of combination blood pressure–lowering
therapy in patients with cerebrovascular disease and on the
possible benefits observed with the combinations that have
been tested.

The PROGRESS trial – results and implications

\textbf{Background}

Stroke kills over 5 million people every year, so that it now con-
stitutes the second largest cause of death across the world.\textsuperscript{12}
Many more people have a stroke and survive it—well over 15
million annually—but around one-third of survivors are dis-
able. Recurrent stroke is also common in survivors and pre-
vention of recurrence is a major challenge. While aspirin ther-
apy has been shown to be effective for reducing recurrence
after ischemic stroke, prior to PROGRESS no strategies were
available to prevent stroke recurrence after a hemorrhagic
stroke.\textsuperscript{13}

The PROGRESS trial was launched as an investigator-initiat-
ed study to test the hypothesis that routine blood pressure
lowering in patients who had suffered a stroke or a transient
ischemic attack, would be both safe and effective in reduc-
ing the incidence of recurrent stroke. A number of small trials
had been conducted before PROGRESS with mixed results,
and there was continuing uncertainty regarding the wisdom
and safety of lowering blood pressure in patients who had sur-
vived a stroke.\textsuperscript{14}

As there was good evidence from observational studies that
the association between blood pressure and both primary and
secondary stroke was positive and continuous, well into
the normal range of blood pressure,\textsuperscript{15,16} all patients with pre-
vious stroke or transient ischemic attack could be enrolled in
PROGRESS, whether they were hypertensive or normoten-
sive.\textsuperscript{6,14} Furthermore, PROGRESS was deliberately planned to
include patients from China and Japan, where stroke is par-
icularly common.

\textbf{Brief description of the PROGRESS trial}

Patients were eligible for PROGRESS if they had a stroke or a
transient ischemic attack in the past five years. They also had
to have no definite indication or contraindication to treatment
with an angiotensin converting-enzyme inhibitor. There were
no blood pressure entry criteria and both hypertensive and
normotensive individuals were eligible. Potentially eligible in-
dividuals entered a 4-week run-in period during which they
received open-label perindopril, 2 mg daily for 2 weeks fol-
lowed by 4 mg daily for another 2 weeks. Participants who
tolerated this treatment were randomly assigned on a double
blind basis to either continuing active therapy or matching pla-
cebo. Active therapy consisted of a flexible regimen whereby
all participants received perindopril 4 mg daily, with addition
of the diuretic indapamide 2.5 mg daily (2 mg in Japan), in pa-
tients without definite indication or contraindication to treatment
with a diuretic. The purpose of allowing combination therapy
was to maximize the magnitude of blood pressure reduction
achieved; and physicians were asked, prior to randomization,
to determine whether the individual participants should be ran-
donized to single therapy with perindopril (or matching place-
bo) or to combination therapy with both perindopril and in-
dapamide (or double placebo). After the first few months,
patients were seen every six months, and blood pressure was
measured with a mercury sphygmomanometer.

The primary study outcome was stroke (fatal or nonfatal),
and secondary outcomes included stroke subtypes, major vas-
cular events (nonfatal stroke, nonfatal myocardial infarction,
or death due to any vascular cause), disability, dementia, and
cognitive decline. Prespecified subgroup analyses included
comparison of treatment effects among participants random-
ized to combination therapy or to single therapy.

\textbf{Patient enrolment, follow-up, and baseline characteristics}

A total of 7121 patients entered the 4-week run-in phase and
1016 were found ineligible or withdrew during that time, so that
6105 were randomized. Of those randomized, 3051 were as-
signed active treatment, with 1770 stratified to the combina-
tion of perindopril 4 mg and indapamide 2.5 mg and 1281
stratified to perindopril alone. A total of 3054 patients were
assigned placebo treatment, with 1774 on double placebo
and 1280 on single placebo. The mean duration of follow-up
was 3.9 years. Only 3 patients were lost to follow-up and had
unknown vital status at the end of the study, 2 on active treat-
ment and 1 on placebo.

The baseline characteristics of all randomized participants are
summarized in Table I (page 428). There was a good balance
between those on active treatment and those on placebo.
There was also a good balance between those stratified to
combination therapy or to single therapy, though as expect-
ed, those on combination therapy or double placebo, were
younger, had higher baseline blood pressures, and were more
likely to be hypertensive or to have coronary disease (Table I).
**HYPERTENSION AND CARDIOVASCULAR PREVENTION: WHERE ARE COMBINATIONS GOING?**

**Fixed-combination antihypertensive therapy in post-stroke patients – Chalmers and Arima**

### Figure 1. PROGRESS trial: Cumulative incidence of stroke among 3051 participants assigned active treatment and 3054 participants assigned placebo (A) and among 1770 participants assigned combination therapy and 1774 assigned double placebo (B).

**Table 1. Baseline characteristics of PROGRESS participants.**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Randomized treatment</th>
<th>Prespecified regimen*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active (n=3051)</td>
<td>Placebo (n=3054)</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>64 (10)</td>
<td>64 (10)</td>
</tr>
<tr>
<td>Women, %</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Asian†, %</td>
<td>39</td>
<td>39</td>
</tr>
</tbody>
</table>

**Cerebrovascular disease history**

<table>
<thead>
<tr>
<th></th>
<th>Randomized treatment</th>
<th>Prespecified regimen*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active (n=3051)</td>
<td>Placebo (n=3054)</td>
</tr>
<tr>
<td>Ischemic stroke, %</td>
<td>71</td>
<td>71</td>
</tr>
<tr>
<td>Hemorrhagic stroke, %</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Stroke of unknown type, %</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>TIA, %</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Median time since qualifying event, months (interquartile range)</td>
<td>8 (2 to 21)</td>
<td>8 (2 to 22)</td>
</tr>
</tbody>
</table>

**Other medical history, %**

<table>
<thead>
<tr>
<th></th>
<th>Randomized treatment</th>
<th>Prespecified regimen*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active (n=3051)</td>
<td>Placebo (n=3054)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>CHD‡</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Carotid disease§</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

**Blood pressure**

<table>
<thead>
<tr>
<th></th>
<th>Randomized treatment</th>
<th>Prespecified regimen*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active (n=3051)</td>
<td>Placebo (n=3054)</td>
</tr>
<tr>
<td>Mean SBP, mm Hg (SD)</td>
<td>147 (19)</td>
<td>147 (19)</td>
</tr>
<tr>
<td>Mean DBP, mm Hg (SD)</td>
<td>86 (11)</td>
<td>86 (11)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>48</td>
</tr>
</tbody>
</table>

**Medication, %**

<table>
<thead>
<tr>
<th></th>
<th>Randomized treatment</th>
<th>Prespecified regimen*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active (n=3051)</td>
<td>Placebo (n=3054)</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>73</td>
<td>72</td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Antihypertensive therapy¶</td>
<td>49</td>
<td>51</td>
</tr>
<tr>
<td>Lipid-lowering therapy</td>
<td>13</td>
<td>15</td>
</tr>
</tbody>
</table>

*Combination=perindopril + indapamide, or double placebo; single= perindopril alone or single placebo.

†Participants recruited from the People’s Republic of China or Japan.

‡History of myocardial infarction or coronary revascularization, or angina (supported by documented electrocardiographic or angiographic evidence).

§Previous carotid endarterectomy, previous carotid angioplasty or carotid stenosis > 50% (confirmed by angiogram or Doppler).

||Systolic ≥160mm Hg and/or diastolic blood pressure ≥90mm Hg.

¶Currently treated hypertension.

**Abbreviations:** CHD, coronary heart disease; DBP, diastolic blood pressure; PROGRESS, Perindopril PROtection aGainst REcurrent Stroke Study; SD, standard deviation; SBP, systolic blood pressure; TIA, transient ischemic attack.

**Effects on blood pressure**
Overall, across the whole 4 years of follow up, blood pressure was reduced by an average of 9.0/4.0 mm Hg among those randomized to active treatment compared with those assigned placebo. The reduction was considerably greater among those treated with combination therapy (12.3/5.0 mm Hg), and was actually twice that observed in participants treated with single therapy (4.9/2.8 mm Hg).

**Effects on stroke**
Active treatment reduced the risk of stroke by 28% overall ($P<0.0001$). The Kaplan-Meier curves diverged early and continued to separate during follow-up (Figure 1). Among participants treated with combination therapy, perindopril plus indapamide, the greater reduction in blood pressure was matched by a greater 43% reduction in stroke risk, compared with those receiving single therapy with perindopril alone (Figure 2, panel A). The reductions in stroke subtypes, particularly hemorrhagic stroke and ischemic stroke, were also markedly accentuated in patients on combination therapy, not only compared with those on single therapy, but also compared with the overall reduction for those on any active treatment, whether single or dual (Figure 3, page 430). Thus, combination therapy achieved a 76% reduction in hemorrhagic stroke, a 36% reduction in ischemic stroke (Figure 3), and a 46% reduction in fatal or disabling stroke.

A subsidiary analysis of PROGRESS data examined the effects of randomized blood pressure-lowering treatment on the risk of stroke by strata of baseline blood pressure. Combination therapy with perindopril and indapamide provided consistently greater benefits, which were significant across a range of subgroups defined by baseline systolic and diastolic blood pressures ranging from $\geq 160/100$ mm Hg to $<120/80$ mm Hg (Figure 2, panel B).

**Effects on major vascular events**
Out of the 6105 randomized patients, 1062 participants experienced a major vascular event, fatal or nonfatal, 458 in the active treatment group and 604 in the placebo group, a reduction of 26% with active treatment ($P<0.001$). The reduction in major vascular events was much greater in participants receiving the combination of perindopril plus indapamide (40%; $P<0.001$).

<table>
<thead>
<tr>
<th>A</th>
<th>Number of events</th>
<th>BP reduction</th>
<th>Favors active</th>
<th>Favors placebo</th>
<th>Risk reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination therapy</td>
<td>150</td>
<td>255</td>
<td>12/5 mm Hg</td>
<td></td>
<td>43% (30 to 54%)</td>
</tr>
<tr>
<td>Single-drug therapy</td>
<td>157</td>
<td>165</td>
<td>5/3 mm Hg</td>
<td></td>
<td>5% (-19 to 23%)</td>
</tr>
<tr>
<td>Total</td>
<td>307</td>
<td>420</td>
<td>9/4 mm Hg</td>
<td></td>
<td>28% (17 to 38%)</td>
</tr>
<tr>
<td>Major vascular events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination therapy</td>
<td>231</td>
<td>367</td>
<td>12/5 mm Hg</td>
<td></td>
<td>40% (29 to 49%)</td>
</tr>
<tr>
<td>Single-drug therapy</td>
<td>227</td>
<td>237</td>
<td>5/3 mm Hg</td>
<td></td>
<td>4% (-15 to 20%)</td>
</tr>
<tr>
<td>Total</td>
<td>458</td>
<td>604</td>
<td>9/4 mm Hg</td>
<td></td>
<td>26% (16 to 34%)</td>
</tr>
</tbody>
</table>

**B**

<table>
<thead>
<tr>
<th>Systolic blood pressure</th>
<th>Number of events</th>
<th>Favors active</th>
<th>Favors placebo</th>
<th>Risk reduction (95% CI)</th>
<th>P homogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active</td>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&gt;160$ mm Hg</td>
<td>57</td>
<td>106</td>
<td></td>
<td></td>
<td>47% (27-62%)</td>
</tr>
<tr>
<td>140 to 159 mm Hg</td>
<td>54</td>
<td>87</td>
<td></td>
<td></td>
<td>41% (16-58%)</td>
</tr>
<tr>
<td>120 to 139 mm Hg</td>
<td>37</td>
<td>58</td>
<td></td>
<td></td>
<td>41% (11-61%)</td>
</tr>
<tr>
<td>$&lt;120$ mm Hg</td>
<td>2</td>
<td>4</td>
<td></td>
<td></td>
<td>36% (-249-88%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diastolic blood pressure</th>
<th>Number of events</th>
<th>Favors active</th>
<th>Favors placebo</th>
<th>Risk reduction (95% CI)</th>
<th>P homogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active</td>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&gt;100$ mm Hg</td>
<td>16</td>
<td>40</td>
<td></td>
<td></td>
<td>64% (35-80%)</td>
</tr>
<tr>
<td>90 to 99 mm Hg</td>
<td>53</td>
<td>84</td>
<td></td>
<td></td>
<td>41% (17-58%)</td>
</tr>
<tr>
<td>89 to 90 mm Hg</td>
<td>52</td>
<td>85</td>
<td></td>
<td></td>
<td>39% (14-57%)</td>
</tr>
<tr>
<td>$&lt;80$ mm Hg</td>
<td>49</td>
<td>46</td>
<td></td>
<td></td>
<td>36% (1-61%)</td>
</tr>
</tbody>
</table>

**Figure 2.** (A) Effects of combination and single drug therapy on stroke and major vascular events and (B) effects of combination therapy on stroke by baseline blood pressure in the PROGRESS trial. Solid boxes represent estimates of hazard ratio of outcomes; the areas of the boxes are proportional to the inverse variance of the estimates; vertical lines represent 95% CI; diamonds represent estimates and 95% CI for overall effects. Abbreviations: CI, confidence interval; PROGRESS, Perindopril RRointervention aGainst REcurrent Stroke Study. Panel A: modified from reference 6: PROGRESS Collaborative Group. Lancet. 2001;358:1033-1041. © 2001, Elsevier. Panel B: after reference 18: Arima and Chalmers. J Clin Hypertens (Greenwich). 2011;13: 693-702. © 2011, Wiley Periodicals, Inc.
Association between the risk of stroke and achieved blood pressure in clinical trials

**The PROGRESS trial**
An observational analysis of PROGRESS revealed that the lowest risk of recurrent stroke was observed in the one quarter of patients who achieved the lowest follow-up blood pressure levels (with a median of 112/72 mm Hg), with no excess of serious complications. Once again, these effects were substantially magnified in the group receiving combination treatment (Figure 3, right panel), where, for example, the reduction in the risk of dementia reached 23% (P<0.05) in those who receiving perindopril and indapamide (Figure 3).9

**Effects on other outcomes**
Active treatment resulted in significant reductions in many secondary outcomes including major coronary events, heart failure, disability and dependency, and cognitive decline (Figure 3, left panel).6,9,10 Once again, these effects were substantially magnified in the group receiving combination treatment (Figure 3, right panel), where, for example, the reduction in the risk of dementia reached 23% (P<0.05) in those who receiving perindopril and indapamide (Figure 3).9

**Randomized trials after PROGRESS**
Several randomized trials completed after PROGRESS have reported the effects of blood pressure lowering on recurrent stroke, though none has looked specifically at the effects of combination therapy.9,10,11,20-23 A meta-regression of these and other observational data are supported by the evidence shown in Figure 2 (panel B), demonstrating the efficacy of combination therapy across subgroups, defined by baseline systolic and diastolic blood pressures down to <120/80 mm Hg.17,18

---

**Figure 3. Effects of blood pressure lowering on serious clinical outcomes in the PROGRESS trial.**
Solid boxes represent estimates of relative risk of outcomes (hazard ratio for stroke, major coronary events, heart failure, major vascular events, vascular death and total death, and odds ratio for disability, dependency, dementia and cognitive decline). Other conventions as for Figure 2.

**Figure 4. Annual rates of ischemic stroke and intracerebral hemorrhage according to achieved follow-up systolic blood pressure levels in the PROGRESS trial.**
Annual incidence rates and 95% confidence intervals. Annual rates are based on the estimated annual incidence rate and at median values of systolic blood pressure; the areas of the boxes are proportional to the number of events. Vertical lines represent 95% confidence interval. P trend=0.0005 for ischemic stroke, <0.0001 for intracerebral hemorrhage. PROGRESS, Perindopril PROtection Against REcurrent Stroke Study.

**Abbreviations:** CI, confidence interval; PROGRESS, Perindopril PROtection Against REcurrent Stroke Study.

---

**Effects on other outcomes**
Active treatment resulted in significant reductions in many secondary outcomes including major coronary events, heart failure, disability and dependency, and cognitive decline (Figure 3, left panel).6,9,10 Once again, these effects were substantially magnified in the group receiving combination treatment (Figure 3, right panel), where, for example, the reduction in the risk of dementia reached 23% (P<0.05) in those who receiving perindopril and indapamide (Figure 3).9

Association between the risk of stroke and achieved blood pressure in clinical trials

**The PROGRESS trial**
An observational analysis of PROGRESS revealed that the lowest risk of recurrent stroke was observed in the one quarter of patients who achieved the lowest follow-up blood pressure levels (with a median of 112/72 mm Hg), with no excess of serious complications.11 Similar relationships were observed for both ischemic and hemorrhagic stroke (Figure 4),12 both in patients with and without chronic kidney disease.10 These observational data are supported by the evidence shown in Figure 2 (panel B), demonstrating the efficacy of combination therapy across subgroups, defined by baseline systolic and diastolic blood pressures down to <120/80 mm Hg.17,18

---

**Figure 3. Effects of blood pressure lowering on serious clinical outcomes in the PROGRESS trial.**
Solid boxes represent estimates of relative risk of outcomes (hazard ratio for stroke, major coronary events, heart failure, major vascular events, vascular death and total death, and odds ratio for disability, dependency, dementia and cognitive decline). Other conventions as for Figure 2.

**Figure 4. Annual rates of ischemic stroke and intracerebral hemorrhage according to achieved follow-up systolic blood pressure levels in the PROGRESS trial.**
Annual incidence rates and 95% confidence intervals. Annual rates are based on the estimated annual incidence rate and at median values of systolic blood pressure; the areas of the boxes are proportional to the number of events. Vertical lines represent 95% confidence interval. P trend=0.0005 for ischemic stroke, <0.0001 for intracerebral hemorrhage. PROGRESS, Perindopril PROtection Against REcurrent Stroke Study.

**Abbreviations:** CI, confidence interval; PROGRESS, Perindopril PROtection Against REcurrent Stroke Study.

---

**Effects on other outcomes**
Active treatment resulted in significant reductions in many secondary outcomes including major coronary events, heart failure, disability and dependency, and cognitive decline (Figure 3, left panel).6,9,10 Once again, these effects were substantially magnified in the group receiving combination treatment (Figure 3, right panel), where, for example, the reduction in the risk of dementia reached 23% (P<0.05) in those who receiving perindopril and indapamide (Figure 3).9

Association between the risk of stroke and achieved blood pressure in clinical trials

**The PROGRESS trial**
An observational analysis of PROGRESS revealed that the lowest risk of recurrent stroke was observed in the one quarter of patients who achieved the lowest follow-up blood pressure levels (with a median of 112/72 mm Hg), with no excess of serious complications.11 Similar relationships were observed for both ischemic and hemorrhagic stroke (Figure 4),12 both in patients with and without chronic kidney disease.10 These observational data are supported by the evidence shown in Figure 2 (panel B), demonstrating the efficacy of combination therapy across subgroups, defined by baseline systolic and diastolic blood pressures down to <120/80 mm Hg.17,18

---

**Figure 3. Effects of blood pressure lowering on serious clinical outcomes in the PROGRESS trial.**
Solid boxes represent estimates of relative risk of outcomes (hazard ratio for stroke, major coronary events, heart failure, major vascular events, vascular death and total death, and odds ratio for disability, dependency, dementia and cognitive decline). Other conventions as for Figure 2.

**Figure 4. Annual rates of ischemic stroke and intracerebral hemorrhage according to achieved follow-up systolic blood pressure levels in the PROGRESS trial.**
Annual incidence rates and 95% confidence intervals. Annual rates are based on the estimated annual incidence rate and at median values of systolic blood pressure; the areas of the boxes are proportional to the number of events. Vertical lines represent 95% confidence interval. P trend=0.0005 for ischemic stroke, <0.0001 for intracerebral hemorrhage. PROGRESS, Perindopril PROtection Against REcurrent Stroke Study.

**Abbreviations:** CI, confidence interval; PROGRESS, Perindopril PROtection Against REcurrent Stroke Study.

---

**Effects on other outcomes**
Active treatment resulted in significant reductions in many secondary outcomes including major coronary events, heart failure, disability and dependency, and cognitive decline (Figure 3, left panel).6,9,10 Once again, these effects were substantially magnified in the group receiving combination treatment (Figure 3, right panel), where, for example, the reduction in the risk of dementia reached 23% (P<0.05) in those who receiving perindopril and indapamide (Figure 3).9

Association between the risk of stroke and achieved blood pressure in clinical trials

**The PROGRESS trial**
An observational analysis of PROGRESS revealed that the lowest risk of recurrent stroke was observed in the one quarter of patients who achieved the lowest follow-up blood pressure levels (with a median of 112/72 mm Hg), with no excess of serious complications.11 Similar relationships were observed for both ischemic and hemorrhagic stroke (Figure 4),12 both in patients with and without chronic kidney disease.10 These observational data are supported by the evidence shown in Figure 2 (panel B), demonstrating the efficacy of combination therapy across subgroups, defined by baseline systolic and diastolic blood pressures down to <120/80 mm Hg.17,18

---

**Figure 3. Effects of blood pressure lowering on serious clinical outcomes in the PROGRESS trial.**
Solid boxes represent estimates of relative risk of outcomes (hazard ratio for stroke, major coronary events, heart failure, major vascular events, vascular death and total death, and odds ratio for disability, dependency, dementia and cognitive decline). Other conventions as for Figure 2.

**Figure 4. Annual rates of ischemic stroke and intracerebral hemorrhage according to achieved follow-up systolic blood pressure levels in the PROGRESS trial.**
Annual incidence rates and 95% confidence intervals. Annual rates are based on the estimated annual incidence rate and at median values of systolic blood pressure; the areas of the boxes are proportional to the number of events. Vertical lines represent 95% confidence interval. P trend=0.0005 for ischemic stroke, <0.0001 for intracerebral hemorrhage. PROGRESS, Perindopril PROtection Against REcurrent Stroke Study.

**Abbreviations:** CI, confidence interval; PROGRESS, Perindopril PROtection Against REcurrent Stroke Study.

---

**Effects on other outcomes**
Active treatment resulted in significant reductions in many secondary outcomes including major coronary events, heart failure, disability and dependency, and cognitive decline (Figure 3, left panel).6,9,10 Once again, these effects were substantially magnified in the group receiving combination treatment (Figure 3, right panel), where, for example, the reduction in the risk of dementia reached 23% (P<0.05) in those who receiving perindopril and indapamide (Figure 3).9

Association between the risk of stroke and achieved blood pressure in clinical trials

**The PROGRESS trial**
An observational analysis of PROGRESS revealed that the lowest risk of recurrent stroke was observed in the one quarter of patients who achieved the lowest follow-up blood pressure levels (with a median of 112/72 mm Hg), with no excess of serious complications.11 Similar relationships were observed for both ischemic and hemorrhagic stroke (Figure 4),12 both in patients with and without chronic kidney disease.10 These observational data are supported by the evidence shown in Figure 2 (panel B), demonstrating the efficacy of combination therapy across subgroups, defined by baseline systolic and diastolic blood pressures down to <120/80 mm Hg.17,18

---

**Figure 3. Effects of blood pressure lowering on serious clinical outcomes in the PROGRESS trial.**
Solid boxes represent estimates of relative risk of outcomes (hazard ratio for stroke, major coronary events, heart failure, major vascular events, vascular death and total death, and odds ratio for disability, dependency, dementia and cognitive decline). Other conventions as for Figure 2.

**Figure 4. Annual rates of ischemic stroke and intracerebral hemorrhage according to achieved follow-up systolic blood pressure levels in the PROGRESS trial.**
Annual incidence rates and 95% confidence intervals. Annual rates are based on the estimated annual incidence rate and at median values of systolic blood pressure; the areas of the boxes are proportional to the number of events. Vertical lines represent 95% confidence interval. P trend=0.0005 for ischemic stroke, <0.0001 for intracerebral hemorrhage. PROGRESS, Perindopril PROtection Against REcurrent Stroke Study.

**Abbreviations:** CI, confidence interval; PROGRESS, Perindopril PROtection Against REcurrent Stroke Study.
a few small earlier trials is shown in Figure 5, and this suggests that each 10-mm Hg reduction in systolic blood pressure is associated with a 33% reduction in the risk of recurrent stroke. This is consistent with analyses from other observational studies reporting that every 10-mm Hg reduction in systolic blood pressure was associated with a 28% lower risk of recurrent stroke.15

**Implications and conclusions**

The totality of the studies and analyses reported here make it clear that reduction in the risk of recurrent stroke in patients with cerebrovascular disease is closely tied to the magnitude of reduction in blood pressure, as well as to the level of blood pressure achieved, at least to below 130/80 mm Hg when this is well tolerated in the individual patient. It is also abundantly clear from the PROGRESS trial, which conducted a rigorous comparison of the effect of combination therapy with the angiotensin-converting enzyme inhibitor perindopril and the diuretic indapamide, that combination therapy is essential in order to achieve sufficient reduction in blood pressure for this to translate into effective reduction in the risk of stroke. The specificity of this message is absolutely in line with the results of numerous national and international studies on the need for combination therapy for effective reduction in the burden of cardiovascular disease, as reflected in all major guidelines.1-5,24

It is also abundantly clear that the combination of perindopril and indapamide is the one specific combination that has been rigorously tested and found to be truly effective for the prevention of recurrent stroke. The absolute risk reductions observed with the combination of perindopril and indapamide suggest that 5 years’ treatment with this combination would avoid one major vascular event, fatal or nonfatal, for every 11 patients treated. Therefore, this combination can be recommended for the prevention of recurrent stroke and associated cardiovascular events in all patients with cerebrovascular disease. ■

**References**


Keywords: combination therapy; hypertension; indapamide; perindopril; PROGRESS; stroke

L’ASSOCIATION FIXE D’ANTIHYPERTENSEURS EST-ELLE NÉCESSAIRE EN POST-AVC ?

Il est désormais recommandé d’utiliser une association antihypertensive pour la plupart des patients nécessitant un traitement antihypertenseur. Les patients ayant subi un accident vasculaire cérébral (AVC) forment un groupe particulièrement important pour lequel une association médicamenteuse s’est montrée bénéfique et supérieure. L’étude PROGRESS (Perindopril pROtection aGainst REcurrent Stroke Study) en est la meilleure preuve car elle a clairement montré qu’un traitement basé sur le péridopril, un inhibiteur de l’enzyme de conversion, auquel est associé un diurétique, l’indapamide, utilisé en fonction des besoins, diminue l’incidence des récidives d’AVC d’environ 25 %. Selon cette étude, l’association thérapeutique péridopril et indapamide diminue encore plus le risque d’AVC (diminution de 43 % du risque relatif), ce qui concorde avec l’importante diminution de la pression artérielle obtenue avec cette association médicamenteuse comparée à celle obtenue avec un seul médicament (12,3/5 mm Hg vs 4,9/2,8 mm Hg). Une tendance similaire (diminution plus importante avec cette même association médicamenteuse) a été observée pour tous les autres résultats comme les événements vasculaires majeurs, les événements coronariens, l’insuffisance cardiaque, l’incapacité, la dépendance, le déclin cognitif et le décès. L’association péridopril et indapamide peut donc être recommandée pour la prévention des AVC récidivants et des événements cardiovasculaires associés pour tous les patients atteints de maladie cérébrovasculaire.
Candidates that will best benefit from the combination of an ACE inhibitor (first line) and a β-blocker are hypertensive patients with concomitant coronary artery disease. Patients that have relatively recently had a myocardial infarction and those with chronic heart failure and low ejection fraction are likely to obtain beneficial outcomes that are predominantly independent of BP lowering. Patients with angina will also benefit from a symptomatic improvement on top of a BP-dependent improvement in prognosis.

More than 50% of patients with uncomplicated hypertension require more than one drug to achieve adequate blood pressure (BP) control. This is because of the limited antihypertensive effect of monotherapy, which, on average, results in reductions of 9.1 mm Hg for systolic BP, and 5.5 mm Hg for diastolic BP. Multiple randomized controlled trials using placebo and active controls, and the majority of meta-analyses, have shown no significant differences in BP lowering and clinical efficacy between the five main classes of antihypertensive drugs when used at adequate doses. For this reason, the European Society of Hypertension (ESH)/European Society of Cardiology (ESC) 2007 guidelines stressed that the
effect of BP-lowering drugs in reducing the risk of serious cardiovascular events and all-cause death is virtually entirely due to BP reduction, and diuretics, β-blockers, calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) should all be considered as equivalent first-line choices for monotherapy and add-on therapy.\(^1\)

**Are all combinations of first-line drugs equal in their effectiveness?**

In contrast with the arbitrary choices made in many earlier randomized controlled trials using a varied assortment of add-on drugs, the design of more recent trials has strictly specified the add-on treatment regimens in all treatment arms. Such an approach has allowed evidence to be obtained that can be used to make claims about the comparable efficacy of particular drug combinations. The results of these trials have enabled the ESH and ESC in the 2009 reappraisal of their guidelines to recommend specific combinations for priority use and to specify certain undesirable or unproven combinations (Figure 1).\(^4\) The former includes combinations of renin-angiotensin system (RAS) inhibitors (ACE inhibitors and ARBs) with a dihydropyridine CCB or diuretic, or a CCB with diuretic, and the latter would be combination of a β-blocker with diuretic (undesirable) or an ACE inhibitor with an ARB (unacceptable). Importantly, the inferiority of the β-blocker/diuretic and ACE inhibitor/ARB combinations in the landmark trials (LIFE [Losartan Intervention For Endpoint reduction in hypertension study],\(^5\) ASCOT [Anglo-Scandinavian Cardiac Outcomes Trial],\(^6\) and ONTARGET [ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial]) was marked not only by an increased frequency of serious side effects (for the β-blocker/diuretic combination this was mainly new-onset diabetes and sexual dysfunction; for the ACE inhibitor–ARB combination it was hard renal end points), but also suboptimal clinical efficacy regarding particular BP reduction targets. In LIFE, combined therapy with a β-blocker and diuretic in high-risk hypertensive patients was associated with a higher incidence of stroke compared with an ARB–diuretic combination, despite identical BP control. ASCOT was stopped prematurely.

---

**Figure 1.** Recommendations of the 2009 reappraisal of the European Society of Hypertension (ESH) and European Society of Cardiology (ESC) regarding optimal drug combinations in patients with uncomplicated hypertension.

**Abbreviations:** ACE, angiotensin-converting enzyme; AT\(\_1\), angiotensin II type 1; CCB, calcium channel blocker.


---

**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>Action in Diabetes and Vascular disease: Preterax and DiaMican MR Controlled Evaluation</td>
</tr>
<tr>
<td>ARB</td>
<td>angiotensin receptor blocker</td>
</tr>
<tr>
<td>ASCOT</td>
<td>Anglo-Scandinavian Cardiac Outcomes Trial</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>CAFE</td>
<td>Conduit Artery Function Evaluation (substudy of ASCOT)</td>
</tr>
<tr>
<td>CAMIs</td>
<td>Carvedilol Acute Myocardial Infarction Study</td>
</tr>
<tr>
<td>CAPRICORN</td>
<td>Carvedilol Post-Infarct survival CControl in left ventricular dysfuncNtion (trial)</td>
</tr>
<tr>
<td>CCB</td>
<td>calcium channel blocker</td>
</tr>
<tr>
<td>CIBIS</td>
<td>Cardiac Insufficiency Bisoprolol Study</td>
</tr>
<tr>
<td>COMET</td>
<td>Carvedilol Or Metoprolol European Trial</td>
</tr>
<tr>
<td>COMMIT</td>
<td>CIOpigolol and Metoprolol in Myocardial Infarction Trial</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>Carvedilol ProspEctive RaNdomized CUmulative Survival</td>
</tr>
<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
</tr>
<tr>
<td>ESH</td>
<td>European Society of Hypertension</td>
</tr>
<tr>
<td>EUROPA</td>
<td>EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease</td>
</tr>
<tr>
<td>GEMINI</td>
<td>Glycemic Effects in diabetes Mellitus: carvedilol-metoprolol comparisoN In hypertensives (trial)</td>
</tr>
<tr>
<td>HOPE</td>
<td>Heart Outcomes Prevention Evaluation</td>
</tr>
<tr>
<td>HYVET</td>
<td>HYPertension in the Very Elderly Trial</td>
</tr>
<tr>
<td>LIFE</td>
<td>Losartan Intervention For Endpoint reduction in hypertension study</td>
</tr>
<tr>
<td>MERIT HF</td>
<td>MEntoprolor CR/XL Randomised Intervention Trial in congestive Heart Failure</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
</tr>
<tr>
<td>ONTARGET</td>
<td>ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial</td>
</tr>
<tr>
<td>RAS</td>
<td>renin-angiotensin system</td>
</tr>
<tr>
<td>SENIORS</td>
<td>Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with heart failure (trial)</td>
</tr>
</tbody>
</table>
because of significantly higher all-cause mortality in the group of uncomplicated high-risk hypertension patients treated with the atenolol-diuretic combination compared with the amlodipine–perindopril combination. This was associated with a higher incidence of coronary events, stroke, and cardiovascular mortality, which, according to the results of the multivariate analysis, could only partly be explained by the small average difference in BP reduction of 2.7/1.9 mm Hg. 7

Inferior cardiovascular protection with β-blockers in hypertension: evidence and reasons

The results of LIFE and ASCOT correspond with the results of several meta-analyses that have reassessed the cardiovascular protection and safety of β-blockers as a first-line therapy for hypertension. 8-10 These have demonstrated that despite antihypertensive therapy based on a β-blocker (mainly atenolol) achieving effective BP reduction compared with placebo, the β-blocker has no impact on all-cause mortality, coronary events, and stroke. β-Blocker therapy was also shown to be inferior to therapy with other first-line drugs when taken together, including diuretics, for all-cause mortality and stroke prevention. 9,10 One meta-analysis comparing specific drug classes found that β-blockers were inferior to CCBs for all-cause mortality, stroke, and total cardiovascular events, and inferior to RAS inhibitors for stroke. 10

According to the results of a meta-analysis by Khan and McAlister that took into account patient age, β-blockers reduced major cardiovascular outcomes in placebo-controlled trials in younger patients but not in older patients. 11 The observed benefits, however, were less than might be expected given the results of epidemiological studies. 12 In active comparator trials, β-blockers were inferior to other therapies for the composite outcome of stroke, myocardial infarction, and death, and particularly inferior for stroke in elderly patients, although not in younger patients.

The principal explanation for the suboptimal cardiovascular protection afforded by β-blockers compared with other drug classes is the inferiority of their BP-lowering effect on central systolic BP despite producing a similar reduction in brachial BP to other antihypertensive drug classes; this has been shown in several small studies and was confirmed in the large CAFE trial (Conduit Artery Function Evaluation) (Figure 2). 13,14 According to the results of the multifactorial analysis of the CAFE data, this inferiority is mainly due to their heart rate–reducing effect, which enables reflected pulse waves to return to the thoracic aorta well before the end of left ventricular systole. Such pulse wave dyssynchrony is facilitated by a proximal shift of its reflection sites in small resistance arteries, absolute or relative to other therapies. The lack of a positive effect of β-blockers on artery compliance, and the structural remodeling of small arteries that β-blockers produce—in contrast with treatment with dihydro-pyridine CCBs and RAS inhibitors with the same brachial BP-lowering effect—has been demonstrated in several studies. 15,16 An important factor influencing the timing of the retrograde pulse wave return to the thoracic aorta and central BP is pulse wave velocity, which increases with aortic wall stiffening in the course of both physiological and premature vascular aging (eg, in hypertension and diabetes). This forms the theoretical background for the inferior clinical effectiveness of β-blockers in older hypertensive patients compared with younger ones.

Position of the guidelines on the use of β-blockers in uncomplicated hypertension

Taking into account the suboptimal cardiovascular protection afforded by β-blockers shown in the aforementioned randomized controlled trials and meta-analyses, as well as the physiological background, the UK National Institute for Health and Care Excellence (NICE) and British Hypertension Societies 17,18 recommended the downgrading of β-blockers from first-line to fourth-line drugs; eg, for use as add-on drugs in patients requiring multiple therapies. 12 Similar recommendations were issued by the South African and Australian national hypertension societies, 19,20 while the Canadian Hypertension Society excluded β-blockers from the list of first-line drugs for patients with diastolic or systolo-diastolic hypertension aged less than 60 years and for all patients with isolated systolic hypertension.21 These discrepancies between the opinions of leading experts regarding
Combination of ACE inhibitors and β-blockers in uncomplicated hypertension: expected benefits and risks

Are there grounds for speculating that combining β-blockers with drug classes other than diuretics (primarily ACE inhibitors) as a cornerstone of cardiovascular prevention may have potential benefits, at least in certain subgroups of patients, eg, younger patients? The combination of β-blocker with ACE inhibitor is very often used empirically in clinical practice for younger patients with a tendency toward a higher heart rate; eg, obese patients with the metabolic syndrome.

The pathophysiology of hypertension in younger people, especially those with short anamnesis, is different from that in older people. Sympathetic activation plays an important role in its development, causing high cardiac output and hyperdynamic circulation, as well as mediation of higher renin release via β receptors on the kidney juxtaglomerular cells. It is reasonable to speculate that treating such a subset of patients who have hyperkinetic circulation (and probably also normokinetic circulation) with an ACE inhibitor–β-blocker combination could produce additive antihypertensive effects: the lowering of cardiac output and inhibition of renin release produced by the β-blocker would combine with the ACE inhibitor neutralization of the undesirable vasoconstrictive effects and insulin resistance amplification produced by the β-blocker. Yoneda et al21 and Holmer et al22 demonstrated that the reactive increase in renin blood concentrations in hypertensive patients starting treatment with ACE inhibitors was largely prevented by concomitant treatment with β-blockers. The hemodynamic effectiveness and clinical implications of such an interaction remain to be demonstrated.

One small prospective study in patients with mild to severe hypertension found that the combination of a β-blocker with an ACE inhibitor lowered diastolic BP significantly more than monotherapy (∼20 mm Hg versus −10 mm Hg), while the lowering of cardiac output and elevation of vascular resistance produced by the β-blockers was attenuated by addition of the ACE inhibitor.23 A more recent retrospective database analysis by Bisognano et al24 in patients treated with β-blockers who were matched for baseline characteristics (n=660; mean age 66 years; basal BP 156/88 mm Hg) showed that add-on therapy with ACE inhibitors produced a more-or-less similar reduction in systolic BP to that of CCBs (−16 mm Hg versus −18.5 mm Hg), and tended to be more effective than therapy with ARBs. However, diastolic BP reduction with ACE inhibitors was inferior to that with CCBs (−4.9 mm Hg versus −9.3 mm Hg; P<0.05) and similar to that with ARBs. The small sample size did not allow for analysis of the results in subpopulations; eg, younger or older patients. Thus, the question of the existence of additive antihypertensive effects with the ACE inhibitor–β-blocker combination in younger hypertensive patients remains open to debate.

A separate comment deserves to be made on the appropriateness of heart rate control as one of the possible therapeutic goals of add-on treatment with β-blockers in younger patients with uncomplicated hypertension. It has become a clinical convention to consider heart rate as a universal risk factor, whose pharmacological slowing, eg, with β-blockers, invariably produces an improvement in outcome. Yet, in contrast with post–myocardial infarction or chronic heart failure patients (ejection fraction <40%),25,26 this contention appears to be wrong for the hypertensive patient; this is despite a multitude of observational data showing a tight association between heart rate and the cardiovascular and all-cause mortality rate in this patient population, similar to that observed in patients with coronary artery disease or chronic heart fail-

---

**Heart rate categories**

<table>
<thead>
<tr>
<th>Heart rate categories</th>
<th>No. events/patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60 bpm</td>
<td>116/640</td>
</tr>
<tr>
<td>60 to &lt;70 bpm</td>
<td>277/1689</td>
</tr>
<tr>
<td>70 to &lt;80 bpm</td>
<td>287/1799</td>
</tr>
<tr>
<td>80 to &lt;90 bpm</td>
<td>185/1080</td>
</tr>
<tr>
<td>90+ bpm</td>
<td>91/544</td>
</tr>
<tr>
<td>Overall</td>
<td>956/5732</td>
</tr>
</tbody>
</table>

**Amlodipine better**

<table>
<thead>
<tr>
<th>0.5</th>
<th>0.8</th>
<th>1.2</th>
<th>Interaction P value = 0.91</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amlodipine better</td>
<td>Atenolol better</td>
<td>Hazard ratio and 95% CI (log scale)</td>
</tr>
</tbody>
</table>

**Figure 3.** Relationship between cardiovascular events and baseline heart rate in the ASCOT trial.

**Abbreviations:** ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; bpm, beats per minute; CI, confidence interval.

The negative impact on the prognosis of hypertensive patients of heart rate reduction with β-blockers used as first-line therapy was convincingly shown by the results of a meta-regression analysis performed by Bangalore et al. Exclusion criteria were previous acute myocardial infarction and chronic heart failure, but not chronic coronary artery disease. Paradoxically, the heart rate lowering attained in the β-blocker group at study end was associated with a proportionate rise in all-cause mortality \( r = -0.51 \), cardiovascular mortality \( r = -0.61 \) (Figure 4), and myocardial infarction rates \( r = -0.85 \); all \( P < 0.0001 \) (Figure 5). The same was true when the difference in heart rate at study end between the two treatment modalities was compared with the relative risk reduction for these events. Importantly, the average age of the patients was 58 years and the mean basal diastolic BP was 100 mm Hg. One can thus conclude that contrary to the situation in post-myocardial infarction and chronic heart failure patients with low ejection fraction, in hypertensive patients, heart rate elevation can be considered a risk marker but not a risk factor.

This finding can be explained by the important negative impact of central systolic and pulse BP elevation that occurs with pharmacological heart rate lowering, even in patients younger than age 60 years with systolic-diastolic hypertension, and probably in the absence of significant aorta stiffening. Thus, in hypertensive patients without recent myocardial infarction or chronic heart failure with low ejection fraction, even in younger patients, heart rate control should not be considered a therapeutic goal.

Based on this reasoning, I consider it inappropriate to use an ACE inhibitor–β-blocker combination in older patients with uncontrolled uncomplicated hypertension, and think that we should be careful when adding β-blockers to ACE inhibitors (particularly regarding dosing) in younger patients (in whom it would probably be for hyperreninemia correction). In my opinion, the safest candidates are patients with concomitant symptomatic tachycardia, and on-treatment resting heart rate should be as high as tolerated, in no case less than 70 beats per minute (better, 75 beats per minute). The use of nonpharmacological approaches should strongly be recommended as a priority for heart rate reduction in such patients with inappropriate tachycardia; ie, regular aerobic training and correction of excessive body mass.

Figure 4. Cardiovascular mortality risk as a function of heart rate.
Relative risk of cardiovascular mortality as a function of heart rate achieved at the end of the study in the β-blocker group. The diameter of the circles represents the weight of each individual trial. Abbreviations: ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; bpm, beats per minute; ELSA, European Lacidipine Study on Atherosclerosis; HAPPHY, Heart Attack Primary Prevention in Hypertension; INVEST, International Verapamil SR and Trandolapril study; IPPPSH, International Prospective Primary Prevention Study in Hypertension; LIFE, Losartan Intervention for End point Reduction trial.


Figure 5. Risk of nonfatal myocardial infarction as a function of heart rate.
Relative risk of nonfatal myocardial infarction as a function of heart rate achieved at the end of the study in the β-blocker group. The diameter of the circles represents the weight of each individual trial. Abbreviations: ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; bpm, beats per minute; ELSA, European Lacidipine Study on Atherosclerosis; HAPPHY, Heart Attack Primary Prevention in Hypertension; INVEST, International Verapamil SR and Trandolapril study; IPPPSH, International Prospective Primary Prevention Study in Hypertension; LIFE, Losartan Intervention for End point Reduction trial; VACS, Veterans Administration Cooperative Study Group on Antihypertensive Agents.

Clinical situations favoring ACE inhibitor–β-blocker combination therapy

In hypertensive patients, the principal indication for combined ACE inhibitor–β-blocker therapy is concomitant coronary artery disease. According to the results of a recent meta-analysis by Law et al., compared with placebo or no treatment, β-blocker-based antihypertensive therapy was highly effective in reducing coronary events, chiefly when given within 4 months of an acute myocardial infarction (29% relative risk reduction; P<0.001). However, in hypertensive coronary artery disease patients without recent myocardial infarction or any myocardial infarction, it was only associated with a tendency toward risk reduction compared with placebo (relative risk 0.87; 95% confidence interval, 0.71-1.06) and did not show any benefits in terms of coronary event prevention compared with the other drug classes. Clearly, the pronounced relatively short-term preventive effect of β-blockers in hypertensive patients with recent myocardial infarction (up to 2 years after myocardial infarction) goes mostly beyond BP lowering and is due to their postinfarction protective effect, because in this particular clinical situation, the very high cardiovascular risk is mainly associated with the recent myocardial infarction. The same presumably holds true for the modification of prognosis seen in hypertensive patients with concomitant chronic heart failure and low ejection fraction who are treated with β-blockers. Aside from these situations, it is appropriate to consider the ACE inhibitor–β-blocker combination as the combination of choice for hypertensive patients with angina, or certain arrhythmias, for symptomatic improvement, if not modification of prognosis. However, for patients with angina, diltiazem or Verapamil add-on therapy would be a better alternative for improvement of outcomes.

Choosing ACE inhibitors and β-blockers

Let us elaborate on which particular ACE inhibitor and β-blocker molecules might be considered as the optimal choices in a fixed-dose combination that could be a useful addition to the existing arsenal of fixed-dose combination antihypertensive drugs.

♦ Trial-based evidence of improvement in outcomes with certain drugs in certain clinical situations (possible “drug effects”)

In the ACE inhibitor drug class, perindopril has the largest body of evidence for prognosis modification in hypertensive patients, both from randomized placebo-controlled trials (ADVANCE [Action in Diabetes and Vascular disease: Preterax and DiamicroN MR Controlled Evaluation], HYVET [Hypertension in the Very Elderly Trial], etc) and active comparator trials (ASCOT).

Perindopril and ramipril are the only ACE inhibitors to have demonstrated a cardioprotective effect, in the landmark placebo-controlled EUROPA (EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease) and HOPE trials (Heart Outcomes Prevention Evaluation). Participants in these trials were chronic coronary artery disease patients, including those post-myocardial infarction, more than half of whom had concomitant hypertension with satisfactory, but not optimal, BP control.

In the modern reperfusion era, the evidence-based β-blockers for the post–myocardial infarction patient are carvedilol (CAPRICORN [CArdiofio Post-infarct surviVal Control in left ventrIcular dystroNction]) and metoprolol succinate XL (COMMIT [ClopIdogrel and Metoprolol in Myocardial Infarction Trial]). For patients with chronic heart failure with low ejection fraction, in addition to carvedilol and metoprolol XL (COPERNICUS [Carvedilol ProspEctive RaNdomized CUMulative Survival] and MERIT HF [MEtoprolol CR/XL Randomised Intervention Trial in congestive Heart Failure]), there is also bisoprolol (CIBIS-II [Cardiac Insufficiency Bisoprolol Study]). Nebivolol demonstrated a benefit versus placebo in the SENIORS study (Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with heart failure), recruited elderly chronic heart failure patients with any level of ejection fraction—low as well as preserved—but nebivolol did not reduce mortality. For patients with uncomplicated coronary artery disease, we do not yet have evidence that any β-blocker treatment can improve prognosis. Although claims have been made that the pharmacodynamic advantages of the third-generation β-blockers (carvedilol and nebivolol) might transform into certain benefits in outcomes, as occurred for carvedilol versus metoprolol tartrate in chronic heart failure patients in the COMET trial (Carvedilol Or Metoprolol European Trial), this is not very likely. The CAMIS trial (Carvedilol Acute Myocardial Infarction Study) did not show any superiority for carvedilol over atenolol in patients with acute coronary syndrome and a mean ejection fraction of 54%; moreover, the aforementioned COMET trial was subjected to serious criticism.

◆ Evidence of pharmacodynamic advantages

Considering the importance of optimal dual RAS inhibition and nitric oxide production for an ACE inhibitor, at least in terms of coronary event prevention, perindopril might be considered a drug of choice owing to it having the highest selectivity for bradykinin versus angiotensin I binding sites in its drug class.

In terms of β-blockers, two small studies in hypertensive patients found that, for an equivalent lowering of brachial BP, therapy with nebivolol was associated with a greater reduction in aortic pulse pressure and a superior impact on the augmentation index than atenolol treatment. This was probably due to the reduction of wave reflection with nebivolol as a result of vasodilation of resistant arteries, as well as higher on-treatment heart rates. One might expect the same from carvedilol. I share the opinion of Sever and Messerli, however, that this complimentary effect of the newer β-blockers.
is unlikely to significantly improve clinical outcomes with full-dose β-blocker therapy in hypertensive patients, because heart rate reduction per se is the cornerstone of the suboptimal effect of β-blockers on central BP, as well as on BP variability.\(^\text{39}\) The latter, in addition to central BP, is considered to be a strong predictor of both stroke and myocardial infarction in hypertensive patients,\(^\text{40}\) and there is no evidence that the newer generation of β-blockers improves BP variability.\(^\text{41}\)

**Evidence of advantages in tolerability**

In hypertensive patients with diabetes, the GEMINI trial (Glycemic Effects in diabetes Mellitus: carvedilol-metoprolol comparison in Hypertensives) showed a decrease in insulin resistance after treatment with carvedilol, but not metoprolol.\(^\text{42}\)

The latter produced an increase in glycosylated hemoglobin levels from baseline, whereas the levels did not change over the course of therapy with carvedilol.\(^\text{43}\) A similar advantage regarding metabolic control in hypertensive patients without concomitant diabetes was shown for nebivolol versus atenolol in a study by Poirier et al.\(^\text{43}\) This can be at least partly explained by the peripheral vasodilatory properties that are unique to both of these third-generation β-blockers.

**Evidence of pharmacokinetic advantages**

In terms of pharmacokinetic advantages, perindopril is preferable to several other ACE inhibitors, including ramipril, and bisoprolol and nebivolol are preferable to carvedilol.

In conclusion, the optimal choice of drugs is likely to be: (i) perindopril, as it has the largest body of evidence showing beneficial outcomes in hypertensive and coronary artery disease patients; and (ii) long-acting β-blockers such as bisoprolol that have evidence of mortality reduction in post-myocardial infarction and heart failure patients. Nebivolol could also be considered due to its advantages in terms of metabolic control and pulse wave reflection, which is associated with relatively mild heart rate lowering and peripheral vasodilation.

---

**References**

PouR QuELs PATiENts UNEs TRAITEMENT IEc-β-BLOQUANT PEut-IL êTRE BÉNÉFique ?

Les patients qui sont à la fois hypertendus et coronariens sont les meilleurs candidats pour recevoir l’association d’un inhibiteur de l’enzyme de conversion de l’angiotensine (IEC) (en première intention) et d’un β-bloquant. Les patients ayant eu récemment un infarctus du myocarde et ceux atteints d’insuffisance cardiaque chronique et ayant une fraction d’éjection ventriculaire basse devraient bénéficier de cette association (indépendamment de l’abaissement de la pression artérielle). Les patients angineux auront, eux, des bénéfices symptomatiques en plus de l’amélioration du pronostic lié à la pression artérielle. Cependant, cette amélioration est probablement moindre que celle obtenue avec une association IEC-β-antagoniste calcique dihydropyridinique, la réduction de la pression centrale étant inférieure, ce qui est inhérent au ralentissement de la fréquence cardiaque. Bien que l’association IEC-β-bloquant semble un choix physiopathologiquement pertinent dans le cas d’un sous-groupe de patients jeunes ayant une hypertension non compliquée, une circulation hypercinétique et une éventuelle hyperréninémie, son efficacité hémodynamique chez de tels patients reste discutable. De plus, la probabilité d’obtenir des résultats comparables à ceux obtenus dans l’étude ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) ne semble pas très élevée avec cette association étant donné la réduction de la fréquence cardiaque inhérente à son utilisation. Il semble que cette association particulière ne soit préférentielle que chez des hypertendus ayant des palpitations et certaines arythmies, qui en tireront des bénéfices symptomatiques. La fréquence cardiaque ne doit pas être considérée comme un but thérapeutique en soi. Il est probable que l’association optimale IEC-β-bloquant repose, d’une part, sur le périndopril, l’IEC pour lequel il existe le plus grand nombre de preuves d’effets bénéfiques chez les hypertendus et les coronariens, et d’autre part, sur les β-bloquants d’action prolongée comme le bisoprolol et le nebivolol.
This fellowship is designed to foster the work of young researchers in the cardiovascular field

Who may apply?

Eligibility: applicants should be 35 years of age or less, PhD or equivalent graduation within the last 3 years, and ISHR-ES members at the time of the application deadline, March 31, 2014. The planned research project is to be completed within one year and should be presented at the ISHR European Section Annual Congress in 2015.

What is the ISHR–ES/SERVIER Research Fellowship?

A €20 000 grant is offered by SERVIER in partnership with the European Section of the ISHR to support a cardiovascular research project within a European research group for a period of up to 1 year.

How to apply

Send a PDF file containing the following information:

- Curriculum vitae
- List of publications
- A description of your research proposal as a 1-page summary + no more than 6 pages of text
- One letter of support from a supervisor

To Prof Peter Ferdinandy
peter.ferdinandy@pharmahungary.com
As well as a copy: office@pharma.sote.hu

Receipt of all applications will be acknowledged.

Please refer to instructions and templates on the ISHR Web site:
www.ishr-europe.org

DEADLINE
FOR APPLICATIONS
March 31, 2014
Servier promotes in-depth understanding of the current body of knowledge on a specific area of cardiovascular medicine through sponsorship of the following grants:

- **The Servier Research Grant in Hypertension** in the amount of €30 000 is awarded every 2 years for a research proposal in the field of hypertension and related diseases with a focus on end-organ damage, surrogate markers, and biomarkers.
- The committee of the Servier Research Grant in Hypertension is composed of internationally renowned experts in hypertension and related cardiovascular diseases. The winner will receive the grant from the President of the ESH, during the award ceremony of the ESH Congress.
- This initiative follows the Servier SNS Research Grant, awarded from 2003 through 2007. The winners were Markus Schlaich, Krzysztof Narkiewicz, and Gino Seravalle.
- The winners of the Servier Research Grant in Hypertension were Konstantin Kotliar (Munich, Germany) in 2011 and Stefano Masi (London, UK) in 2013.
- The **Servier Research Grant in Hypertension** is limited to PhDs or MDs under 45 years of age on July 1 in the year of the award.

Next deadline for applications: **January 30, 2015**
Applications should be sent to: Prof Giuseppe Mancia, Clinica Medica, Ospedale San Gerardo, Via Pergolesi 33, 20052 Monza (MI), Italy
E-mail: giuseppe.mancia@unimib.it
More information is available at [www.eshonline.org](http://www.eshonline.org) and on the Servier Web site: [www.servier.com](http://www.servier.com)

- Servier, with the European Society for Microcirculation (ESM), is offering a research award: **the Servier Award in Microcirculation**.
- A €4000 grant is offered every 2 years for an outstanding clinical or basic research publication in the fields of microcirculation and vascular biology. The call for applications is advertised on the ESM Web site and by related societies and journals.
- The last winners were Jacqueline Fields and Marc Fleury (Switzerland), Jun Yin (Toronto, Canada) and Abigail Woodlin (London, United Kingdom).
- The 2013 Servier Award in Microcirculation was presented to Helge Wlig and Agnes Schröder who received the prize during the 27th European Society for Microcirculation Congress in Birmingham (UK), July 21-26, 2013.
- Applications should be submitted no later than September 2014, and will be reviewed by a committee composed of some members including officers of the ESM. Scientists under 40 years of age on January 31 in the year of the award may apply.

Next deadline for applications: **September 30, 2014**
Applications should be sent to the ESM general secretary Prof Akos Koller: akos.koller@aok.pte.hu
More information is available on the ESM Web site: [www.esmicrocirculation.eu](http://www.esmicrocirculation.eu) and on the Servier Web site: [www.servier.com](http://www.servier.com)

- Servier is a partner of the Union Internationale de Phlébologie (UIP).
- **Every 2 years, the UIP/Servier Research Fellowship** provides a €25 000 grant for a 2-year research project consisting of original clinical or basic research in the areas of phlebology and lymphology, including the following topics: anatomy, physiology, pathophysiology, diagnostic methods, and clinical research.
- Review of the proposals submitted and selection of the best candidate are carried out by a committee of internationally recognized specialists in the field of phlebology and lymphology, including the President of the UIP.
- The 2011 Servier/UIP fellowship was awarded to Gyozó Szolnoky (Hungary). The 2013 Servier/UIP fellowship was awarded to Markus Fokou (Cameroon) at the World Congress of the UIP in 2013 (Boston, Massachusetts, USA).
- The next grant will be awarded at the World Congress of the UIP in 2015 (Seoul, Korea).
- Candidates less than 45 years old and belonging to a National Society affiliated with the UIP may apply.

Next deadline for applications: **March 31, 2015**
More information is available at [www.servier.com](http://www.servier.com), together with the electronic application file.

For further information and deadline applications please visit our Web site: [www.servier.com](http://www.servier.com)
THE QUESTION

Hypertension guidelines have been increasingly recommending fixed-dose multiple-drug combinations to achieve adequate blood pressure control and cardiovascular prevention. These combinations are more effective due to their complementary and synergistic effects, and safer since they are associated with fewer side effects due to the reduced dosages of individual agents. Are such combinations restricted to secondary prevention, or are there situations in which they should also be used in primary prevention?

Multiple-drug combinations in hypertension and cardiovascular prevention: should they be used in primary or secondary prevention?

1. M. Alami, Morocco
2. C. Amodeo, Brazil
3. I. Attia, Egypt
4. M. Bastos, Portugal
5. A. Bhagwat, India
6. K. J. Filipiak, Poland
7. R. O’Hanlon, Ireland
8. E. J. Ramos, Philippines
9. H. A. Remah Mohammed, Saudi Arabia
10. M. Rizzo, Italy
11. R. S. Tan, Singapore
12. S. L. Tokgozoglu, Turkey
13. M. Vrablik, Czech Republic
Cardiovascular prevention is “sick” and the prognosis is bad in developing countries: by 2020, 80% of cardiovascular mortality will occur in low- and middle-income countries. One optimistic solution is the multiple-drug combination or polypill. Combining two or three blood pressure–lowering drugs and a statin and aspirin in the same pill should improve adherence and reduce cost. In terms of primary prevention, the initial concept was “a polypill for all, starting at age 55,” with no screening and no monitoring. In theory, this strategy would reduce heart attacks and strokes by more than 80%.1 In practice, putting apparently healthy people on a polypill with the risk of adverse events (from four to five drugs) and no proven benefit on mortality is not at all convincing at this time. In addition, it seems wiser to advise people to improve their diet and exercise than to rely on pills. Several trials have used a polypill in people without cardiovascular disease but with moderate to high risk. The TIPS study (The Indian Polycap Study) evaluated the use of a polypill in people with one risk factor.2 The effect of simvastatin was lower than expected, but the polypill formulation reduced multiple risk factors and the global cardiovascular risk. A feasibility study by the World Health Organization showed a reduction in systolic blood pressure, total cholesterol, and 10-year risk of cardiovascular disease with use of a multiple-drug combination, which was highly accepted by physicians and study individuals.3 The PILL pilot trial (Program to Improve Life and Longevity) used a polypill with aspirin (75 mg), lisinopril (10 mg), hydrochlorothiazide (12.5 mg), and simvastatin (20 mg) in individuals with a Framingham score of more than 7.5% at 5 years. There was a significant reduction in blood pressure and cholesterol, but side effects were present in about 1 in 6 people. TIPS-3 is evaluating the polypill without aspirin versus placebo in 5000 individuals without cardiovascular disease over 5 years.

In secondary prevention, proven therapies are underused (80% of patients in developing countries do not receive any preventive drug),4 and long-term adherence to treatment is low (of ten less than 50% in developed countries). A combination of four drugs—aspirin, β-blocker, statin, and angiotensin-converting enzyme (ACE) inhibitor—should, in theory, reduce vascular events by 75% in those with prior vascular disease. This approach has been established as being cost-effective in developing countries. However, in practice, is there any level of evidence of a reduction in events in patients with vascular disease with the use of such a polypill? TIPS-2 compared the use of high doses with low doses (used in TIPS) of the polypill components in patients with previous vascular disease. The study showed a more effective reduction in blood pressure and cholesterol with the high doses. The ongoing FOCUS trial (Fixed-dose Combination Drug for Secondary cardiovascular prevention) is assessing adherence and access to the polypill (aspirin, ACE inhibitor, statin) in 4000 post-myocardial infarction patients. SPACE (Single Pill to Avert Cardiovascular Events) is a collaboration of ongoing trials assessing the role of multiple-drug combinations mainly in patients with vascular disease: UMPIRE (Use of a Multidrug Pill In Reducing cardiovascular Events), IMPACT (IMProving Adherence using Combination Therapy), KANYINI-GAP (Kanyini Guidelines Adherence with the Polypill) and similar studies will collectively enroll around 7000 people. Data on safety and adherence, blood pressure– and cholesterol-lowering efficacy, and mortality, will be decisive.

In conclusion, multiple-drug combination will probably get its “approval” soon in secondary prevention. For primary prevention, the debate will last longer and has already raised a crucial question for the medical community. “Firefighting” cardiovascular diseases: should we add more water (pills) or stop the fuel (risk factors)? Please, answer… and act!  ■

References
Hypertension is a major independent risk factor for the development of coronary artery disease, stroke, and renal failure. Systolic blood pressure (BP) above 115 mm Hg explains 60% of the population-attributable stroke risk.1 Cardiovascular risk in hypertension can be diminished with multidrug antihypertensive therapy. The major reductions in cardiovascular morbidity and mortality over the past 50 years have been attributed mainly to increased availability and combined utilization of various antihypertensive drugs. Randomized trials have shown that BP lowering produces rapid reductions in cardiovascular risk.2 Moreover, it appears that some drug classes may have additional cardiovascular protective effects beyond BP reduction. Studies such as HOPE (Heart Outcomes Prevention Evaluation)3 and EUROPA (European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease)4 have shown a beneficial effect of angiotensin-converting enzyme (ACE) inhibitors on cardiovascular risk in hypertensives and nonhypertensives, indicating that the protective effect of ACE inhibition could be, in part, independent of BP reduction. Antihypertensive medications should thus be selected not only for their potential to reduce BP, but also for potential effects on concomitant diseases and other cardiovascular risk factors.

Hypertension treatment aims to prevent associated morbidity and mortality through reduction of BP and cardiovascular risk status. Multiple-drug therapy implies the use of lower doses of several antihypertensive classes. This not only offers the possibility of greater therapeutic efficacy, but also a reduced incidence of side effects.

Stroke is the most serious complication of hypertension and better BP control is the only way to avoid stroke. A reduction of 5 to 6 mm Hg in diastolic BP maintained over 5 years was shown to reduce the incidence of stroke by 40%.5 In the Chinese PATS study (Post-stroke Antihypertensive Treatment Study), patients with previous stroke history were treated with 2.5 mg/day of indapamide or placebo. After 2 years, indapamide decreased BP by 5 mm Hg systolic and 2 mm Hg diastolic and reduced stroke recurrence by 29% (P=0.0009).6 In the PROGRESS study (Perindopril pROfite in aGInst REcurrent Stroke Study), patients in the active treatment group received perindopril (4 mg/day) alone or together with indapamide (2.5 mg/day). Combination therapy lowered systolic and diastolic BP by 12.3 mm Hg and 5.0 mm Hg, respectively, and reduced stroke recurrence by 43% (P<0.001). Perindopril monotherapy lowered BP by 5.0 mm Hg systolic and 2.0 mm Hg diastolic, but the relative risk reduction was only 4% (95% confidence interval, 19% to 23%).

Because hypertension control generally requires more than one medication, particularly in patients with comorbid conditions, choosing a “first-line” agent may be less important than identifying beneficial combinations for an individual patient. The presence of “compelling indications” may necessitate treatment with antihypertensive agents that have demonstrated a particular benefit in primary or secondary prevention. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends diuretics and ACE inhibitors for secondary stroke prevention. In a study evaluating angiotensin receptor blockers (ARBs) versus calcium channel blockers for secondary stroke prevention, two-thirds of patients in both treatment arms required at least one additional agent to achieve adequate BP lowering. Despite equivalent BP lowering in both groups, patients in the ARB-based treatment group had lower stroke incidence (absolute risk reduction, 8%; number needed to treat, 12.5).

Multiple-drug combination has the added advantage of less need to switch medications. Initial management with combination therapy should be considered in patients whose BP is >20 mm Hg above systolic goal or >10 mm Hg above diastolic goal. The optimal choice of multiple antihypertensives remains controversial as doubts remain regarding the mechanisms of beneficial treatment effects: are they simply a function of BP-lowering, or do certain drug classes exert protective effects in addition to lowering BP? ■

References
Although primary prevention measures are a key component of any public health strategy to reduce the burden of cardiovascular disease, a large proportion of potential candidates do not receive adequate treatment. Defective prescription of medication, noncompliance with treatment, side effects, and unaffordable costs are some of the causes of this treatment gap. Fixed-dose combination therapy can overcome most of these issues. Poor compliance with drug treatment is related to social, psychological, economic, and clinical factors. Advanced age, psychiatric disorders, and complexity of treatment have been repeatedly identified as predictors of poor compliance, and there is a clear correlation with the number of pills a patient needs to take daily.1

These factors led to the concept of a multidrug combination with the potential to improve the management of cardiovascular risk factors. However, arguments against multidrug combinations have been that the estimated risk reduction could be too optimistic, that many patients will remain undertreated, and that patient and doctor acceptability will be less than expected. An additional source of concern is the potential adverse effects related to some of the components of cardiovascular multidrug combinations such as aspirin (gastrointestinal complications). Adverse effects from one or more of the drugs could lead to discontinuation of treatment and, therefore, loss of the benefit of all the other drugs included in the formulation. Furthermore, the need for the efficacy of a multidrug combination in primary prevention remains to be proven in large, randomized trials before it can be accepted in clinical practice.

In addition, the pharmaceutical development of a cardiovascular multidrug combination presents several unique challenges, including the selection of components and doses, the type of pharmaceutical formulation, and regulatory problems. From a formulation development standpoint, an almost linear relationship exists between the number of active components in a multidrug combination and the technical problems of formulation development. The association of different drugs in a single pharmaceutical dosage form may have an effect on the physicochemical properties of each and every individual component. In fact, increasing the number of active components in a multidrug combination also increases the likelihood of interactions between them.2

On the other hand, when it comes to secondary prevention in hypertension, a meta-analysis of four hypertension trials published in 2007 by Bangalore et al showed that fixed-dose combination therapy decreased the risk of medication noncompliance by 24% compared with conventional treatment.3 Pan et al have also shown a 29% improvement in treatment adherence with a fixed-dose combination treatment in patients with hypertension.4

Thus, it appears that combination therapy for primary cardiovascular prevention is not yet ready for widespread use; but for secondary prevention in hypertension, combination therapy with two or more agents in a fixed-dose combination pill will help most patients with hypertension to reach their target blood pressure and reduce morbidity. In many cases, combination therapy improves rates of blood pressure control and requires less time to achieve target blood pressure, with equivalent or better tolerability than higher-dose monotherapy. Additional benefits may include cost savings and better compliance.

References
A rticular hypertension is the most prevalent risk factor for cardiovascular (CV) disease in developed countries. With the exception of the USA and Canada, arterial hypertension is characterized by a low percentage of controlled patients. A recent observational study carried out by the Portuguese Society of Hypertension, the PHYSIA study (Portuguese Hypertension and SAIt), concluded that 42.2% of the adult Portuguese population has arterial hypertension and that 55.7% of these patients have uncontrolled hypertension. When the Portuguese population was analyzed for CV risk, 43.9% had moderate-to-high risk. Poloníia et al analyzed the CV risk of Portuguese hypertensive patients using the criteria of the European Society of Hypertension (ESH)/European Society of Cardiology (ESC), and found that 73.4% of hypertensive patients attending primary care centers and 83.9% of hypertensive patients attending hospitals had moderate-to-very-high CV risk. According to the 2007 ESH/ESC hypertension guidelines, those who are at least at moderate CV risk should commence antihypertensive treatment, possibly with a low fixed-dose combined medication. In PHYSIA, 56.4% of controlled patients were treated with two or more antihypertensive medications. Of these, 65% were fixed combinations.

Fixed combinations enhance treatment compliance, as shown by a meta-analysis of nine studies using fixed combinations, which demonstrated a 24% reduction in noncompliance compared with the use of free drug combinations. Another advantage of fixed combinations is better blood pressure control, as shown in the open-label AVANT’AGE study (Age VAsculaire et risque résiduel chez l’hypertendu Traité vu en médecine Générale), which analyzed 7032 patients with hypertension whose blood pressure was not at goal and for whom general practitioners had the intention of modifying their treatment. A fixed combination of perindopril plus amlodipine was added for 6256 patients, which resulted in the majority of patients meeting the criteria for controlled hypertension (74.4% for systolic or diastolic values, 63.3% for both). Since the sooner blood pressure control is reached, the better in terms of CV prognosis, fixed combinations can have added value. A post-hoc analysis of the VALUE study (Valsartan Antihypertensive Long-term Use Evaluation) suggested that the earlier blood pressure control was achieved, the lower the incidence of CV events. If drugs that act through different pathways are used simultaneously, the probability of achieving hypertension control is higher. With fixed combinations, classes of drugs with complementary mechanisms of action can be used (eg, renin-angiotensin system inhibitors and calcium antagonists).

Multiple-drug combinations are indicated in primary prevention, as shown by the trials ACCOMPLISH (Avoiding Cardiovascular events in Combination therapy in Patients Living with Systolic Hypertension), ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial), and HYVET (Hypertension in the Very Elderly Trial) (reviewed in reference 6). HYVET showed that a combination of an angiotensin-converting enzyme (ACE) inhibitor with indapamide decreased stroke and heart failure incidence and overall mortality in the elderly.

Also, in secondary prevention, ADVANCE (Action in Diabetes and cardiovAscular disease: Preterax and DiamicroN MR Controlled Evaluation) and PROGRESS (Perindopril pROtection against REcurrent Stroke Study) showed clear benefits for CV outcomes with use of the same combination (reviewed in reference 6). Overall mortality and CV mortality, and stroke incidence and major vascular events, respectively, were decreased in these two studies.

In conclusion, according to the present state of the art, multiple-drug combinations appear to be superior to monotherapy for both primary and secondary prevention of CV events.

References
The World Health Organization estimates that 70% of patients do not take their prescribed antihypertensive medication. One reason for this poor compliance is the occurrence of side effects. In antihypertensive drug trials, compliance is at best 78%. In a meta-analysis of 38 antihypertensive drug trials, of all the strategies examined, use of once-daily instead of twice-daily therapy improved adherence by 8% to 20%.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends initiation of antihypertensive treatment with a two-drug combination in patients with systolic blood pressure (BP) ≥ 160 mm Hg and/or diastolic BP ≥ 100 mm Hg, and in patients who are 20/10 mm Hg above their BP goal. In fact, most patients require more than one medication to achieve target BP. One method to simplify treatment is to use fixed-dose combinations.

Combination treatment allows synergistic use of drugs with complementary actions. In a meta-analysis of 42 trials, combination antihypertensive treatment was fivefold more effective in lowering BP than doubling the dose of single agents. Moreover, the lower dose of each individual agent reduces the risk of side effects, thereby improving compliance. Multiple dosing decreases compliance. Use of a fixed-dose combination (FDC) overcomes this. In a meta-analysis of four hypertension studies, FDC treatment improved compliance by 24% compared with individual agents given separately. A more recent meta-analysis confirmed this finding, and also reported a 50% increase in persistence with treatment with the use of FDCs. However, FDCs have some limitations: loss of flexibility in adjusting the dose of each agent, ineligibility for medical insurance plans, as well as some formulations possibly not being safe or practical for first-line treatment. Another benefit of combination treatment—particularly with calcium channel blockers (CCBs), diuretics, and angiotensin-converting enzyme inhibitors—may be a reduction in BP variability, a risk factor associated with myocardial infarction and stroke. The key issue then is selecting the best combination for most patients.

### Renin-angiotensin-aldosterone system inhibitors plus calcium channel blockers

The ACCOMPLISH trial (Avoiding Cardiovascular events in COMbination therapy in Patients Living with Systolic Hypertension) showed that a FDC of benazepril and amlodipine was superior to benazepril and hydrochlorothiazide in reducing cardiovascular events and death in patients with hypertension. In the ACCELERATE trial (Aliskiren and the Calcium ChannEL BlockER Amlodipine combination as an initial Treatment Strategy for HyperTension), patients who took aliskiren and amlodipine achieved greater reduction in systolic BP than patients taking either drug as monotherapy. It should be noted that there are no outcome studies with angiotensin receptor blocker/CCB or direct renin inhibitor/CCB combinations. However, the combination of a renin-angiotensin-aldosterone system (RAAS) inhibitor with a CCB is a rational and effective choice. In this regard, the only randomized trial evidence comparing separate drug regimens comes from the ASCOT trial (Anglo-Scandinavian Cardiac Outcomes Trial), which found that the combination of the newer agents, perindopril plus amlodipine, was significantly better in reducing cardiovascular risk than the older combination of β-blocker plus diuretic.

### Renin-angiotensin-aldosterone system inhibitors plus diuretics

Diuretics decrease volume, which in turn activates RAAS. This activation leads to vasoconstriction, salt and water retention, and increased BP. When added to a thiazide-like diuretic, an inhibitor of RAAS overcomes these untoward effects and provides additional BP lowering. Furthermore, hypokalemia and glucose intolerance—both commonly associated with diuretic use—are alleviated with the addition of a RAAS inhibitor, making this a rational combination for hypertensive patients. In the HYVET trial (HYpertension in the Very Elderly Trial), the combination of perindopril and indapamide significantly reduced stroke and heart failure in an elderly population, compared with placebo.

In conclusion, use of a fixed-dose combination or selection of complementary drug classes in the management of hypertension allows patients to achieve their BP goal quickly, reduces adverse drug reactions, and improves compliance.
Aadherence to medical treatment is universally poor, with estimates indicating that less than half of patients prescribed an antihypertensive, lipid-lowering, or antidiabetic drug continue treatment beyond 1 year. Smith et al postulated that including key medications necessary to reduce cardiovascular risk in a single pill could increase the use of effective and inexpensive medications, improving treatment adherence.2

What more can be done to speed up incorporation of multiple-drug combinations (MDCs) into everyday practice and clinical guidelines? We have still not defined proper target groups for the different MDCs in “primary” and “secondary” prevention. Thus, I would like to propose at least four stages of prevention: (i) zero-order prevention; (ii) primary prevention; (iii) secondary prevention; and (iv) tertiary prevention (Figure). “Zero-order prevention” would be for those without hypertension but with high normal arterial blood pressure, and/or with hypercholesterolemia, but with slightly elevated serum C-reactive protein concentrations. Such patients benefited from receiving renin-angiotensin blockers (reducing the probability of hypertension) in TROPHY (TRial Of Preventing Hypertension) and PHARAO (Prevention of Hypertension with the Angiotensin-converting enzyme inhibitor RAmpirol in patients with high nOrmal Blood Pressure) or statins (reducing the number of deaths, myocardial infarctions, and strokes) in JUPITER (Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin). We could thus here propose polypill A, comprising an angiotensin-converting enzyme (ACE) inhibitor and a statin. Pill B, with two antihypertensives, a statin, and aspirin, could be proposed for those with established hypertension as the newly-defined “primary prevention.” Pill C would be for “secondary prevention” in those diagnosed with coronary artery disease or equivalent, and should also contain a β-blocker. Pill D could be used as “tertiary prevention” after a stroke, myocardial infarction, or revascularization, and might consist of two antiplatelets and more potent antihypertensives, with indapamide. I believe this is the right time for such a new classification of prevention and polypills.3 There is also an emerging need for polypills in heart failure (HF). New guidelines advocating at least four or five drugs in patients with systolic HF with reduced ejection fraction should speed up the commercialization of polypills in this field. If a patient must take a diuretic, β-blocker, ACE inhibitor, eplerenone, and ivabradine, one may wonder what level of adherence is forecasted. The question is why we still do not have: (i) a polypill with once-daily ACE inhibitor and eplerenone, the aldosterone antagonist of choice; and (ii) a polypill with ivabradine and a β-blocker. Although a combination of two drugs affecting the renin-angiotensin system is not recommended in hypertension, use of such a combination in HF is routine in patients with NYHA classes II-IV and an ejection fraction of ≤35% without hypertension, hyperkalemia, or severe renal failure. A polypill with ivabradine and a β-blocker should probably include carvedilol (given twice daily like ivabradine), which has been well evaluated in patients at all NYHA stages. Vasodilatory third-generation β-blockers like carvedilol reduce the heart rate in a self-restricting manner because of a simultaneous decrease in peripheral resistance. Therefore, additional rate reduction with ivabradine might be crucial.4

In conclusion, many different MDCs will emerge in the coming years, both in hypertension and cardiovascular prevention, and in HF. We look forward to using them to improve patient adherence in zero-order, primary, secondary, and tertiary prevention, as well as to reduce the number of pills taken in diseases like HF.5

References

Figure. The four stages of cardiovascular risk prevention.

<table>
<thead>
<tr>
<th>Pill A</th>
<th>Pill B</th>
<th>Pill C</th>
<th>Pill D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin + ACE inhibitor + statin</td>
<td>Aspirin + ACE inhibitor + second antihypertensive drug (amlodipine?) + statin</td>
<td>Aspirin + ACE inhibitor + β-blocker + statin</td>
<td>Aspirin 75 mg or aspirin/clopidogrel 75/75 mg + ACE inhibitor (full dose) + β-blocker (full dose) + statin (full dose) + diuretic (indapamide)</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; JUPITER, Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin; PHARAO, Prevention of Hypertension with the Angiotensin-converting enzyme inhibitor RAmpirol in patients with high nOrmal Blood Pressure; TROPHY, TRial Of Preventing Hypertension.
Fixed-dose or flexible-dose combination antihypertensives have been studied in the medical literature for over 20 years, with publications dating back to 1990 demonstrating the beneficial effects of combining three antihypertensives in a single tablet. Indeed in 2003, the Joint National Council–VII hypertension guidelines stated that fixed-dose combination (FDC) therapies are more convenient as they simplify blood pressure (BP) treatment regimens, with more patients achieving target BP reduction with combination agents than through up titration of single agents to maximum doses. It is also widely recognized that the majority of hypertensive patients require two or more different agents to achieve adequate BP control. This need for multiple agents to control BP is reflected in the recent European guidelines published in 2009. Initial treatment with combination antihypertensives leads to a number of beneficial effects, and the majority of studies demonstrate more effective BP control at introductory doses of combination agents. Furthermore, side effects associated with higher doses of single agents are reduced with combination therapies, which use smaller doses of the individual agents. Compliance is also improved for a number of reasons. Typically, there is less need for frequent physician visits for drug up titration; single-tablet regimens are always more preferable to patients than multiple tablet regimens; and as mentioned, the smaller doses of individual agents used in combination pills are associated with fewer side effects. As recently as 2003, Law et al demonstrated in a meta-analysis of over 350 randomized controlled trials of antihypertensive therapies that the side effects of all antihypertensive agents—apart from renin-angiotensin-aldosterone system (RAAS) inhibitors—are dose-responsive. Furthermore, in certain situations, the effects of a second agent taken in combination reduced the side effects of the first agent. The prime example is ankle edema caused by calcium antagonists, an effect that is reduced by combination of the calcium antagonist with a RAAS inhibitor.

It is reassuring to note that combination agents incur significant cost savings to health economies. There are a number of reasons for this, including improved patient compliance and more appropriate BP reduction, leading to significant improvements in cardiovascular and stroke incidence and mortality. Furthermore, combination agents are frequently less expensive to prescribe than the individual drug components. Bangalore et al published a nice paper in 2007 in which they analyzed 68 studies investigating FDCs, identified through a Medline search. This totaled just under 12 000 patients on FDCs versus just under 8500 patients on free drug component regimens. While the study was not restricted to FDCs for hypertension, the authors did demonstrate a reduction in noncompliance of 24% to 26% with the use of an FDC versus single medication regimens. The question of compliance was also studied by Gupta et al, who published a meta-analysis in 2009 that included 15 studies, with just under 18 000 patients included from trials reporting on drug compliance. The use of FDCs (two antihypertensive agents in a single tablet) was associated with significantly better compliance than the corresponding free drug combinations, with beneficial improvements in BP and a reduction in adverse events.

This wealth of data in favor of FDCs should therefore encourage primary care physicians to use combination agents with confidence and in the knowledge that, compared with single drug regimens, adverse events are less common, costs are reduced, compliance is improved, and more patients will achieve target BP reductions, thereby requiring fewer clinic visits. These recommendations were incorporated into the updated British Hypertension Society guidelines published in September 2012, and have been endorsed by the National Institute for Health and Clinical Excellence. These guidelines are also not secondary care–driven, but are instead primary care–focused.

References
Addressing the issue of hypertension is a challenge not only because it is in many instances an asymptomatic condition, but also because reaching and maintaining BP targets is not easy and eventually requires the use of multiple drugs, with the need to take into account respective efficacy profiles and adverse effects. The impact of antihypertensive drugs on clinical outcomes along the continuum of cardiovascular and vasculature injury and vascular diseases has been well documented, with many landmark trials. All of these drugs reduce BP, but do not all show positive effects on clinical outcomes. These trials have provided us with sufficient documented evidence to significantly influence medical decision-making, but this remains suboptimally utilized in clinical practice. The tendency to extrapolate data and attribute positive outcomes to “class effects” contributes to the wide gap between progress in our knowledge of hypertension per se and the effectiveness of antihypertensive treatment in primary and secondary prevention settings.

Uncontrolled hypertension eventually leads to end-organ damage, not only because of the adverse effects of increased pressure on the vasculature, but also because of the neurohormonal abnormalities that occur. It stands to reason, therefore, that whatever it takes to control BP—by monotherapy at the start, or by combination therapy eventually—must be started early and chosen well, not on the basis of BP reduction efficacy, but also of the drugs’ impact on the metabolic changes in hypertension, which—ironically—may be aggravated by some drugs themselves. Right from the start, therefore, drug choices must be based on what the evidence demonstrates, particularly on whether or not the drugs actually improve clinical outcomes.

While a significant reduction in BP by any antihypertensive may positively impact a clinical outcome—for example, reduce the risk of stroke—the metabolic changes that some classes of antihypertensives cause, such as the increased risk of diabetes posed by β-blockers or thiazide diuretics, should compel astute clinicians to nuance their choices and look beyond simple BP reduction. This is particularly the case as even if populations at risk start with monotherapy, effective BP control will eventually require the use of combination therapy involving two, three, or even four drugs. Moreover, there are significant differences among drugs belonging to the same class, which should warn clinicians against assuming a “class effect” and extrapolating clinical benefits. For example, angiotensin-converting enzyme (ACE) inhibitors, which have been shown to have positive outcomes in primary and secondary prevention settings, cannot just be substituted with angiotensin receptor blockers, even if the latter also affect the renin-angiotensin-aldosterone system. Then again, not all ACE inhibitors are the same. This is where the treatment challenge is compounded, particularly when multiple drugs are used in combination.

The landmark trials in hypertension are there to guide the clinician, yet the clinician’s choice of which multiple-drug combination to use can be flawed by erroneous or inconsistent interpretation of data. One such landmark trial is the ASCOT trial (Anglo-Scandinavian Cardiac Outcomes Trial), which has provided the clinician with evidence that can be used to decide which drug combination works in preventing cardiovascular events, and which just lowers BP. In evidence-based medicine, it behooves the clinician to choose drugs that: (i) have synergistic or complimentary benefits when used together, none of which should cause or aggravate the metabolic abnormalities in hypertension; (ii) have protective effects on the endothelium and target organs affected by hypertension; (iii) can retard or reverse the structural changes brought about by remodeling after organ injury; and (iv) most importantly, have documented evidence of a positive impact on clinical outcomes based on controlled randomized trials, when taken singly or in combination, in both primary and secondary prevention settings.

References
Evidence from the Blood Pressure–Lowering Treatment Trialsists Collaboration (BPLTTC) showed that the cardiovascular benefits associated with blood pressure (BP) lowering are directly related to the degree of BP control, irrespective of the agents used. However, the question of whether certain agents—alone or in combination—exert a benefit beyond BP reduction is the source of longstanding controversy. A meta-analysis of several major randomized clinical trials suggested that the use of angiotensin-converting enzyme (ACE) inhibitors in patients with coronary heart disease provides a benefit beyond BP lowering. Similarly, it has been suggested that calcium channel blockers (CCBs) and angiotensin receptor blockers (ARBs) have beneficial effects for stroke prevention beyond their BP-lowering effects, suggesting differential effects on other determinants of cardiovascular outcomes not related to BP. It is therefore not too difficult to believe that for the same level of BP control, different agents may generate different effects in terms of primary and secondary cardiovascular protection.

The relative benefits of ACE inhibitors and ARBs have been controversial. Meta-analyses have suggested that ACE inhibitors may be superior to ARBs in terms of preventing coronary heart disease events. On the other hand, other analyses have suggested that ARBs have superior benefits for stroke prevention that go beyond BP lowering. With great anticipation, the ONTARGET trial (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) studied the effect of ACE inhibitors, ARBs, and their combination in a large-scale trial of high-risk individuals. Overall, it was shown that neither agent was superior to the other or to the combination. Moreover, in stark contrast to the expected results, the combination induced a significant increase in hard renal endpoints, although proteinuria was significantly improved. By contrast, the HYVET trial (Hypertension in the Very Elderly Trial) was stopped early due to the observation of large benefits for all cardiovascular events in the active intervention group (ACE inhibitors and thiazide-like diuretics). The VALUE trial (Valsartan Antihypertensive Long-term Use Evaluation) studied cardiac morbidity and mortality among hypertensive patients with high cardiovascular risk, and reported no differences in the primary composite end point; however, myocardial infarction and stroke occurred less commonly in patients receiving CCBs than ARBs. The ASCOT trial (Anglo-Scandinavian Cardiac Outcomes Trial) evaluated two combination antihypertensive regimens in patients with three or more common cardiovascular risk factors but without established coronary heart disease: a standard regimen (β-blocker/thiazide) versus a newer regimen (CCB/ACE inhibitor). The newer regimen was clearly superior in terms of preventing cardiovascular events overall, and significantly so for most of the primary, secondary, tertiary, and post hoc end points studied. CAFÉ (Conduit Artery Function Evaluation) and other substudies of the BP-lowering arm of ASCOT found that lower central BP and nocturnal systolic BP control—strong predictors of cardiovascular outcomes—were in part responsible for the differential effects on cardiovascular outcomes in favor of the new regimen.

Interestingly, a recent meta-analysis of clinical trials in hypertension looked at 20 randomized controlled morbidity-mortality trials with 158,998 patients using either ACE inhibitors or ARBs in the active treatment arm.1 Only 3 out of 20 trials—ASCOT, ADVANCE (Action in Diabetes and cardioVAscular disease: Preterax and DiamicroN MR Controlled Evaluation), and HYVET (34,242 patients)—demonstrated significant reductions in all-cause mortality (13% when pooled; 95% confidence interval, 0.81-0.93; P<0.0001). All three trials had treatment strategies that included perindopril, while indapamide was used in two of the trials and amlodipine in one. Neither the level of patient risk nor the trial duration could explain the results. This indicates that fixed-combination perindopril/amlodipine may provide physicians with the opportunity to replicate the cardiovascular risk reduction seen in ASCOT in daily clinical practice.

Reference
Combining multiple drugs in a single pill offers a convenience that can significantly improve poor adherence to therapy, as well as therapeutic inertia. Additional benefits of combining agents from different classes include improved efficacy and safety and a reduction in cardiovascular events. In patients for whom dual therapy is inadequate, multiple-drug therapy in a single pill offers a simplified and effective treatment strategy. The burden of hypertension is increasing in Europe and North America, and it has been estimated that hypertension affects about 80 million adults in the USA; yet, although antihypertensive agents are able to significantly improve blood pressure levels, only 50% of hypertensive patients achieve blood pressure control.

In recent years, a large number of randomized clinical trials and meta-analyses have demonstrated that blood pressure reduction is the main determinant of primary and secondary cardiovascular prevention. Indeed, the goal of antihypertensive therapy is to reduce the cardiovascular risk associated with the elevation in blood pressure levels. Many patients require at least two antihypertensive agents, and current international guidelines emphasize the need for combination regimens for initial antihypertensive therapy.

Furthermore, for those patients requiring three drugs, it has been shown that an effective approach is to use a combination of agents with complementary mechanisms of action, such as a renin-angiotensin-aldosterone system blocker, a calcium channel blocker, and a diuretic. Recently, it has been suggested that novel approaches to multiple-drug combinations for cardiovascular prevention should be considered, including tablets manufactured with the drugs placed at opposite ends with a drug-free layer placed between them, or tablets divided into discrete, separate segments, which may provide additional benefits for initial close titration and dosage adjustments.

Bangalore and Ley published a comprehensive review of all the available clinical evidence and scientific guidelines proposing multiple-drug combinations in hypertension, including combinations of an angiotensin II receptor blocker or angiotensin-converting enzyme inhibitor plus a calcium channel blocker or diuretic. Once-daily treatment with a single pill was effective and well-tolerated, reducing the pill burden, simplifying the treatment regimens, and improving adherence to therapy. These significant beneficial effects helped patients to reach and maintain their blood pressure targets, and ultimately, to achieve their short-term and long-term treatment goals for comprehensive cardiovascular risk reduction in both primary and secondary prevention.

It should also be highlighted that triple-combination regimens resulted in a greater proportion of patients achieving control of blood pressure compared with patients receiving dual-combination regimens, with significantly lower levels of blood pressure reported after only 2 weeks at maximum doses. In summary, multiple-drug combinations in hypertension and cardiovascular prevention offer a convenience that can address the barriers to reaching therapeutic targets, both for primary and secondary prevention. Physician acceptance of a single-pill combination of drugs for reducing cardiovascular risk is moderate to high, at least when considering the clinical approach to its use. The perspectives of physicians may, however, evolve towards a still greater acceptance with more availability of such multiple-drug combinations for use in both primary and secondary cardiovascular prevention.

References
combination therapy, the time to blood pressure goal attainment is shortened considerably. The latter has an important impact on the reduction of cardiovascular outcomes, independent of drug treatment, which should garner support for the use of combination therapy in high-risk patients. With combination therapy, adverse event rates are not additive; this is either because of fewer dose-dependent side effects or neutralization of adverse events by complementary drug interactions. Even in mild hypertension, where attainment of blood pressure goals is deemed less urgent, a persuasive case should be made for initiating combination therapy on the grounds of improved tolerability with no compromise on efficacy.

Single-pill combinations, preferably comprising long-acting drugs taken once daily, should be used where possible. In a meta-analysis comparing two-drug single-pill combinations with equivalent free doses of component drugs, treatment adherence was significantly enhanced by more than 20% with single-pill combinations. Moreover, there were nonsignificant trends toward lower adverse events (20% reduction), larger absolute blood pressure reduction, and improved goal attainment (50% increase), the latter possibly driven by higher compliance. Currently, various two-drug and three-drug single-pill combinations with various dose permutations are commercially available for hypertension treatment. By simplifying hypertension management, they improve treatment adherence and persistence, as well as the success rate and speed of blood pressure goal attainment. They constitute a feasible and promising strategy for combating treatment barriers to achieving and maintaining blood pressure goals in all risk categories of hypertensive patients.

References
The border between primary and secondary prevention is not clearly defined in the continuum of cardiovascular disease. Since the introduction of methods to determine subclinical atherosclerosis, we see more and more patients who initially categorize as being candidates for primary prevention, but who are found to have atherosclerotic vascular disease on imaging. A more clinically-relevant approach would be to categorize the patients according to their risk level. As the risk increases, more aggressive therapies for prevention and treatment should be used. There are several risk prediction scores, and in Europe, the one that should be used to determine the risk of an individual patient is the SCORE system (Systematic COronary Risk Evaluation). Moreover, it has been shown that adding markers of organ damage to the SCORE risk estimation improves risk prediction in the hypertensive patient. According to the 2012 prevention guidelines of the European Society of Cardiology, individuals having any of the following are categorized as having very high risk: documented cardiovascular disease by invasive or noninvasive testing; diabetes mellitus (type 1 or type 2) with one or more cardiovascular risk factors and/or target organ damage; severe chronic kidney disease and a calculated SCORE of ≥10%. High-risk individuals are defined as those having any of the following: markedly elevated single risk factors, such as familial dyslipidemia and severe hypertension; diabetes mellitus (type 1 or type 2) but without cardiovascular risk factors or target organ damage; moderate chronic kidney disease or a calculated SCORE of ≥5%, and 10% for 10-year risk of fatal cardiovascular disease.

Our main aim in treating the hypertensive patient is to decrease cardiovascular mortality and morbidity and prevent end organ damage. To achieve this aim, optimal control of blood pressure and other risk factors is necessary. The relationship between blood pressure and cardiovascular risk is strong and graded, and reaching target blood pressure is important to achieve maximum benefit. Most hypertensive patients will need at least two agents to reach the targets that have been defined in the guidelines. Patients also need to be compliant in order to maintain the target levels throughout their lifetime. A meta-analysis of 42 studies showed that combining two agents from any two classes of antihypertensive drugs increases the blood pressure reduction much more than doubling the dose of one agent. For a combination to be more effective, synergistic combinations should be chosen. The guideline-recommended initial preferred combinations are a renin-angiotensin-aldosterone system antagonist with either a calcium channel blocker or a diuretic, according to current evidence. Large-scale trials such as ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) and ACCOMPLISH (Avoiding Cardiovascular events in COMbination therapy in Patients Living with Systolic Hypertension) have shown a decrease in cardiovascular events with the use of these combinations in high-risk patients.

The 2007 European Society of Hypertension/European Society of Cardiology guidelines recommend that combination of two drugs be considered as initial treatment whenever hypertensive patients have high initial blood pressure or are classified as being at high/very high cardiovascular risk because of the presence of organ damage, diabetes, renal disease, or a history of cardiovascular disease. This is both because of higher effectiveness and lower discontinuation rates, both of which are extremely important for high-risk patients or those with high initial blood pressure.

In conclusion, we should start thinking about the risk of the patient rather than whether he or she is a primary or secondary prevention case, and regardless of whether the patient has known cardiovascular disease or not, high-risk hypertensive patients should be considered for combination therapy.

References
There is overwhelming documentation from clinical trials and epidemiological studies providing evidence of measures that improve outcomes in cardiovascular patients. Every year, we learn about novel effective therapies in the cardiovascular field and gain new information on combinations of pharmacological therapies for use in specific patient groups. As cardiovascular disease has multiple origins, the approach to its prevention and treatment must be multifaceted and rely on the use of combination therapy. The first and essential component of successful cardioprotective combination therapy is, of course, a lifestyle change. However, such an approach does not lead to satisfactory control of risk factors in most patients. Thus, drug therapies represent a necessary adjunct in most clinical situations.

The decision to start a patient on medication is based on several factors, the most important of which is careful risk stratification. Assessment of a patient’s risk status determines their treatment goals as well as the modes of achieving these goals. Initiation of pharmacotherapy, and any further approach to management of individual cardiovascular risk factors, depends on the patient’s risk. As there is a very thin line between so-called primary and secondary prevention (usually a few seconds when atherothrombosis occludes an artery and myocardial infarction or ischemic stroke develops), it seems more feasible to categorize patients according to their risk. High-risk or very-high-risk patients deserve the same attention and aggressive risk factor management regardless of whether they have had a vascular event or not. There is ample evidence supporting this approach as a number of clinical trials both in primary and secondary prevention have yielded similar results, and preventing the first event seems to be even more important than averting a recurrence.

Having said this, we have almost answered our controversial question and it does not seem to be controversial anymore. Those with increased cardiovascular risk require intensive management of their risk factors, and we must offer these patients pharmacotherapy to bring them to guideline-recommended targets. Only well-proven medications should be used to avoid unnecessary polypragmasia, and in most cases, risk factor control requires use of drug combinations. Hypertension can be controlled with monotherapy in less than 20% of patients. Increasingly stringent goals for low-density lipoprotein cholesterol levels can be achieved with statins, but in some patients, statin-fibrate or statin-ezetimibe combinations might be needed. All type 2 diabetics should be treated with metformin, but this medication alone does not usually lead to satisfactory control of hyperglycemia. Moreover, patients with advanced atherosclerosis should receive antiplatelet therapy. Therefore, a high-risk individual with diabetes may require at least five different medications. Nevertheless, every now and then, voices calling for “a conservative approach” avoiding the use of multiple medications can be heard.

However, there is no documentation supporting such an approach. Experience from clinical trials conducted over the last decade, together with positive trends in cardiovascular morbidity and mortality in developed countries, provide a clear answer. There are combinations of drugs that have been proven unambiguously to bring benefit to a variety of clinical situations. Just one example: the ASCOT trial (Anglo-Scandinavian Cardiac Outcomes Trial). The combination of an angiotensin-converting enzyme inhibitor, calcium channel blocker, and statin reduced the risk of myocardial infarction by more than 50% in a high-risk population with no history of atherothrombotic events, thus showing a synergistic effect among the therapies used.

In conclusion, the use of drug combinations in the treatment and prevention of cardiovascular disease is not only recommended by current guidelines and evidenced by the results of well-conducted clinical trials, but most importantly, it is justified by the decline in cardiovascular disease mortality that has accompanied wider implementation of this approach to all individuals at increased risk.

References
Advances in the field of cardioprotection have established the value of combination therapy for hypertensive patients. If lowering blood pressure remains the primary goal of antihypertensive treatment, decreasing cardiovascular morbidity and mortality has emerged as the true objective of hypertension management. Combining drugs with complementary modes of action in a single pill offers a real advantage in terms of efficacy and rapidity of action. Patient adherence and tolerance to treatment are also enhanced, ultimately resulting in greater cardiovascular protection. Major landmark trials in hypertension such as ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial), ADVANCE (Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation), or HYVET (Hypertension in the Very Elderly Trial) have demonstrated the clear advantage of combining the leading drugs in their respective class—the angiotensin-converting enzyme inhibitor perindopril, the thiazide-like diuretic indapamide, and the calcium channel blocker amlodipine—in reducing mortality. Recent meta-analyses have confirmed not only that treatment with perindopril-based combinations results in a 13% reduction in all-cause mortality and a 22% reduction in cardiovascular mortality in hypertensive patients, but also that these combinations are the cornerstone of cardiovascular prevention in high-risk patients and diabetic patients. Additional therapeutic needs should be fulfilled in the near future, when new fixed combinations of these three drugs become available.

Current guidelines in hypertension support the view that, whatever the drug used, monotherapy will only control the blood pressure in a limited number of patients in the long term. Of course, treatment initiation with monotherapy with consecutive up titration at full-dose remains the most widely applicable strategy for hypertensive patients. However, a recent meta-analysis of 42 studies has shown that in most cases, the blood pressure reduction obtained by combining two agents from any two classes of antihypertensive drugs is five times that obtained with doubling the dose of one agent. This observation is supported by the obvious advantage of combining the complementary pharmacological mode of actions of two or more drug classes. Not only are blood pressure reduction and cardiovascular protection enhanced, but tolerance is also improved by initially lowering the dose of each component and offsetting their potential side effects.

Optimizing combination therapy for cardiovascular protection: evidence from landmark trials

by N. Clavreul, France
productive when trying to reach the target objective of treating hypertension: to lower cardiovascular morbidity and increase life expectancy. Indeed, patients tend to be less reluctant to follow their treatment when they reach blood pressure targets with their initial treatment as opposed to having to go through multiple switches from one monotherapy to another.

Several recent studies have demonstrated the need to achieve rapid blood pressure control in order to obtain better outcomes. It was already apparent in a post-hoc analysis of the VALUE study (Valsartan Antihypertensive Long-term Use Evaluation) that, independently of the treatment, the rate of cardiovascular events was lower during the whole study for patients who initially reached blood pressure control within the first month. This observation was reinforced further in a recent Italian cohort study in more than 200 000 patients who were newly treated with antihypertensive drugs. Initiation with a combination treatment resulted in a significantly better protection over the 6 years of follow-up, with a lower rate of coronary and cerebrovascular events. It seems reasonable to suggest that the more rapid and sustained reduction in blood pressure afforded by combination treatment accounts for these results. Newer single-pill formulations for combination therapy also contribute greatly to helping patients attain controlled blood pressure by improving compliance. A 1-year study in more than 100 000 patients showed that patients whose antihypertensive treatment was initiated with a single-pill combination reached blood pressure targets more rapidly than their counterparts who were treated with either monotherapy or free combinations. Single-pill combinations are, therefore, expected to improve not only the rapidity of blood pressure control, but also the survival rate.

### How combining perindopril and indapamide in a single pill contributed to better hypertension management

Investigations aiming to demonstrate the potential benefit of combination therapy in cardiovascular protection began early on. Based on the assumption that combining a long-acting angiotensin-converting enzyme (ACE) inhibitor, perindopril, with a metabolically neutral diuretic, indapamide, as first-line treatment would be more effective than a classic monotherapy strategy, the STRATHE trial (STRAtegies of Treatment in Hypertension: Evaluation) compared treatment initiation with Preterax (perindopril/indapamide) with a sequential strategy (starting with a β-blocker and then adding an angiotensin receptor blocker [ARB] and a calcium channel blocker [CCB]), or a step-by-step strategy (uptitration of an ARB and addition of a thiazide diuretic) in grade 2 hypertensives. Preterax was shown to rapidly control a greater number of patients than the other strategies, paving the way for the first recognition of combination therapy as an option for treatment initiation in patients with marked hypertension or at high cardiovascular risk. Preterax was also shown to be superior to enalapril or atenolol in reducing blood pressure in hypertensive patients with left ventricular dysfunction or diabetes. Preterax’s ability to preserve and regenerate the microcirculation to improve target-organ function was observed in the PICXEL study (Perindopril/Indapamide in a double-blind Controlled study versus Enalapril in Left ventricular hypertrophy), in which it achieved a greater reduction in left ventricular hypertrophy than enalapril. In the PREMIER study (PREterax in albuMinuria eRgression), there was also a significantly greater reduction in albumin secretion with Preterax than with enalapril, which led to fewer major cardiovascular outcomes.

Although blood pressure was recognized as an important determinant of the risk of initial stroke in both normotensive and hypertensive patients, and a linear correlation between

### SELECTED ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABPM</td>
<td>ambulatory blood pressure monitoring</td>
</tr>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ARB</td>
<td>angiotensin receptor blocker</td>
</tr>
<tr>
<td>CAD</td>
<td>coronary artery disease</td>
</tr>
<tr>
<td>CCB</td>
<td>calcium channel blocker</td>
</tr>
<tr>
<td>DBP</td>
<td>diastolic blood pressure</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>RAAS</td>
<td>renin-angiotensin-aldosterone system</td>
</tr>
<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
</tr>
</tbody>
</table>

### SELECTED TRIAL ACRONYMS

<table>
<thead>
<tr>
<th>Trial Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVANCE</td>
<td>Action in Diabetes and Vascular disease: Preterax and DiamicroN MR Controlled Evaluation</td>
</tr>
<tr>
<td>ASCOT</td>
<td>Anglo-Scandinavian Cardiac Outcomes Trial</td>
</tr>
<tr>
<td>ASCOT-ABP</td>
<td>Anglo-Scandinavian Cardiac Outcomes Trial – Ambulatory Blood Pressure</td>
</tr>
<tr>
<td>CAFE</td>
<td>Conduit Artery Function Evaluation</td>
</tr>
<tr>
<td>EUROPA</td>
<td>European trial on Reduction Of Cardiac events with Perindopril in stable coronary Artery disease</td>
</tr>
<tr>
<td>HYVET</td>
<td>Hypertension in the Very Elderly Trial</td>
</tr>
<tr>
<td>PICXEL</td>
<td>Perindopril/Indapamide in a double-blind Controlled study versus Enalapril in Left ventricular hypertrophy</td>
</tr>
<tr>
<td>PREMIER</td>
<td>PREterax in albuminuria eRgression</td>
</tr>
<tr>
<td>PROGRESS</td>
<td>Perindopril pROtection aGainst REcurrent Stroke Study</td>
</tr>
<tr>
<td>QUIET</td>
<td>QuInapril Ischemic Event Trial</td>
</tr>
<tr>
<td>ROADMAP</td>
<td>Randomized Olmesartan And Diabetes Microalbuminuria Prevention Study</td>
</tr>
<tr>
<td>STRATHE</td>
<td>STRAtegies of Treatment in Hypertension: Evaluation</td>
</tr>
<tr>
<td>UKPDS</td>
<td>United Kingdom Prospective Diabetes Study</td>
</tr>
<tr>
<td>VALUE</td>
<td>Valsartan Antihypertensive Long-term Use Evaluation</td>
</tr>
</tbody>
</table>
blood pressure levels and occurrence of ischemic stroke and cerebral hemorrhage was established; clinical uncertainty remained about the efficacy and safety of routine administration of a blood-pressure-lowering regimen in this population. In the PROGRESS study (Perindopril PROtection aGainst Recurrent Stroke Study), 6105 patients with a history of stroke or transient ischemic attack, half of them hypertensive, were randomized to placebo or perindopril with addition of indapamide, as required, on top of their current standard treatment. In patients assigned to the active treatment, blood pressure was lowered by an average of 9 mm Hg for systolic blood pressure (SBP) and 4 mm Hg for diastolic blood pressure (DBP). In patients who had received the combination of perindopril and indapamide since randomization, the reduction in SBP/DBP was even greater (–12.3/–5 mm Hg). This was associated with a 43% relative reduction in the risk of stroke and a 42% reduction in all major vascular events (Table I). Interestingly, the protection afforded by combination therapy was similar whether patients were hypertensive or not.

Later on, these encouraging effects of Preterax on microvascular and macrovascular events spurred the launch of the ADVANCE trial (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation), which evaluated the benefit of tight blood pressure control with Preterax in patients with diabetes, irrespective of whether they were hypertensive or not. The primary hypothesis was that a further reduction in SBP below the 145 mm Hg achieved in the hypertensive diabetic patients of UKPDS (United Kingdom Prospective Diabetes Study) would provide even greater protection in this high-risk population. A total of 11 140 patients in 20 countries were enrolled in ADVANCE. To be eligible, patients had to have been diagnosed with type 2 diabetes at the age of 30 years old or older, be 55 years old or older at study entry, and show evidence of elevated cardiovascular risk. Patients were randomized to perindopril/indapamide or matching placebo, on top of their previous standard therapy, with progressive up titration. Baseline blood pressure was 145/81 mm Hg on average, and active treatment led to a further 5.6/4.2 mm Hg decrease in blood pressure. In these conditions, perindopril/indapamide treatment was associated with a significant improvement in cardiovascular morbidity and mortality compared with standard therapy alone. As well as a significant 9% (P=0.04) reduction in the primary end point, a composite of major macrovascular events (cardiovascular death, nonfatal stroke, and nonfatal MI) and microvascular events (new or worsening renal or diabetic eye disease), there were also significant reductions in cardiovascular death and all-cause death, of 18% (P=0.04) and 14% (P=0.04), respectively (Table I).

The positive impact of perindopril/indapamide on the microcirculation was illustrated by a 21% reduction in the relative risk of renal events, which was driven by a marked reduction in microalbuminuria. A subsequent subanalysis of renal events in ADVANCE revealed a consistent beneficial effect on kidney function, independently of the blood pressure level achieved, with no threshold effect. Similarly, analysis of the 10 640 patients with chronic kidney disease revealed a consistent benefit in terms of renal and cardiovascular outcomes across all stages of chronic kidney disease.

<table>
<thead>
<tr>
<th>End point</th>
<th>PROGRESS</th>
<th>ADVANCE</th>
<th>HYVET</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>NA</td>
<td>0.86 (0.75-0.98)</td>
<td>0.79 (0.65-0.95)</td>
</tr>
<tr>
<td>CV mortality</td>
<td>0.72 (0.55-0.95)</td>
<td>0.82 (0.68-0.98)</td>
<td>0.77 (0.60-1.01)</td>
</tr>
<tr>
<td>Fatal and/or nonfatal stroke</td>
<td>0.58 (0.38-0.89)</td>
<td>0.86 (0.76-0.98)</td>
<td>0.72 (0.30-1.70)</td>
</tr>
<tr>
<td>Fatal and/or nonfatal MI</td>
<td>0.57 (0.46-0.70)</td>
<td>0.94 (0.80-1.10)</td>
<td>0.61 (0.38-0.99)</td>
</tr>
</tbody>
</table>


In addition to increased survival with perindopril/indapamide in diabetic patients, ADVANCE was the first and only trial to provide evidence of parallel reductions in microalbuminuria and cardiovascular and all-cause mortality. In contrast, in the recent ROADMAP trial (Randomized Olmesartan And Diabetes Microalbuminuria Prevention Study), the 20% reduction in microalbuminuria obtained with olmesartan treatment was not associated with a reduction in cardiovascular outcome. A recent meta-analysis in diabetic patients confirmed that only ACE inhibitors, and not ARBs as a class, were associated with a significant improvement in renal protection, with a 29% reduction in micro/macroalbuminuria that was mostly driven by the results of ADVANCE. This effect resulted in a 16% reduction in all-cause mortality in the trials including ACE inhibitors, while there was no effect with ARBs. For all these reasons, the SBP target for diabetics was based on the results of ADVANCE and set at 135 mm Hg. This threshold has not been modified since then, not even following more recent trials.

The most recent demonstration of the cardiovascular protective effect of Preterax has come from an as-yet poorly documented fringe of the hypertensive population: very elderly hypertensive patients. The pilot study for HYVET (Hypertension in the Very Elderly Trial) in 2003 did not do much to clar-
ify the situation, with the observation that an antihypertensive strategy based on lisinopril and hydrochlorothiazide was associated with an increase in all-cause mortality, despite a significant reduction in stroke.\textsuperscript{19} In the main HYVET trial, which included hypertensive patients aged 80 years or older, the combination of perindopril and indapamide was clearly shown to have effective blood pressure-lowering benefits in the very elderly.\textsuperscript{20} The study results showed a 39% reduction in fatal stroke ($P=0.046$), a 21% reduction in all-cause mortality ($P=0.02$), a 23% reduction in cardiovascular mortality ($P=0.06$), and a 64% reduction in the incidence of fatal or nonfatal heart failure ($P=0.001$) (Table I). The one-year extension of the trial also confirmed the need for early treatment initiation in this population.\textsuperscript{21}

The recently published ambulatory blood pressure monitoring (ABPM) data of the HYVET study confirmed that blood pressure reduction with the perindopril/indapamide combination, which averaged 8/5 mm Hg over 24 hours, was the main explanation for the difference in outcome.\textsuperscript{22} Interestingly, this substudy revealed that, on account of their 24h-blood pressure, half of the HYVET population could be considered to have “white-coat hypertension” and that, therefore, treatment with perindopril/indapamide would have been beneficial for them as well. In the absence of clear recommendations for these patients in the guidelines, this study could help to improve prevention in this group of patients.

HYVET and ADVANCE also both provided evidence of the antihypertensive efficacy and metabolic neutrality of therapeutic strategies including indapamide. The 2011 British guidelines for hypertension management now recommend using thiazide-like diuretics such as indapamide rather than conventional thiazide-type diuretics such as hydrochlorothiazide.\textsuperscript{23}

Why a fixed-drug combination of perindopril and amlodipine made sense

Coveram was launched as a fixed-combination of amlodipine and perindopril after the publication of the results of the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial), which was considered to be a breakthrough in the management of hypertension.\textsuperscript{24} Indeed, in order to reach the newly recommended blood pressure levels of 140/90 mm Hg set by both the American and British guidelines,\textsuperscript{25,26} the need for combination therapy had become more acute. However, there was limited comparative data on treatment strategies. The investigators of ASCOT therefore decided to address the question of whether a strategy based on combining newer drugs (amlodipine and perindopril) might provide additional benefits over the popular drugs used at the time (atenolol and a thiazide diuretic). A total of 19 257 hypertensive patients (baseline blood pressure, 164/95 mm Hg) with at least three risk factors, but who were free of coronary artery disease (CAD) were enrolled in ASCOT. Despite there being only a small difference in brachial blood pressure reduction, the reduction in all-cause mortality was significantly greater in the perindopril/amlodipine arm (relative risk reduction, 11%; $P=0.0247$), and this motivated the decision to stop the trial early, after 5.5 years. In addition, cardiovascular mortality was reduced by 24% ($P=0.001$), coronary events by 13% ($P=0.007$), and strokes by 23% ($P=0.0003$), all in favor of the perindopril/amlodipine combination (Table II and Figure 1). In particular, the rates of cardiovascular death in the two treatment arms diverged at the very point where the majority of patients (78%) were treated with perindopril in addition to amlodipine rather than by amlodipine alone (indicated by a red arrow on Figure 1).\textsuperscript{27}

Substudies of ASCOT have provided clinical proof that reduction in brachial blood pressure alone cannot predict prognostic benefits. Indeed, since then, the importance of key blood pressure parameters such as blood pressure variability, 24-hour blood pressure control, and central blood pressure has emerged following the demonstration that the 2.7 mm Hg difference in SBP reduction in favor of the amlodipine/perindopril group could only account for half of the differences in coronary and stroke events.\textsuperscript{28}

<table>
<thead>
<tr>
<th>End point</th>
<th>Unadjusted HR (95% CI)</th>
<th>RRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>0.89 (0.81-0.99)</td>
<td>-11%</td>
</tr>
<tr>
<td>CV mortality</td>
<td>0.76 (0.65-0.90)</td>
<td>-24%</td>
</tr>
<tr>
<td>Total coronary events</td>
<td>0.87 (0.79-0.96)</td>
<td>-13%</td>
</tr>
<tr>
<td>Fatal and nonfatal stroke</td>
<td>0.77 (0.66-0.89)</td>
<td>-23%</td>
</tr>
</tbody>
</table>

Table II. Treatment effects of amlodipine/perindopril in ASCOT.

Abbreviations: ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; RRR, relative risk reduction.


Figure 1. ASCOT: Reduction in cardiovascular mortality in patients treated with amlodipine/perindopril versus atenolol/thiazide diuretic.

Abbreviations: ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; CV, cardiovascular; HR, hazard ratio; RRR, relative risk reduction.


458 MEDICOGRAPHIA, Vol 35, No. 4, 2013 Optimizing combination therapy for CV protection: evidence from landmark trials – Claverud
Variability in SBP in patients with arterial hypertension has been shown to be a powerful predictor of stroke and coronary events, independent of mean SBP.23 In ASCOT, perindopril/amlodipine was more effective in controlling intra-visit blood pressure variability (variability between repeated measures in a single medical visit) and between-visit blood pressure variability, a parameter considered to be a predictive indicator of long-term prognosis in guidelines. Statistical adjustment confirmed that this reduction in blood pressure variability contributed to the better cardioprotection afforded by perindopril/amlodipine, a combination that the UK’s National Institute for Health and Clinical Excellence (NICE) declared to be “the best available evidence-based treatment option to suppress blood pressure variability.”23

In the ASCOT-ABP substudy (Anglo-Scandinavian Cardiac Outcomes Trial–Ambulatory Blood Pressure), ABPM demonstrated an early and effective reduction in nocturnal blood pressure, which was observed during the entire follow-up, with a mean difference of 2.2 mm Hg in nighttime SBP in favor of the perindopril/amlodipine regimen.30 In addition, the CAFÉ study (Conduit Artery Function Evaluation), which was initiated one year after randomization—when all treatments were already uptitrated in order to reach the blood pressure targets—evaluated central aortic pressures and hemodynamic indexes in a subset of patients.31 Despite a minimal and nonsignificant difference in brachial blood pressure between the two arms (ΔBP, 0.7 mm Hg; P=0.2), the difference in central blood pressure was largely in favor of the perindopril/amlodipine group (Δ central aortic SBP, 4.3 mm Hg; Δ central aortic pulse pressure, 3 mm Hg; P<0.0001 for both). This discovery offered a potential additional explanation to the better outcome observed with this combination.

The clinical complementarity and synergy of perindopril and amlodipine used in combination was further demonstrated in a recent subanalysis of the EUROPA trial (European trial on Reduction Of cardiovascular events with Perindopril in stable coronary Artery disease).32 The purpose of this substudy was to determine the effect on cardiovascular outcomes of adding perindopril to long-term treatment with a CCB in the CAD patients of EUROPA. This substudy, therefore, focused on patients who received a CCB for the whole duration of the trial, including those who were randomized to the perindopril group or the placebo group. The two populations had exactly the same baseline characteristics and the addition of perindopril to a CCB was shown to result in a 46% reduction (P<0.01) in all-cause mortality and in a 35% reduction (P<0.05) in the primary end point, a composite of cardiovascular mortality, nonfatal myocardial infarction (MI), and resuscitated cardiac arrest. Interestingly, when compared with the population who received placebo without a CCB, the benefit provided by the perindopril/CCB combination reached a 69% reduction in all-cause mortality and a 71% reduction in cardiovascular death!

Thus, Coveram, which is indicated in both hypertension and CAD, stands out among the currently available combinations of renin-angiotensin-aldosterone system (RAAS) inhibitors and CCBs in having proven efficacy in decreasing the risk of death and cardiovascular events.

<table>
<thead>
<tr>
<th>ACE inhibitor trial (ACE inhibitor)</th>
<th>n</th>
<th>Cardiovascular mortality HR (95% CI) (random effects model)</th>
<th>P value</th>
<th>n</th>
<th>Cardiovascular mortality HR (95% CI) (random effects model)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLHAT (lisinopril)</td>
<td>42 373</td>
<td>0.99 (0.89 to 1.10)</td>
<td>0.818</td>
<td>42 373</td>
<td>1.02 (0.92 to 1.11)</td>
<td>0.747</td>
</tr>
<tr>
<td>ANBP-2 (enalapril)</td>
<td>34 242</td>
<td>0.87 (0.81 to 0.93)</td>
<td>&lt;0.001</td>
<td>34 242</td>
<td>0.78 (0.70 to 0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pilot HYVET (lisinopril, enalapril)</td>
<td>76 615</td>
<td>0.90 (0.84 to 0.97)</td>
<td>0.004</td>
<td>76 615</td>
<td>0.88 (0.77 to 1.00)</td>
<td>0.051</td>
</tr>
</tbody>
</table>

**Figure 2.** Perindopril-based combinations and mortality reduction in hypertension trials.

*Abbreviations:* ACE, angiotensin-converting enzyme; ADVANCE, Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation; ALLHAT, Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial; ANBP-2, Second Australian National Blood Pressure (study); ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; CV, cardiovascular; HR, hazard ratio; HYVET, Hypertension in the Very Elderly Trial; JMIC-B, Japan Multicenter Investigation for Cardiovascular diseases B.


Optimizing combination therapy for CV protection: evidence from landmark trials – *Clavreul*
A recent meta-analysis by van Vark et al, which considered 20 trials evaluating RAAS inhibitors in hypertension and included 158,998 patients, reported that only in three trials was the active treatment significantly better at reducing mortality than the comparator: ASCOT, ADVANCE, and HYVET.33 These three trials all had perindopril as part of their active treatment, combined with amlodipine in ASCOT, and with indapamide for ADVANCE and HYVET. Treatment with perindopril-based combinations resulted in a 13% reduction in all-cause mortality and a 22% reduction in cardiovascular mortality (Figure 2, page 459).34,35 In contrast, none of the ARB trials showed any further decrease in mortality. The results of this study were echoed in a very recent new meta-analysis including 108,212 high-risk patients without heart failure where ACE inhibitors and ARBs were compared with placebo, and ACE inhibitors were shown to reduce all-cause death by 8.3% while ARBs had not such effect.36 In PROGRESS and EUROPA, perindopril-based regimens were once again the only ones to reduce both the primary outcome (cardiovascular death, MI, and stroke) and MI (Figure 3).

The consistent evidence showing the ability of ACE inhibitors to further reduce morbidity and mortality in hypertensive and high-risk patients is now acknowledged not only in the literature, but also in guidelines,37 and even by some health authorities,38 who recommend ACE inhibitors for first-line use and reserve ARBs for patients who are intolerant to ACE inhibitors.

New combinations... for unsatisfied medical needs

New complementary combinations aiming to fulfill the needs of all patients are on the horizon: Natrixam, the first and only combination of amlodipine and indapamide, which specifically addresses the issue of uncontrolled systolic hypertension, and Triplixam, the triple combination of perindopril, amlodipine, and indapamide.

The 2009 reappraisal of the European guidelines on Hypertension Management acknowledged the protection afforded by CCB/diuretic single-pill combinations against stroke and cardiac outcomes, and gave this combination preferred status based on promising results from randomized controlled trials, including VALUE.39 Indeed, in this high-risk population, the amlodipine/diuretic combination protected patients against MI (~19%) significantly better than the valsartan/diuretic strategy and showed a positive trend on stroke as well.

Diuretic/CCB combinations have also been shown to successfully reduce outcomes in patients with hypertension in other trials.40,41 In van Vark’s recent meta-analysis of mortality in hypertension trials, amlodipine and indapamide were also found to be among the only three antihypertensive drugs to significantly reduce mortality.33

Indapamide SR directly lowers peripheral resistance and has a direct vasorelaxant effect on blood vessels which complements the vasodilation produced by amlodipine and enhances the overall blood pressure reduction (Figure 4). Both drugs control blood pressure over 24 hours, have been shown to reduce SBP variability,42 and share the common advantage of being the most effective in lowering central blood pressure.43 In particular, a meta-analysis has shown that indapamide is more effective than hydrochlorothiazide in reducing blood pressure.44 Moreover, its neutral metabolic profile has led NICE to recommend that, when a diuretic is needed, a thiazide-like diuretic such as indapamide be preferred to hydrochlorothiazide.23

The complementary action of these two strongly active drugs appears to be particularly effective in lowering SBP, a parameter for which there remains a critical clinical need. A recent publication confirmed that, while DBP is frequently controlled in clinical practice, SBP is rarely, if ever, controlled.45 In addition, a low active RAAS is found in approximately 25% to 30% of hypertensive patients; as a result, a combination of RAAS blockers will not be of much benefit in these patients. The new amlodipine/indapamide combination will, therefore, be a welcome addition to the range of therapeutic strategies available to physicians.

Indeed, there is still a great need for better blood pressure control. Despite improvements in the treatment of hypertension, blood pressure remains uncontrolled in 60% of patients treated with a two-drug therapy,46 as demonstrated in a large pool of patients.
patients (11,182 patients), whatever their sex or the initial two-drug therapy used. Triple therapy is more effective than two-drug therapy and monotherapy in reducing both SBP and DBP. This superiority in blood pressure lowering ultimately results in organ protection, with a superior reduction in stroke and ischemic heart disease. This was shown in a subanalysis of ADVANCE focusing on the patients who received a CCB at baseline and all through the trial. There was a significant 28% reduction in total mortality and an almost significant 24% reduction in cardiovascular mortality in the patients who received the perindopril/indapamide/CCB triple combination compared with the patients who received placebo in addition to CCB. In addition, a prospective, multicenter, observational study in 12,064 patients with stage 1 or stage 2 primary hypertension reported a further reduction of 30 mm Hg in SBP with perindopril/amlodipine/indapamide combination after 4 months of treatment. This efficacy was maintained over 24 hours, as demonstrated in an ABPM subanalysis, and was clinically significant on account of the fact that 70% of patients with uncontrolled hypertension at inclusion were already receiving treatment with ACE inhibitors/ARBs ± hydrochlorothiazide.

Conclusion

Over the years, therapeutic advances in the management of hypertension have emerged as a result of landmark trials which have contributed to the recognition by all guidelines that the purpose of treating hypertension is, above all, to reduce cardiovascular morbidity and mortality. Modern trials with combination therapy were true breakthroughs and have erected evidence-based medicine as the gold standard. Indeed, not only have they demonstrated the lifesaving benefits of perindopril-based combinations such as Coveram or Preterax in a wide range of populations, from hypertensive patients to CAD or diabetic patients, but they have also provided the first clinical demonstrations that a reduction in all key blood pressure parameters (brachial blood pressure, 24-hour blood pressure, central blood pressure, and blood pressure variability), as well as microcirculatory disorders and target-organ damage, can contribute to a greater reduction in cardiovascular complications. This successful combination of some of the most active drugs will be expanded by the arrival of new fixed-dose combinations, for the benefit of both doctors and patients.

References

Optimizing combination therapy for CV protection: evidence from landmark trials —

10. Blood pressure; cardiovascular protection; combination therapy; hypertension management


Keywords: blood pressure; cardiovascular protection; combination therapy; hypertension management
Les récentes avancées dans le domaine de la protection cardiovasculaire ont mis en évidence l’intérêt d’utiliser des associations médicamenteuses dans l’hypertension. Si la réduction de la pression artérielle demeure la finalité première d’un traitement antihypertenseur, la prévention de la morbidité et de la mortalité cardiovasculaire représente désormais l’objectif à atteindre lors de la prise en charge du patient hypertendu. Associer des médicaments ayant des modes d’action complémentaires dans un seul comprimé offre un réel avantage en termes d’efficacité et de rapidité d’action. En outre, la meilleure adhérence des patients à leur traitement ainsi que l’amélioration du profil de tolérance se traduisent aussi par un plus haut niveau de protection. Les grands essais cliniques que représentent ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial), ADVANCE (Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation) et HYVET (Hypertension in the Very Elderly Trial) ont d’ailleurs clairement démontré l’avantage d’associer les médicaments antihypertenseurs leaders dans leur classe : l’inhibiteur de l’enzyme de conversion perindopril, le diurétique thiazidique indapamide ainsi que le bloqueur des canaux calciques amlodipine. De récentes méta-analyses ont en effet confirmé, d’une part, que les traitements en association basés sur le perindopril permettent une réduction de 13% de la mortalité toutes causes ainsi qu’une réduction de 22% de la mortalité cardiovasculaire, et d’autre part, que ces traitements sont désormais reconnus comme le fondement de la prévention cardiovasculaire du patient à haut risque et du patient diabétique. Avec les nouvelles associations fixes combinant ces mêmes molécules à venir, ce sont bientôt de nouveaux besoins thérapeutiques qui trouveront une réponse adaptée.
The correct use of combination therapy is crucial both to improve blood pressure control and to reduce cardiovascular events. Antihypertensive drugs can be effectively combined if they have different and complementary mechanisms of action. Thus, a typical combination contains drugs blocking (angiotensin-converting enzyme [ACE] inhibitor or angiotensin receptor blocker) and stimulating (calcium antagonist or diuretic) the renin angiotensin system. An effective combination therapy is a combination with additive or synergistic effects. The effect of a combination is additive when the blood pressure reduction it induces is the sum of the single effects of each of its components, while it is synergistic when its clinical efficacy is greater than the sum of the effects of the single components. A synergistic effect is clearly demonstrated when, despite similar blood pressure control, one drug combination leads to a better outcome than another drug combination. This was the case in ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm) and ACCOMPLISH (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension), two trials that demonstrated that ACE inhibitor/calcium antagonist combination results in significant better protection than β-blocker/diuretic or ACE inhibitor/diuretic combination, respectively. It is worth noting that there is currently no evidence showing that angiotensin receptor blocker/calcium antagonist combination is as effective as ACE inhibitor/calcium antagonist combination. In conclusion, in hypertensive patients, optimal treatment should be based on combination therapy, and the combination of an ACE inhibitor with a calcium antagonist should be the first choice. This strategy should lead to improved blood pressure control and better protection from cardiovascular events.

What are the advantages of combining multiple-action drugs from the pharmacological and clinical perspectives?

Usually, in the treatment of essential hypertension, a great emphasis is placed on choosing the right drug for treatment initiation, despite the demonstration that monotherapy can normalize blood pressure values in no more than 30% to 40% of patients with grade 1 and 2 hypertension, and that it is absolutely not effective in patients with grade 3 hypertension. Thus, for the majority of patients, combination therapy should not be an option, but the cornerstone of antihypertensive treatment.
However, merely combining antihypertensive drugs together is not enough to obtain an effective combination treatment, and expert selection of specific compounds with definite characteristics leading to a positive interaction is required. This is a crucial issue since the combination of antihypertensive drugs can lead to different results. In terms of blood pressure reduction, combining antihypertensive drugs can theoretically produce the following effects. (i) A combination that is not rational may have negative effects, which means that it produces the same (or lower!) blood pressure reduction as each of its single components. Combinations with a positive interaction can either have (ii) additive or (iii) synergistic effects. The effect of a combination is additive when its blood pressure-lowering effect is the sum of the effects of each single component. In contrast, a combination has a synergistic effect when it produces an effect that is greater than the sum of the effects of its single components. However, while negative or additive effects are defined according to the extent of blood pressure reduction, synergistic effects are related to blood pressure–independent cardiovascular protection.

Basically, when used rationally, combination therapy should overcome the several limitations of antihypertensive drugs used as monotherapy. The mechanisms determining the superiority of combination therapy over single-drug administration involve the pharmacological and clinical characteristics of drug classes. Concerning antihypertensive efficacy, one major problem of monotherapy is the activation of reflex mechanisms that counterbalance, and therefore limit, the degree of blood pressure reduction. For example, diuretics and calcium antagonists may cause reflex activation of the renin angiotensin system (RAS), while angiotensin receptor blockers (ARBs) increase plasma concentrations of angiotensin II (whose beneficial effect on AT₁ receptors has never been demonstrated in clinical conditions), and reductions in angiotensin II and aldosterone plasma concentrations with ACE inhibitors can be counterbalanced by angiotensin escape. This explains why the antihypertensive potency of drugs used as monotherapy is relatively modest: a single drug can easily lower blood pressure values, but only in rare cases will it be able to normalize this clinical parameter.

In contrast, combination therapy can overcome these limitations, but only if the drugs to be combined are selected on account of their different and complementary mechanisms of action. Thus, it is wise to combine a drug blocking the RAS (ACE inhibitors, ARBs, β-blockers) with drugs that stimulate this system (calcium antagonists, diuretics, vasodilators). In the same way, drugs activating the sympathetic nervous system should be combined with drugs blocking sympathetic activity. This is a fundamental aspect, which should be considered when choosing combinations of antihypertensive drugs. Unfortunately, this is not always the case in clinical practice. A typical example is the combination of an ACE inhibitor with a β-blocker. This combination is used in the treatment of hypertensive patients because of its effective cardiovascular protection in specific clinical conditions such as post-myocardial infarction or heart failure. However, it has no additive effect on blood pressure reduction since both drugs block the RAS, as clearly demonstrated in the ALLHAT study (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), where the blood pressure reduction obtained with the combination of lisinopril and atenolol was significantly inferior to that obtained with the combination of chlorthalidone oramlodipine with atenolol.

Other limitations of monotherapy are related to adverse metabolic effects or the incidence of side effects. It is well established that diuretics can significantly alter carbohydrate and lipid profiles, and that patients very often have to stop treatment with calcium antagonists, despite effective blood pressure reduction, because of ankle edema. Most of these limitations can be significantly reduced by combination therapy and it has been demonstrated that RAS blockers can limit both metabolic alterations induced by diuretics and ankle edema caused by calcium antagonists.

Finally, combination therapy can also offer adjunctive advantages from a clinical point of view. Rapid normalization of blood pressure is an important target of antihypertensive treatment, especially in patients at high or very high risk. In line with this recommendation, recent evidence, although obtained by retrospective analysis, indicates that antihypertensive treatment initiated with combination therapy can induce a more rapid blood pressure reduction and/or normalization than monotherapy, and that this more rapid blood pressure control is associated with a better outcome. In addition, combination therapy results in a significantly greater reduction in global cardiovascular, coronary, and cerebrovascular events than monotherapy, independent of drug classes or blood pressure control.

**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCOMPLISH</td>
<td>Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension</td>
</tr>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>Action in Diabetes and Vascular Disease</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial</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>EUROPA</td>
<td>EUropean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease</td>
</tr>
<tr>
<td>HYVET</td>
<td>Hypertension in the Very Elderly Trial</td>
</tr>
<tr>
<td>RAS</td>
<td>renin angiotensin system</td>
</tr>
</tbody>
</table>
Thus, there is solid evidence that combination therapy offers great advantages over monotherapy, not only in terms of blood pressure reduction, but also because it provides specific cardiovascular protection. However, there are differences in efficacy among the different possible combinations of antihypertensive drugs, and, therefore, it is crucial to choose certain combinations over others.

**Which properties/effects of combination therapy are considered to be additive?**

As previously mentioned, the effects of combination therapy that are considered to be additive are related to blood pressure reduction. Usually, the combination of drugs with complementary mechanisms of action makes it possible to obtain a reduction in blood pressure that is the sum of the effects of its single components. Thus, from a clinical point of view, it is important to avoid those combinations that do not produce an additive effect or those that have been clearly demonstrated to be inferior to other options. In addition to the already mentioned ACE inhibitor (or ARB)/β-blocker combination, other drug classes that should never be combined are ACE inhibitors and ARBs, since both block the RAS. Finally, another combination that should be absolutely avoided because of its negative effect is that of doxazosin—an α1-blocker—with clonidine—an α2-agonist. In this case, considering that the specificity for a receptor subtype is always relative, especially in clinical conditions, one drug reduces the blood pressure–lowering effect of the other, and the outcome is, therefore, negative.

Apart from these specific examples, all other combinations of antihypertensive drugs have additive effects and are, therefore, useful to obtain better blood pressure control. This is highlighted by the availability of fixed combinations that increase the compliance of hypertensive patients considerably. In addition to classical fixed combinations of RAS blockers or β-blockers with diuretics, new fixed combinations of RAS blockers with calcium antagonists are now available and increase the chance of choosing the best therapeutic strategy for hypertensive patients.

Is there any clinical difference between the use of a RAS blocker/diuretic combination and a RAS blocker/calcium antagonist combination? Concerning blood pressure lowering, both regimens seem to be similarly effective. Their tolerability is also similar, especially considering that RAS blockers reduce the metabolic alterations induced by diuretics and ankle edema induced by calcium antagonists.

However, blood pressure reduction is not the only mechanism for cardiovascular protection and since scientific evidence clearly indicates that some drug classes are better than others, as a consequence, some drug combinations are also better than others.

**What does pharmacological and/or clinical synergy mean?**

A combination has a clearly demonstrated synergistic effect when, despite similar blood pressure control, it leads to a better outcome than another drug combination. This kind of evidence indicates that the beneficial effect of treatment is determined by specific mechanisms that amplify the outcome related to blood pressure reduction.

In line with this are the results of ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm) and ACCOMPLISH (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension), which demonstrated that the combination of an ACE inhibitor with a calcium antagonist results in significantly greater cardiovascular protection than β-blocker/diuretic or ACE inhibitor/diuretic combinations, respectively.

It is clear from this line of evidence that (i) different combinations of antihypertensive drugs, while producing a similar blood pressure reduction, have a different impact on clinical outcomes, and that (ii) the combination of an ACE inhibitor with a calcium antagonist offers the best cardiovascular protection in hypertensive patients. In addition to the previously mentioned ASCOT and ACCOMPLISH trials, an interesting analysis of the results of EUROPA (E URopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease) demonstrated a significant synergy between perindopril and calcium antagonists, with a significant supplementary impact on cardiac outcomes and mortality.

Whether the beneficial effect of ACE inhibitor/calcium antagonist combination might be extrapolated to ARB/calcium antagonist combination is an interesting question. It should be stated that it is scientifically incorrect to credit ARBs with the same efficacy as ACE inhibitors. A meta-analysis evaluating studies performed in hypertensive patients has demonstrated that ACE inhibitors, but not ARBs, can significantly reduce total mortality further than comparators, the most important clinical end point. It is worth noting that this beneficial effect was essentially driven by the results of ASCOT, ADVANCE (A ction in Diabetes and Vascular Disease), and HYVET (H ypertension in the Very Elderly Trial), which are all perindopril-based clinical trials. This evidence was further reinforced by another meta-analysis comparing the effect of ACE inhibitors or ARBs versus placebo in high-risk patients. The results of this study confirmed that ACE inhibitors significantly reduce several hard end points such as myocardial infarction, heart failure, and total mortality, but that ARBs, as a class, do not.

Another fundamental argument against the equivalence of ARB/calcium antagonist combination and ACE inhibitor/calcium antagonist combination is the lack of specific trials, such as ASCOT-BPLA or ACCOMPLISH, evaluating the effective-
ness of ARB/calcium antagonist combination versus any other combination of antihypertensive drugs, a lack of evidence which was clearly highlighted in the European Hypertension Guidelines.

In conclusion, combination therapy should be the first option for effective hypertension management. This therapeutic strategy can lead to a more rapid reduction, and possibly normalization, of blood pressure values and to a consequent decrease in cardiovascular risk. In addition, available scientific evidence clearly indicates that combining ACE inhibitors and calcium antagonists can specifically provide additive protection from clinical events.

Although ACE inhibitors are considered to be first-choice drugs, especially on the basis of the results of recent meta-analyses,1–10 maybe it is time for us to change our attitude in clinical practice and start considering ACE inhibitor/calcium antagonist combination as the first-choice treatment for the best protection from cardiovascular events.

References


Keywords: ACE inhibitors; angiotensin receptor blockers; calcium antagonists; essential hypertension; cardiovascular risk; perindopril

Les associations dans l’hypertension et la prévention cardiovasculaire sont-elles synergiques ou additives ?

Bien utiliser les associations médicamenteuses est essentiel afin d’améliorer le contrôle de la pression artérielle et de diminuer le nombre d’événements cardiovasculaires. Des antihypertenseurs aux mécanismes d’action différents et complémentaires peuvent être associés efficacement. Une association classique contiendra donc des médicaments bloquant le système rénine angiotensine (inhibiteur de l’enzyme de conversion [IEC] ou antagoniste du récepteur de l’angiotensine [ARA]) et d’autres le stimulant (antagoniste calcique [AC] ou diurétique). Un traitement d’association efficace combine des effets additifs ou synergiques. L’effet est additif lorsque la diminution de pression artérielle induite représente la somme de chacun des effets de chaque composant. L’effet est synergique lorsque l’efficacité clinique est supérieure à la somme des effets des composants pris isolément. L’action synergique est évidente lorsque les résultats d’une association médicamenteuse sont meilleurs que ceux d’une autre, et ce, malgré un contrôle identique de la pression artérielle. C’était le cas des études ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm) et ACCOMPLISH (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension) dans lesquelles, respectivement, la protection obtenue par l’association IEC/AC s’est montrée significativement meilleure que celle des associations bêtabloquants/diurétiques ou IEC/diurétiques. Remarquons qu’il n’existe actuellement pas de preuves d’une équivalence d’efficacité entre l’association ARA/AC et l’association IEC/AC. Pour conclure, un traitement antihypertenseur optimal est une association qui comporte en première intention un IEC et un AC, ce qui devrait offrir un meilleur contrôle de la pression artérielle et une meilleure protection contre les événements cardiovasculaires.
In this early postgenomic era, the field of pharmacogenomics is now progressively entering a phase of clinical utility evaluation. In terms of therapeutics, many genomic markers have been identified that have an impact on drug metabolism, transport, and targets. Companion diagnostics is a rapidly evolving field that exists in parallel to the development of drugs, and will have future applications for personalized health care. When an opposite effect is observed with two different combinations of antihypertensive drugs in a clinical trial, differences can be expected at the level of genomic polymorphisms or transcriptional effects between subsets of study participants. With the increasing availability of effective fixed-dose combinations of antihypertensive drugs, the development of companion diagnostics may offer rational guidance for selection of the most appropriate combinations for long-term use in individuals.

Medicographia. 2013;35:468-472 (see French abstract on page 472)

Genetic influence on key blood pressure parameters

Cardiovascular death remains the number one cause of mortality and number one health burden in Canada and throughout the world, with hypertension the leading risk factor. It is thus relevant that hypertension remains one of the most difficult complex diseases to resolve at the causal genetically-driven level, with many other pathological conditions in recent years having had fundamental aspects of their genetics revealed through the use of novel global genomic technologies. The complexity of hypertension is reflected in the fact that only about 30% to 40% of blood pressure variability is genetically determined, with environment playing a major causal role and interactions between genetic and environmental factors also being of great importance. The past debate on the relative importance of nature versus nurture in shaping human development is nowadays understood in terms of gene-environment interactions. Although still not fully accepted, it is now evident that a more relevant question is not which of the two is the most important, but rather how these two determinants of life can—and do—interact. In diseases such as hypertension, it is evident that a better understanding of the mechanisms of the interactions between genetics and a variety of environmental factors is of the utmost importance. These include interactions between stress, sodium intake/other nutritional factors, physical activity, or antihypertensive medications, and specific genetic polymorphisms, copy number variants, and other genetic variants. There are several examples in the literature of the impact of a single allelic variant with a pleiotropic effect not restricted to a specific phenotype. One example is the fat mass and...
obesity–associated gene, FTO. A single nucleotide polymorphism (SNP) in this gene (rs9939603) has been widely described as being associated with obesity and other components of the metabolic syndrome, but recent evidence also points to a specific impact of the environment in the form of high levels of dietary saturated fat, which accentuates the risk of obesity in carriers of a specific allele of this particular SNP.1 We showed that the association of the FTO gene with blood pressure is only apparent after withdrawal of antihypertensive medication, as the latter overshadows the relationship of the gene with blood pressure without affecting its relationship with obesity.2 It has also been demonstrated that the genetic risk for hypertension, as defined by an aggregate of most of the known risk alleles for obesity discovered in recent genome-wide association studies (GWAS), may be attenuated by as much as 40% by physical exercise.3 Most of the phenotypes associated with cardiometabolic regulation—including hypertension and its cardiovascular outcomes—are polygenic in nature. This has best been demonstrated by a multistage GWAS performed in nearly 200 000 individuals of European descent, which identified 29 previously-known or new SNP variants that influence blood pressure through pathways leading to the development of hypertension and its outcomes, including stroke and coronary heart disease.4 We have shown a similar polygenic contribution in the French-Canadian founder population, which points to synaptic plasticity pathways as forming a crossroads between hypertension, habitual substance use, obesity, and mental and physical stress5 in a paradigm of gene-environment interactions.

We strongly believe that the ingredients required for resolution of the pathophysiology of hypertension include much more detailed phenotyping, lifelong observation of pathogenetic evolution, reduction of disease heterogeneity, and integration of environmental data using ecogenomic6 and epigenomic tools (www.epigenome.org).

Genetic influence on pharmacodynamic and pharmacokinetic properties of hypertension
In humans, genetic variation is recognized as being an important determinant of drug response variability. Between 20% and 95% of individual variability is genetically based, a result of sequence variations in drug target proteins, drug-metabolizing enzymes, or drug transporters, which can alter drug efficacy, drug side effects, or both. Genetic polymorphisms of proteins involved in drug targeting (ie, pharmacodynamics) and drug metabolism and transport (ie, pharmacokinetics) are the most important causes of individual variability in drug safety and efficacy. Some genetic variations can affect these factors by changing the biological context or environmental sensitivity of the drug response. Examples of genetic polymorphisms of antihypertensive drug targets are the well-known insertion/deletion (I/D) variants located in intron 16 of the angiotensin-converting enzyme (ACE) gene. McNamara et al demonstrated that the ACE D allele was associated with significantly poorer survival in patients with heart failure and systolic dysfunction.6 The finding of increased left ventricular dimensions in patients with the DD genotype was in accordance with previous reports, and could be explained by presumably greater concentrations of circulating and tissue angiotensin II associated with the DD genotype. In addition, high doses of ACE inhibitors and β-blockers had the greatest impact in patients with the DD variant (P=0.001) and the least impact in those with I/D and II genotypes (P=0.38). The ACE I/D genotype was also associated with the occurrence of cough, a common side effect of ACE inhibitors. In a recent meta-analysis of 11 trials that included 906 cases of ACE inhibitor–related cough and 1175 controls, Li et al confirmed a significant association between the ACE I/D polymorphism and ACE inhibitor–related cough in those studies that involved participants with a mean age of >60 years,7 but not in studies in which the mean age of participants was ≤60 years. This supports the notion that the ACE I/D polymorphism is an age-dependent predictor of risk for ACE inhibitor–related cough. The genetics of drug-metabolizing enzymes (pharmacokinetics) also plays a critical role in interindividual differences in antihypertensive drug response and adverse drug reactions. The most important class of drug interactions involves the cytochrome P450 microsomal enzyme system.8 The ability to metabolize a drug along a specific pathway of the cytochrome P450 enzyme system can be modulated by genetic polymorphisms. With CYP450 polymorphisms, individuals may process the medication too rapidly (ultrarapid metabolizers) rendering it ineffective, or too slowly (poor metabolizers) causing drug concentrations to build up in the blood, potentially causing adverse reactions, or in the case of prodrugs, ineffective activation. The CYP2C9, CYP2C19, and CYP2D6 enzymes are highly polymorphic and together account for about 40% of hepatic human phase I metabolism. The polymorphisms of CYP1A2, CYP2A6, CYP2B6, and CYP2C8 also contribute to interindividual differences in drug metabolism. CYP2D6 is prob-

**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCOMPLISH</td>
<td>Avoiding Cardiovascular events in COMbination therapy in Patients Living with Systolic Hypertension (trial)</td>
</tr>
<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>ASCOT</td>
<td>Anglo-Scandinavian Cardiac Outcomes Trial</td>
</tr>
<tr>
<td>GWAS</td>
<td>genome-wide association study</td>
</tr>
<tr>
<td>HCTZ</td>
<td>hydrochlorothiazide</td>
</tr>
<tr>
<td>I/D</td>
<td>insertion/deletion (genotype variant)</td>
</tr>
<tr>
<td>SNP</td>
<td>single nucleotide polymorphism</td>
</tr>
</tbody>
</table>
ably the most extensively studied drug-metabolizing enzyme in humans; its polymorphism has high clinical importance and was the first among the polymorphic CYP450s to be characterized at the molecular level. Today, more than 48 different drug substrates have been identified for this enzyme, and CYP2D6 is responsible for about 25% of the metabolism of known drugs. About 10% of the general population has a slow-acting form of this enzyme, and 7% have a super-fast-acting form. In total, 35% are carriers of an abnormally functioning CYP2D6 allele. The pharmacokinetics of β-adrenergic blocking agents such as propranolol are strongly affected by inducers and inhibitors of CYP2D6. Calcium channel blockers are substrates for, and inhibitors of, CYP3A4. Most ACE inhibitors (eg, enalapril, fosinopril, perindopril, quinapril, ramipril, and trandolapril) are prodrugs metabolized in the liver, although captopril and lisinopril are not. Some animal studies indicate that prodrugs may undergo CYP3A4-dependent biotransformation. However, ACE inhibitors are not involved in significant cytochrome P450-mediated interactions with other drugs. The angiotensin receptor blockers losartan and irbesartan seem to be primarily metabolized by CYP2C9, but hydrochlorothiazide (HCTZ) and chemically-related diuretics are not metabolized by CYP450s, but rather are eliminated by the kidney.15

A growing number of drugs have companion diagnostics, and more than a dozen marketed medications propose or recommend genetic testing for optimal treatment. These examples of the successful use of pharmacogenetic testing, unraveling the basis for certain individual drug responses caused by single-gene polymorphisms, can guide future pharmacogenomics research and its application. Realistically, pharmacogenomics will require complex polygenic and gene-environment considerations in order to prove its clinical utility.

The final response to a drug is determined not only by the aforementioned polymorphisms in genes involved in its metabolism, transport, and target, but also importantly in its gene function, ie, transcriptomic consequences. These, in turn, are the final reflection of complex regulation at the gene expression level, which is subject to intergenic DNA sequence influences, such as those of noncoding RNA. Research into gene pathways and networks, the integration of genetics and genomics, proteomics, metabolomics and epigenetics, noncoding RNA derived from hypothesis-free investigation through GWAS, and prospective clinical trials evaluating the utility and cost-effectiveness of genetic testing in drug therapy are a few examples of areas of exploration that must continue.

Pharmacological target polymorphisms that can modify treatment efficacy

Drug/test combinations (Rx-Dx) using companion diagnostics have the potential to provide many clinical benefits to patients, including identification of potential responders to a specific drug, identification of individuals at risk of adverse events, or use as an adjunct tool for monitoring responses to drugs. A new drug and its companion diagnostics should be developed in parallel, with a cross-reference in the labeling information of both products. The US Food and Drug Administration has recently decided to accelerate the approval of drugs accompanied by companion diagnostics.16 In cancer treatment, it is now possible to prioritize small therapeutic molecules by integrating various omics databases.17

Rationalized drug selection is progressing in such difficult areas as hepatocellular carcinoma, where combination of whole-tumor genomic and transcriptomic data with epigenomic analysis is leading to improved tumor classification and drug selection.18 Similarly, in renal cell carcinoma, assessment of resistance to sorafenib is based not only on genomic polymorphisms, but also its reversibility as detected in studies of tumor transcriptome.19

In the field of hypertension, as mentioned, an international consortium of blood pressure GWAS identified 29 SNPs associated with hypertension, which also predicted heart failure, stroke, and ischemic heart disease.6 Marques et al published a meta-analysis of 74 available microarray experiments integrating genome-transcriptome approaches to identifying genes exhibiting altered expression in the kidney, adrenal gland, heart, and artery of spontaneously hypertensive rats and Lyon hypertensive rats compared with normotensive controls.20 When possible, they separately analyzed the results obtained in young animals (less than 6 weeks of age) from the results obtained in adult rats to differentiate between the onset and maintenance phases of hypertension. While both phases may share common pathophysiological mechanisms, they suggested that different gene sets are responsible for the development and maintenance of hypertension. In another study, transcriptional analysis was performed in spontaneously hypertensive rats with left ventricular hypertrophy treated with different classes of antihypertensive agents, which confirmed the importance of cell growth/proliferation, signal transduction, development, and muscle contraction/cytoskeleton functional groups.21 Although similar genes were affected by the use of different antihypertensives during the course of reduction of left ventricular hypertrophy, therapy with: (i) quinapril; (ii) doxazosin and quinapril combination; and (iii) losartan showed distinct patterns of gene expression. We can expect that when biological differences are noted between two drugs, their functional impact at the gene level will also be different.

Thus, for instance, the effects of HCTZ on blood pressure and metabolism are different from those of indapamide. We found that when indapamide or HCTZ were given to patients for a period of 6 months, different proliferative activities were seen in platelet extracts from these patients, depending on which drug they had been given. Indapamide treatment resulted in much lower proliferative activity, despite HCTZ causing a more pronounced blood pressure reduction, actually similar to that
of an ACE inhibitor. As HCTZ is the most frequently-used antihypertensive drug in combination therapy, but combination therapy with indapamide has been shown to be effective in lowering total mortality, we recently compared the transcriptomic profile of kidneys from spontaneously hypertensive rats treated with indapamide or HCTZ. Our preliminary results showed that while the expression of 218 genes was modulated in the same direction by both drugs, 645 and 593 genes were differentially expressed with use of HCTZ and indapamide, respectively. Our data indicate that the differences observed between the two drugs could reside in their differential capacity to induce hypotensive and proliferative genes. It is important to underline here that this type of study is feasible in humans: genomic DNA (for SNPs, copy number variations, epigenetics) is readily obtained from circulating nuclear cells from whole blood or from lymphocytes. Moreover, mRNA and DNA can now be obtained from the same sample of blood using RNAase inhibitors and specialized tubes for relatively easy separation of DNA and RNA. Importantly, RNA extracted from blood has proven useful in the study of the expression of many genes, including those of drug metabolizing enzymes.

The therapeutic orientation in hypertension is rapidlychanging from single drug therapy to fixed-drug combinations, even as initial therapy, as combinations are more effective in reaching therapeutic targets and are sometimes subject to fewer side effects through combination of complementary pathways. Since “hard” clinical outcome studies are currently a prerequisite for uptake of a drug by physicians, the decline observed in total mortality with use of the combination of amlopidine and perindopril versus atenolol and HCTZ in the ASCOT trial (Anglo-Scandinavian Cardiac Outcomes Trial) was seminal in supporting the amlopidine–perindopril combination; ADVANCE (Action in Diabetes and Vascular disease: Preterax and Diamicron MR Controlled Evaluation) was similarly seminal for support of the combination of perindopril with indapamide versus “usual therapy.” ACCOMPLISH (Avoiding Cardiovascular events in COMbination therapy in Patients LIVING with Systolic Hypertension) compared the combinations of amlopidine and benazepril with amlopidine and HCTZ. The calcium channel blocker and ACE inhibitor combination demonstrated a significant superiority on the composite outcome of death and cardiovascular events (primary end point), and renal events, as revealed by estimated glomerular filtration rate (eGFR) levels. However, the biological difference between these two combinations was revealed through a subanalysis of diabetic individuals in ACCOMPLISH. While the ACE inhibitor–calcium channel blocker combination was superior to the ACE inhibitor–HCTZ combination in lowering eGFR levels (-2.2% versus -9.9%), it actually led to an increase in microalbuminuria of 92.2 mg/g. By contrast, the ACE inhibitor–HCTZ combination produced a decrease of 20.1 mg/g in microalbuminuria levels at the end of the study. Our interpretation of these results is that a subset of diabetic individuals

**References**


7. Noël A, Seda O, Tremblay J, et al. The impact of pharmacological environment...
LA GÉNÉTIQUE PEUT-ELLE INFLER SUR LE CHOIX DES ASSOCIATIONS ANTIHYPERTENSIVES ?

A l’aube de cette ère post-génomique, le domaine de la pharmacogénomique entre maintenant progressivement dans une phase d’évaluation de son utilité clinique. En termes de traitement, de nombreux marqueurs génomiques ayant un impact sur le métabolisme, le transport et les cibles médicamenteuses ont été identifiés. Le domaine des tests diagnostiques dits « compagnons » évolue rapidement, en parallèle au développement des médicaments, et aura à l’avenir des applications en matière de médecine personnalisée. Lorsque dans une étude clinique on observe des effets opposés avec deux associations différentes d’antihypertenseurs, on peut s’attendre à ce qu’il y ait des différences au niveau des polymorphismes génomiques ou des effets transcriptionnels entre des sous-groupes de participants. Étant donné le nombre croissant d’associations à doses fixes d’antihypertenseurs efficaces disponibles, le développement de tests diagnostiques compagnons pourrait permettre de choisir de façon rationnelle les associations les plus appropriées pour une utilisation à long terme.

Keywords: companion diagnostics; gene-environment interaction; genetic polymorphism; hypertension; pharmacogénomics
A TOUCH OF FRANCE

Step back in time to celebrate the centenary of one of the most beautiful performing venues in Paris, the Théâtre des Champs-Elysées, which held the premiere of *The Rite of Spring* 100 years ago, and the bicentenary of the birth of French physiologist and philosopher Claude Bernard, who introduced the experimental method in medicine. Taking nothing for granted, Bernard was convinced that knowledge progressed constantly and evolved over time. Read on to find out more...

Claude Bernard (1813-1878) and experimental medicine

“Physiology, physiology, it’s in me...”

C. Régnier, France

The Théâtre des Champs-Elysées: the venue that launched a masterpiece

D. Marsh, France

---

La leçon de Claude Bernard by Léon Lhermitte shows Bernard with his pupils in his Collège de France laboratory.

© Wellcome Library, London.

---

Every year some 300,000 people come to the Théâtre des Champs-Élysées in Paris for concerts and recitals in the main auditorium, plays at the Comédie, and exhibitions in the Studio.

© Bertrand Rindoff Petroff/Getty Images.
Despite his preference for literature, Claude Bernard was urged to take up the study of medicine. He became an “intern” at the Hôtel-Dieu de Paris where he met the great physiologist François Magendie whom he succeeded at the Collège de France. For Bernard, scientific truth had to be objective and demonstrable: “Theories are only hypotheses, verified by more or less numerous facts. Those verified by the most facts are the best but even then they are never final, never to be absolutely believed.”

As a pioneer of modern physiology, then as a philosopher who laid the foundations of the experimental method in medicine, Claude Bernard (1813-1878) is an emblematic figure in French science of the mid-19th century. His method, discoveries, and vocabulary left a lasting mark on medicine. He worked on a range of topics in parallel between 1844 and 1865: hepatic glycogenesis, nutrition and pancreatic secretion, the effects of curare, gas exchange in red blood cells, and sensory and motor innervation. This colossal undertaking had but a single aim: to define the concept of the milieu intérieur (‘environment within’) that subtends all animal or plant life. Pasteur, who concentrated on much more practical research topics, was his ardent supporter. In 1865, he was one of the few scientists to offer an enthusiastic welcome to the publication of Claude Bernard’s Introduction to the study of experimental medicine, a philosophical manifesto on medical research and the conditions subtending life. Yet the two scientists fell out around 1877 over conflicting interpretations of anaerobic alcoholic fermentation. Claude Bernard was the first French scientist to receive a State funeral. On February 16, 1878, after the service in the church of Saint-Séverin, 4000 mourners followed the cortège to Père Lachaise cemetery. Republicans lost no time in claiming this agnostic Second Empire senator as their own, thus marking the entry of modern science into the political arena: politicians transposed to the social sciences the experimental method that Claude Bernard had applied to medicine.

To use a word which he himself introduced into the vocabulary of French science, nothing “determined” Claude Bernard to become a doctor, an experimenter of genius, a pioneer of modern physiology, and a man of whom a former student, the physiologist and politician Paul Bert (1833-1886), recalled: “He made discoveries the way that others breathe. With grace and good faith. It was his cardinal quality. In everything he did he showed the same deep sincerity of the scientist in search of the truth for its own sake and for the sake of the truths that follow.”

Born on July 12, 1813 into a family of winemakers in Saint Julien en Beaujolais, near Villefranche sur Saône (department of the Rhône), Claude Bernard learned Latin, Greek, geometry, and arithmetic from the fathers in the diocesan school, but did not sit the baccalaureate. He was imbued with Cartesian philosophy and the Romantic movement.
At 19, he was taken on as an assistant by a pharmacist in nearby Vaise, and began delivering some of his preparations to the School of Veterinary Medicine in Lyon. This introduced him to their laboratories, operating rooms, and animal houses. He stayed with the pharmacist for 19 months, at which point his apprenticeship was abruptly terminated after he made a mistake in one of his concoctions.2,3 After tasting fleeting success with several performances of his vaudeville La rose du Rhône in a Lyon theater, he came to Paris in November 1834 to deliver a newly-completed historical romance, Arthur de Bretagne, to Saint-Marc Girardin (1801-1873), a member of Parliament, professor of literature at the Sorbonne, and theater critic. Legend has it that this illustrious figure advised him: “You have a background in pharmacy, young man. Why not study medicine? You could do better writing scientific articles. Keep literature for relaxation.”2-4

Claude Bernard acted on this advice without further ado. After passing an Arts baccalaureate, he enrolled in the Paris Faculty of Medicine in November 1834, qualifying as a junior resident five years later, although only 26th out of 29. On December 7, 1843, he defended his doctoral thesis Gastric juice and its role in nutrition, only to fail the university lecturer examination, the agrégation, the following year. He made friends during his student years with the future psychiatrist Ernest-Charles Lasègue (1816-1883), and the pioneering bacteriologist and microbiologist Casimir Davaine (1812-1882).2,5

In the footsteps of the master, François Magendie
Claude Bernard spent most of his residency at the since demolished La Charité hospital in Paris under Alfred Velpeau (1795-1867) in surgery and Pierre Rayer (1793-1867) in medicine. Rayer took him under his wing, introducing him to the positivist Émile Littré. Future physician to Napoleon III (1808-1873), Rayer’s interests were in kidney disease, diabetes, and dermatology; he was impressed by the young doctor’s powers of deduction. Claude Bernard also did residencies at the Hôtel-Dieu under the surgeon Jacques Gilles Maisonneuve (1809-1897) and at the Salpêtrière under the psychiatrist Pierre Falret (1794-1870).3,5

By pure chance, in 1841 at the Hôtel-Dieu, he came under François Magendie (1783-1855), for whom the chair in experimental medicine had been established at the Collège de France ten years previously. A former surgeon, Magendie had published multiple papers on experimental physiology between 1809 and 1816, including the celebrated Elementary compendium of physiology, which for long had been a standard work in the field. As a member of the Academy of Sciences since 1821, he had founded the first French physiology journal, the Journal de physiologie expérimentale et pathologique (which folded in 1831). Magendie described the mo-
tor function of the ventral spinal nerve roots and provided a partial explanation of the sensorimotor reflex. He also studied the mechanism of action of strychnine using methods that heralded modern pharmacology.

Having noted Claude Bernard’s skill with the scalpel (so the legend goes), Magendie appointed him as his assistant from 1841 to December 1844; he taught him the discipline required to conduct experiments using live animals, introduced him to vivisection, and trained him in the critical appraisal of scientific dogmas and systems. Master and pupil worked together on neurophysiology, cerebrospinal fluid, thermoregulation, and pharmacology.3,5,6

In 1844, after failing the agrégation, Claude Bernard experienced a period of doubt compounded by disagreement with his mentor, who shut him out of the laboratory. Magendie accused him of privileging theory at the expense of practice. Claude Bernard was also having financial problems conducting his own research in his laboratory in the Cour Saint André des Arts. Rayer found him some additional income preparing dissections for the lithographer Jacob who was illustrating Bourgery’s celebrated Anatomical Atlas.

In 1845, with his friend Lasègue, he opened a laboratory and private physiology school which closed fairly quickly due to a lack of students. In May of the same year, he married Marie Françoise Martin, the financially well-endowed daughter of a Paris physician, putting money troubles behind him. After patching up the relationship with Magendie (thanks to peace-making by Rayer), he stood in for him at the Collège de France in 1847, teaching the winter semester. Magendie then transferred his laboratory and chair to him from 1852; Claude Bernard became his official successor on Magendie’s death in 1855.3,5,6

In his inaugural lecture on February 29, 1856, Claude Bernard paid tribute to his departed mentor: “Mr Magendie felt a truly extraordinary repulsion towards thinking in systems […] His predominant idea was to fix the experimental method in medicine and physiology once and for all […] When people said to him: ‘According to such and such a law, things should happen in such and such a way’ or ‘Analogy shows that events will follow such and such a course’, he’d reply: ‘I have no idea; conduct an experiment and tell me what you find.’ ‘Conduct an experiment’ was his stock answer for forty years to all questions of this kind. […] He only said what his eyes had seen, and he would wait for other experiments and experiences to supply new items of evidence that might solve the problem […] So finally, gentlemen, you can see that although science has had the misfortune to lose Mr Magendie, he remains with us in spirit and the method we received from him is what continues to guide us today.”7

Claude Bernard was always attached to the style of teaching dispensed at the Collège de France, describing it as being directed at science in the making rather than at science made: “It must always reflect the state of the art in medical science,” in contrast to the teaching dispensed in the faculties which he characterized as based on the acquisitions of the past.

Claude Bernard was an indifferent public speaker but he interspersed his lectures with impromptu experiments, attracting a large audience from around the world, some of whom became his disciples: Arsène d’Arsonval, Paul Bert, Albert Dastre, Louis Gréhant, Willy Kühne, Élie de Cyon, Louis Ranvier, Ivan Setchenov, Angelo Mosso, Edmé Vulpian, Louis Charles Malassez, Peter Ludwig, Benjamin Ball, Austin Flint, and William Horner.3,5,6

Skills and methods
Claude Bernard conducted his experiments in the modest laboratory of the Collège de France (known as “the cellar”), at the Sorbonne, in the National Museum of Natural History, at the School of Veterinary Medicine in Maisons-Alfort, and in slaughterhouses. His friend Ernest Renan (1823-1892), who held the Hebrew chair at the Collège de France, recalled: “It was a striking spectacle to see him in his laboratory, thoughtful, sad, absorbed, totally focused, and unsmilng. He felt he was doing sacred work, celebrating a kind of sacrifice. His long fingers delved into the wounds like those of an augur in Antiquity, chasing mysterious secrets within the entrails of victims.”
La leçon de Claude Bernard by Léon Lhermitte shows Bernard with his pupils in his Collège de France laboratory. © Wellcome Library, London.
Renan took over Claude Bernard’s chair at the French Academy. The practice of vivisection earned the physiologist the profound disapproval of many detractors, in particular his own wife and two daughters who joined anti-vivisectionist leagues such as the Animal Protection Society (registered as being of public utility in 1866). Bernard had a solid grounding in anatomy, “a simpler science than physiology, and one which thus should be subordinate to it, rather than dominate it. Any explanation of the phenomena of life based exclusively on anatomical considerations is necessarily incomplete.” He had no time for “vitalism”, a theory still in vogue at the start of the 19th century which held that the phenomena of life were subject not to the laws of physics and chemistry but to a “vital force” emanating from living tissues. Yet he admired the work of Xavier Bichat (1771-1802), “the greatest anatomist of the modern era,” without sharing the vitalist theories contained in his Treatise on membranes (on tissue anatomy) published in 1800.

Bernard was an excellent chemist. He admired the discoveries made by Antoine Laurent de Lavoisier (1743-1794) and Pierre de Laplace (1749-1827). He worked with the chemist Charles Barreswill (1817-1870) in the laboratory of Théophile-Jules Pelouze (1807-1867) in rue Dauphine. He also studied the biochemistry of fats with his chemist friend Marcellin Berthelot (1827-1907). In his doctoral thesis (1843) on the role of gastric juice in digestion, he used his chemistry training to measure fasting and postprandial gastric acidity.

Unlike the German physiologists, he made little use of measuring instruments to quantify the phenomena of life; he even criticized German physiology for too often being reducible to a series of physicochemical reactions. The Germans reciprocated by considering Claude Bernard an impulsive and romantic experimentalist overinclined to generalization. He also made little use of the microscope, on the grounds that it “narrowed the mind.” In the Red notebook where he entered his more private thoughts, he wrote: “An excess of microscopy does a disservice to physiology. It ends up making everything the same, leaving us with effects without causes.” This accounts for his reservations over the cell pathology research by Rudolf Virchow (1821-1902) that failed to take cell chemistry reactions into account.

While acknowledging the contribution of mathematics and statistics in establishing quantitative demonstrations, Bernard issued this warning to fellow experimentalists: “It is not that I wish to outlaw the application of mathematics to biological phenomena, since this ultimately is where the future of the science lies; but my conviction is simply that a general equation is impossible for the moment: the qualitative study of phenomena must necessarily precede their quantitative study.

Claude Bernard made daily jottings of his observations, thoughts, and comments, together with lecture and reading notes, on the most varied of materials, mostly backs of envelopes, loose sheets of paper, and little notebooks. Archived in the Collège de France, Academy of Sciences, Academy of Medicine, and the Claude Bernard Museum in Saint Julien en Beaujolais, this scattered material was assembled and classified in the late ‘60s by Mirko D. Grmek, who tracked and unraveled the innermost thoughts and intellectual trajectory—marked by failure, frustration, and success—of a man in search of truth.

Determined to pursue his research in the absence of any preconceived ideas and to keep his mind entirely free, Claude Bernard worked on several fronts simultaneously. Comparing and contrasting his experiences and experiments, he was always reworking his notes and observations in the conviction that knowledge constantly progressed and evolved over time. The thread running through all his experiments and discoveries was his drive to understand the milieu intérieur, or environment within.
Main research interests:5,10,11,13

- **Glycogenesis (1843-1857).** His research on “animal glycogenesis” began with the famous “liver wash-out” experiment (1855). Later, with Charles Barreswill, he chemically identified glycogen as the precursor of glucose. His doctor of science thesis on hepatic glycogenesis (1853) paved the way for enzymology.

- **Nutrition (1843-1860).** The publication in 1859 of his Report on the pancreas and the role of pancreatic juice in digestion marked the first stage of his studies in nutrition. He discovered the function of bile in protein digestion and in 1860 published his Lectures and physiological experiments on nutrition.

- **Mechanism of action of curare and strychnine (1843-1853).** “Curare simply interrupts something motor that creates an electrical connection between muscle and nerve through movement.” Claude Bernard predicted the existence and role of the motor plate but could not prove it experimentally. However, he was wrong about the site of action of curare, locating it at the distal extremity of the motor nerve.

- **Carbon monoxide poisoning and the mechanisms of oxygen-carbon dioxide exchange (1846-1856).** He explained the role of red blood cells in respiration, showing that oxygen bound to hemoglobin: “These respiratory elements circulate with the blood and alternately absorb oxygen on contact with air, at the lung surface, then transport it into the depths of the milieu intérieur, in contact with the fixed histological elements of living tissues.”

- **Nervous system (1844-1858).** In addition to his unfinished studies on the anatomy and physiology of the chorda tympani, he described in particular the role of vagal inhibition of the heart, and the vasoconstrictor and vasodilator nerves of the sympathetic system. In 1858, he published his Lectures on the physiology and pathology of the nervous system.

The milieu intérieur concept was his major work. He built it brick by brick between 1851 and 1878. He expounded the concept in December 1857: “Physiologic phenomena in higher organisms take place in organic and highly perfected milieux intérieurs possessing balanced physicochemical properties.” The milieu intérieur regulates blood acidity and body temperature, adjusting them to changes external to the body. “The milieu intérieur has to be liquid because water is essen-
tial for chemical reactions and for displaying the properties of living matter.” In studying the vectors of cell interaction (although without developing the concept of remote-acting hormones), he expounded the concept of “internal secretion,” namely an organ’s ability to secrete a substance and release it directly into the bloodstream. The French philosopher Georges Canguilhem (1904–1995) pronounced the milieu intérieur concept as having constituted a sort of “Copernican revolution.” 5,10,11,14

1865: The experimentalist mutates into a philosopher

On December 30, 1913 at the Collège de France on the centenary of Claude Bernard’s birth, the philosopher Henri Bergson (1859–1941) declared: “The Introduction to the study of experimental medicine is for us a little like what the Discours de la méthode was for both the 17th and 18th centuries. In each case we find ourselves in the presence of a genius who began by making great discoveries and then wondered how one had to proceed in order to have done so: although paradoxical in appearance, this is the only natural order of events, since the reverse order has been attempted much more often and has never succeeded.”15

The issue of philosophy in medico-scientific experimentation was far from an academic abstraction for Claude Bernard: it was the direct result of the questions and doubts that assailed him on achieving experimental results that overthrew conventional scientific thinking. “There comes a time in one’s scientific career when it is good to collect one’s thoughts, take stock and ask where one has arrived and where one is heading,” he wrote in his Principles of experimental medicine. “I believe this to be particularly useful when studying a science as complex, obscure, and poorly defined as medicine.”

Physiology in the hands of Claude Bernard was not just a branch of anatomy, physics, or chemistry; it involved the development of multiple temporary hypotheses that were reworked in the light of experimentation and the responses of the live animal. Claude Bernard also set physiology apart from the empiricism of medicine by endowing it with its own concepts developed through specific methods of investigation.10,11

The principles of Bernard’s philosophy can be found in notes, lectures, and several of his publications throughout his life, the best known being the Introduction to the study of experimental medicine published in 1865, written when resting and...
convalescing at his house in Saint Julien en Beaujolais, bought in 1861. One year previously, he had experienced the first symptoms of colitis, together with migraine and joint pain, diagnosed by Rayer and Davaine as a “a chronic form of cholera.” It was during one of these stays that he read, criticized and was inspired by the work of Auguste Comte (1798-1857), the founder of positivism. “Comte’s idea of considering positivist philosophy in terms of scientific generalities is wrong. It is absolutely essential to get down to the details.”

The Introduction was the first chapter in Claude Bernard’s major contribution to philosophy (it remains part of the philosophy baccalaureate curriculum). As well as in the notes contained in the Red notebook and Principles of experimental medicine (collated and published in 1947 by Léon Delhoume), he developed his philosophical ideas in his Lectures on the phenomena of life common to animals and plants, published posthumously in 1878-1879, in which he insisted on the fundamental unity between the two worlds.

As for his 1867 Report on the progress and practice of general physiology in France, this was more political, in that it was commissioned by Victor Duruy (1811-1894), minister of public education, in preparation for the Third Universal Exhibition to be held in Paris the same year. It was Napoleon III’s intention to use the Exhibition to showcase French science, in direct competition with science in German-speaking countries where heavy investment and decentralized organization had produced remarkably effective results.

Already esteemed by the Emperor and his wife—in 1864 they had invited him to spend a week at the Château de Compiègne—Claude Bernard wrote in the report that “general physiology” should be established as a science in its own right and receive the same level of State funding as that earmarked for “the long-established sciences securely positioned within the social fabric.”

The Introduction to the study of experimental medicine received a lukewarm welcome from physicians both in France and abroad; physiology journals ignored it on the grounds that its subject matter fell outside their scientific purview. Yet the book was a more than positive report on over 20 years of successful research rewarded by its author’s appointment to the Faculty of Sciences and Collège de France. The book was not translated into English until 1927, into Spanish in 1936, and into German in 1961.

Claude Bernard invented “determinism,” a word that he introduced into French. “The primordial principle in the basic sciences is determinism. […] All vital phenomena, whatever they may be, are subject to strict determinism, and this determinism cannot possibly be anything other than physico-chemical determinism. […] Determinism is everything. It is inescapable. […] We must take it as an experimental axiom that in living beings as much as in inanimate matter, absolute determinism governs the conditions under which every phenomenon exists. This means, in other words, that once the condition for a phenomenon is known and met, the phenomenon should always recur necessarily, at the experimenter’s command. To deny this would amount to nothing less than denying science itself.” This principle influenced future generations of scientists: an experiment must be reproducible in order to be validated.

Maintaining that scientific truth is objective and demonstrable, not revealed or imposed, and that phenomena must always be approached with the question “how” rather than “why,” Claude Bernard based his “method” on three cardinal principles: observation, experimentation, and deductive reasoning. Because Nature only allows a limited number of facts to be observed, these need to be prolonged or evoked by experiment. By combining with chemistry, physics, and all the exact sciences, physiology becomes able to explain all living phenomena, whether normal or pathological.
In wanting hospitals to be equipped with integrated laboratories so that physicians could relate their clinical knowledge to physiologic experimentation, Claude Bernard looked forward to proclaiming the imminent demise of empirical medicine. However, he came up against the hostility of the Academy of Medicine, for whom the primacy of the anatomo-clinical method—another great pride of 19th century French medicine—was sacrosanct.

Claude Bernard versus Louis Pasteur: the issue of modern biology

Already crowned in glory for his at once "patriotic" and practical approach to medicine, Louis Pasteur (1822-1895) was immediately alert to the importance of the Introduction in guiding medical research methodology. An already recognized scientist, Pasteur had attended Claude Bernard's lectures at the Faculty of Sciences in 1860 and those on "experimental medicine" given in the winter of 1862-1863 at the Collège de France.

In 1859, Claude Bernard had written a favorable report to the Academy of Sciences supporting the award of the Montyon prize in experimental physiology to Pasteur for his work on alcoholic fermentation and the isomers of tartaric acid; he had drawn attention to the "physiological bent to his research" and the "experimental skills of this distinguished scientist." The two leading lights in French 19th century medical research appeared to be working in perfect harmony.4,5,8,17

However, they were to fall out around 1877 when in his Principles of experimental medicine Claude Bernard deplored the fact that "Pasteur follows his ideas and wants to bend the facts accordingly, whereas I follow the facts and aim to coax out the ideas more or less by themselves. Pasteur wants to direct Nature, whereas I let Nature direct me: I follow Nature […] I am Nature's secretary. Pasteur and the a priorists are out to dictate Nature's responses to suit their own ideas." Bernard was skilled at exploiting serendipity starting from hypotheses that were not always correct; Pasteur performed
experiments to confirm his intuitions. Pasteur immediately threw back at Claude Bernard the accusation that he was using a system-based approach.

In reality the two men disagreed on the factors and conditions for alcoholic fermentation. Having devoted many years of his life to this question (one of national interest), Pasteur attributed the transformation of sugar into alcohol under anaerobic conditions to the presence of microorganisms. Claude Bernard believed that this chemical transformation depended on soluble “culture agents” (ferments), and not exclusively on living cells, but was unable to demonstrate this experimentally and published nothing on the question in his lifetime. His notes on alcoholic fermentation were published in July 1878 by the chemist Marcellin Berthelot, five months after his death; they aroused the wrath of Pasteur.

This dispute between the two giants of French science raised the whole question of modern biology. For Claude Bernard, a functioning live organism was an organism that destroyed itself by itself little by little via physicochemical phenomena tending towards death. Pasteur was something of a “vitalist” and thought along different lines, focusing on the external insults that threatened the fine balance of living organisms. As a prisoner of his “determinism” and hence of his “ideas”, Claude Bernard became unable to grasp the full implications of cell pathology and germ theory. The heated debate between the two giants of French science paved the way to modern scientific medicine, with Claude Bernard considering disease as a process disruptive of the milieu intérieur while Pasteur viewed it as an external interference independent of any determina-

**QUOTATIONS BY CLAUDE BERNARD**

“When we encounter a fact that contradicts a prevailing theory, we must accept the fact and abandon the theory, even if the theory is backed by great names and generally accepted.”

“The fixity of the internal world is the precondition for free and independent life.”

“It is what we think we already know that prevents us from learning.”

“If we really wanted to recognize services rendered to science, the frog would have pride of place.”

“A fact is nothing in itself, its only value lies in the idea attached to it or by the evidence it provides.”

“Observation is the investigation of a naturally-occurring phenomenon, and experiment the investigation of a phenomenon modified by the investigator.”

“Science proceeds by revolution and not by pure and simple addition. This is because of theories that are always consecutive.”

“The experimenter forces Nature to reveal her secrets by attacking and questioning her from every direction; but he must never respond on her behalf or pay lip service to her responses, by recognizing only those results that favor or confirm his hypothesis.”

“The only certainty is inside us. We are conscious of a fact, it is what is true. We are not absolutely conscious of a theory; it is always provisional.”

“It is not enough to say; I made a mistake; one must say how the mistake was made.”

The “culture agent” turned out to be an enzyme, zymase, isolated in 1897 by the German scientist Eduard Büchner (1860-1917). “Pasteur fully acknowledged what discouraged Claude Bernard, who proved the victim of his definitions, beholden despite himself to Lavoisian biochemistry (oxygen as the condition of life) […] It was his respect for Lavoisian dogma that made him unable to accept certain data in physiology […] That is why he preferred to define alcoholization as simple molecular degradation,” wrote the philosopher-physician François Dagognet.

This dispute between the two giants of French science raised the whole question of modern biology. For Claude Bernard, a functioning live organism was an organism that destroyed itself by itself little by little via physicochemical phenomena tending towards death. Pasteur was something of a “vitalist” and thought along different lines, focusing on the external insults that threatened the fine balance of living organisms. As a prisoner of his “determinism” and hence of his “ideas”, Claude Bernard became unable to grasp the full implications of cell pathology and germ theory. The heated debate between the two giants of French science paved the way to modern scientific medicine, with Claude Bernard considering disease as a process disruptive of the milieu intérieur while Pasteur viewed it as an external interference independent of any determina-
Claude Bernard (1813-1878) et la médecine expérimentale
« Physiologie, physiologie, c’est en moi... »

Pionnier de la physiologie moderne puis philosophe ayant jeté les bases de la méthode expérimentale en médecine, Claude Bernard (1813-1878) est une figure emblématique de la science française de la seconde moitié du XIXe siècle. Sa méthode, ses découvertes, son langage marquèrent durablement la médecine. Ses travaux furent variés et menés simultanément entre 1844 et 1865 : la fonction glycopénique du foie, la nutrition et la sécrétion pancréatique, la diarrhéses, les échanges gazeux érythrocytaires, les nerfs sensitifs et moteurs. Cette œuvre colossale tendait vers un but unique : définir la notion de “milieu intérieur”, à l’origine de toute vie animale ou végétale. Pasteur qui aborda des thèmes de recherche beaucoup plus pratiques fut un fervent partisan de Claude Bernard. En 1865, il fut l’un des rares scientifiques à le soutenir lors de la parution de l’Introduction à la médecine expérimentale, manifeste philosophique sur la recherche médicale et les conditions de la vie. Les deux savants se broyèrent vers 1877 pour une divergence d’interprétation sur la fermentation alcoolique anaérobie... Claude Bernard fut le premier scientifique auquel la République accorda des funérailles nationales. Le 16 février 1878, après la cérémonie religieuse en l’église Saint Séverin, 4000 personnes suivirent le cortège jusqu’au cimetière du Père Lachaise. Agnostique, sénateur d’Empire, Claude Bernard fut très vite récupéré par les républicains, ce qui marqua l’entrée de la science moderne en politique ; sa méthode expérimentale appliquée à la médecine fut transposée par les hommes politiques aux sciences sociales.

References
12. Michel J, ed. La nécessité de Claude Bernard [The necessity of Claude Ber-

Claude Bernard and experimental medicine – Régnier
The Théâtre des Champs-Elysées: the venue that launched a masterpiece

by D. Marsh, France

The wealthy and fashionable set took umbrage that May evening in Paris. Catcalls and whistles filled the theater, derisive laughter, cries of “Tagueule!” (“Shut your trap!”). A frightful ruckus. The Countess de Pourtalès, the doyenne of Parisian society, flourished her fan and shouted: “This is the first time in sixty years that anybody has dared make fun of me!” The pandemonium drowned out the music. Backstage, perched atop a chair, the ballet-master shouted instructions unheard by the dancers. The composer fled the auditorium and watched from the wings. “I have never again been that angry.” Thus was Igor Stravinsky’s ballet The Rite of Spring launched upon an unsuspecting world one hundred years ago, at the newly opened Théâtre des Champs-Élysées, the brainchild of Gabriel Astruc, journalist, theater manager, and impresario. His ‘new temple of art’ nigh on bankrupted Astruc, but years later he wrote: “I do not regret my folly, for from my ruin sprang The Rite of Spring.”


Gabriel Astruc flicked open the lid of his pocket watch. Just twenty-four hours till the fulfillment of the dream that had occupied his thoughts night and day for the past seven years: the opening of the—of his—Théâtre des Champs-Élysées. An achievement worthy of this, his fiftieth year. As he turned into the Avenue Montaigne, the leaden sky over Paris was clearing and the rain fell lighter. The theater’s frontage gleamed in the gaslit street, its rectilinear design broken only by a white marble bas-relief of ‘Apollo and the Muses,’ hinting at music and dance within.

Standing there that late March evening in 1913, thinking through the last details of the grand opening the next day, little could Gabriel Astruc have guessed that a riotous assembly in his theater would soon change the world of classical music forever. And write his ‘new temple of art’ into the pages of history.
Clio, the Muse of History, has looked kindly upon the Théâtre des Champs-Élysées. And upon its creator, Gabriel Astruc. Our story begins in the early years of the 20th century. Director of a Parisian music society, journalist and impresario, Astruc found Paris wanting. Where was its Royal Opera House (London, 1858), its Festspielhaus (Bayreuth, 1876), its Prinzregententheater (Munich, 1901)? Of the French capital’s 43 theaters, only the Opera, the Théâtre du Châtelet, La Gaîté, and, at a pinch, the Opéra-Comique, were equipped for full-scale concerts or operatic productions. And they were hidebound, saw modernity as a threat, and shunned innovation. Astruc vowed to build a theater forward-looking in its architecture and bold in its choice of music.

Things began well. In 1906, Paris City Hall promised Astruc a site on the Champs-Élysées (whence the theater’s name), where once an old circus had stood, and the architectural studies began. But three years later, the plans now well advanced, City Hall reneged on its promise following an anti-Semitic campaign (Astruc was Jewish) orchestrated by Charles Maurras, the principal ideologist of Action Française, an extreme right-wing political movement.

Every year some 300,000 people come to the Théâtre des Champs-Élysées in Paris for concerts and recitals in the main auditorium, plays at the Comédie, and exhibitions in the Studio. © Bertrand Rindoff Petroff/Getty Images.
A new conception of the performing arts

City Hall’s shameful back down was perhaps a blessing in disguise, for it triggered the ‘shift westwards’ of the capital’s cultural center of gravity, for which Astruc claimed kudos. A plot of land was found on the Avenue Montaigne (named for Michel de Montaigne, the 16th century essayist). Formerly called ‘Widows’ Alley,’ until the mid-19th century this street conjured images of horse-drawn carriages bearing the bereaved, forbidden by society to appear in public during mourning. Thereafter it transmuted into an avenue lit by streetlamps, an atmosphere suggestive of a nightlife lived openly and not in the shadows.

To drum up investment for his theater project, Astruc appointed Gabriel Thomas to oversee a limited liability company. Thomas, a former stock marketer, discerning art lover, auditor and later CEO of the Musée Grévin (waxwork museum) in Paris, raised 3 500 000 francs, equivalent today to about 11.5 million euros (15 million US dollars). Among the investors were the Rothschild banking family, Sir Ernest Cassel (British merchant banker), and John Pierpoint Morgan (American financier), who brought gravitas and financial clout to the venture. Their backing was rewarded by privileges such as personal admission to the theater and its stage, and a box for dress rehearsals. Shareholders were no longer bystanders, but took part in the life of the theater and its creative process. Set apart from other music venues, the theater on Avenue Montaigne embodied a new conception of the performing arts: the quest for entertainment had yielded to the wish to appreciate singular and original works. Revelers looking for an evening’s amusement gave way to men and women seeking a deeper more lasting experience. The very design—perfect visibility from every seat, comfort, feeling of well-being—showed that the theater was no longer a place of fleeting impressions, of transience, but rather one of contemplation, where audiences were encouraged to linger, to reflect, to seek inspiration.

The first season

The Théâtre des Champs-Élysées opened its doors on 31 March 1913 for the ‘first inaugural gala’ and the first of six performances of Hector Berlioz’s opera *Benvenuto Cellini*, based on the life of the eponymous Florentine polymath of the High Renaissance. It had premiered at the Opéra de Paris in 1838, with just four performances, but had not been heard since.
Astruc had been at pains to revive this vocally demanding work deemed unplayable by some musicians and unloved by the public. Writing years later, a tad immodest but rightly so, Astruc described his delight at the response of the critics who “praised to the skies the daring manager who had rehabilitated the memory of Berlioz.”

Maestro Ingelbrecht opened the concert with Chabrier’s Ode à la musique followed by Lalo’s Scherzo symphonique, before handing the baton to Saint-Saëns who conducted his symphonic poem Phaéton. Fauré directed his La Naissance de Vénus for soloists, choir, and orchestra, d’Indy and Dukas conducted their music, Debussy led the orchestra in a performance of Prélude à l’après-midi d’un faune, and Saint-Saëns then returned to the stage to close the concert with excerpts from his cantata La Lyre et la harpe.

The 1913 season continued with a series of concerts of Beethoven’s nine symphonies conducted by Felix Weingartner and the premiere of Fauré’s opera Pénélope on 10 May. And then, on Thursday 29 May, came the much-awaited premiere of Igor Stravinsky’s new ballet, The Rite of Spring.

As musical expectancy rose, so did the mercury. The temperature soared to 30°C, a record for the month of May in Paris, which stands to this day. A fine test indeed of the audience’s cool and of the theater’s newfangled system of ventilation. The latter passed muster, but the former was lost as harsh rhythms and dissonant sounds from Pagan Russia filled the hall and foot-stomping dancers trampled on two centuries of ballet tradition.

Not everyone was caught unawares. The critic of L’Écho de Paris had foreseen as much when he attended the final rehearsals, fearing that the public would react badly if they felt they were being mocked. Some clearly did. The smart set were there to pay homage to orchestral and balletic convention, not to be scandalized, to have people cocking a snook, to be a laughingstock. They wasted no time in making their feelings known. The conductor that evening, Pierre Monteux, recalled that “Everything available was tossed in our direction.” The ‘Bohemians,’ on the other hand, the writer and filmmaker Jean Cocteau asserted, were there to hail the avant-garde, “to acclaim, right or wrong, anything that is new, because of their hatred of the boxes” (ie, the smart set).

In this centennial year of both the Théâtre des Champs-Élysées and The Rite of Spring, it is hard to credit the uproar sparked by a work which has become a staple of the repertoires of all the leading orchestras and which the American composer and conductor Leonard Bernstein called “the most important piece of music of the 20th century.”

Astruc’s first season was a triumph; it was also his last. Financially overextended, he was ejected from the theater and the sets and costumes were impounded. For the following stopgap season Covent Garden and the Boston Opera Company presented operas, and then the theater fell silent at the outbreak of the Great War. Theater life resumed in 1919 with a short season presented by Anna Pavlova’s ballet company, followed later by innovative performances and premieres,
like the Swedish Ballets’ production of Francis Picabia’s ‘instantanéist’ ballet Relâche, with “two acts and one cinematographic intermission, and the tail of Francis Picabia’s dog,” and music by Erik Satie. Astruc meanwhile took his business nous and organizational skills to radio and advertising, worked as a theater manager for Philippe de Rothschild, and helped Marcel Proust proofread the first edition of Du Côté de chez Swann (Swann’s Way), a favor that Proust returned by offering Astruc advice when he was writing his memoir, Le Pavillon des fantasmes.

Modern times

The Théâtre des Champs-Élysées was the first modern building in France to be listed as a historic monument, in 1957. Later, threatened by real estate plans, it was bought by the Deposits and Consignments Fund, a governmental institution, which renovated the theater in the 1980s and agreed to the construction of a rooftop panoramic restaurant. Structurally, the theater could bear no additional weight, so the restaurant—Maison Blanche—was suspended above it, like a bridge.

Although it alters the building’s three-dimensional space, the restaurant is invisible from the Avenue Montaigne and is more part of the roofscape of Paris than of the street-level architecture. The theater continues to stage operas, symphonic and chamber concerts, recitals, dance, and pop events, and is home to the Orchestre National de France and the Orchestre Lamoureux. The Orchestre Philharmonique de Radio France and the Ensemble Orchestral de Paris play here often, and guest orchestras come from Vienna, Munich, London, Amsterdam, Saint Petersburg, New York, and beyond.

The Théâtre des Champs-Élysées: the venue that launched a masterpiece – Marsh

One-tenth scale model (2.4 x 0.5 m) by Maurice Denis of the dome of the Théâtre des Champs-Élysées. © RMN-Grand Palais (musée d’Orsay)/Gérard Blot/ADAGP.

Detail from the frescoes by Maurice Denis which encircle the base of the dome of the Théâtre des Champs-Élysées. © All rights reserved.
THE BALLETs RUSSES

By the early 1900s, the 200-year-old art of ballet had seen better days. Lackluster productions, second-rate music, feeling trumped by technique (albeit in decline for decades). Then came Sergei Pavlovich Diaghilev and his Ballets Russes.

Yet it might never have happened. Had it not been for the conservatism of the art world in turn-of-the-century Russia, an exasperated Diaghilev may not have tried his luck in Paris, where art lovers flocked to see his “Exhibition of Russian Art.” The following years he offered the Parisians music and opera by Russian composers, and in 1909 presented a “Russian Season” devoted entirely to dance. Thus were born the Ballets Russes.

The early seasons of ballets to music by Borodin, Chopin, Arensky, Ravel, and Debussy, and above all Stravinsky (The Firebird and Petrushka), were a critical and popular success. To bring the Ballets Russes to his newly opened Théâtre des Champs-Elysées for the 1913 season, concert promoter Gabriel Astruc paid Diaghilev 25,000 francs for each performance (equivalent today to about 82,000 euros or 107,000 US dollars). On the program was Stravinsky’s new ballet, The Rite of Spring.

The conductor Pierre Monteux later admitted that on hearing Stravinsky play a piano version of The Rite of Spring his “one desire was to flee that room and find a quiet corner in which to rest [his] aching head.” Diaghilev, persuasive as always, won him over: “This is a masterpiece, Monteux, which will completely revolutionize music and make you famous, because you are going to conduct it.” The premiere at the Théâtre des Champs-Elysées has entered the annals variously as the “most important moment in the history of twentieth-century music” and ‘a near-riot,’ throughout which, Stravinsky later wrote, Monteux continued conducting, “apparently impervious and as nerveless as a crocodile.”

The dancers and choreographers: 19th century male dancers cut a sorry figure—neglected by choreographers, ignored by ballet audiences, playing second fiddle to ballerinas. The Ballets Russes changed all this by raising technical standards and introducing some of the most gifted danseurs in the history of ballet—Michel Fokine, Serge Lifar, Léonide Massine, George Balanchine, and Vaslav Nijinsky—who partnered luminaries like Anna Pavlova, Tamara Karsavina, Mathilde Kschessinska, Ida Rubinstein, and Bronislava Nijinska.

Some also left their mark on the history of ballet as choreographers. Nijinsky worked for Diaghilev on Debussy’s L’Après-midi d’un faune and Jeux, and most famously on The Rite of Spring. Nijinsky’s younger sister, Bronislava Nijinska, also choreographed productions, including Stravinsky’s Les Noces and Milhaud’s Le Train Bleu. Other dancer-choreographers included Léonide Massine, who replaced Nijinsky both as ballet-master and Diaghilev’s lover, and George Balanchine.

The designers and costumiers: Alexandre Benois, who had collaborated with Diaghilev from their student days in Saint Petersburg, contributed stage sets and costume designs to early productions by the Ballets Russes, notably Petrushka. Léon Bakst worked on The Firebird, L’Après-midi d’un faune, and Daphnis et Chloé. And Nicholas Roe-
rich, the Russian polymath, created a daring aesthetic that played no small part in the sensation that accompanied the premiere of The Rite of Spring.

Pablo Picasso worked on three Diaghilev ballets, including Pulcinella by Stravinsky, who was excited by the idea of working with the Spanish master. Diaghilev was less than enthused after seeing Picasso’s first offering. His vision was of an abstract version of commedia dell’arte, yet here was Picasso aping something out of a frothy operetta. Diaghilev threw Picasso’s drawings on the floor, stamped on them, and angrily demanded that he start anew, before walking out and slamming the door behind him.

Henri Matisse, initially reluctant to become involved with the Ballets Russes, was in the end won over by Diaghilev’s legendary charm, deployed on one occasion at an unannounced visit to Matisse’s home outside Paris, accompanied by Stravinsky, who played through some of his music for Le Chant du Rossignol on the artist’s grand piano. When despite himself Matisse voiced a few ideas for the scenery, Diaghilev clinched it by flattery: “There’s your décor all settled. It’s absolutely essential you do it, there’s no one but you who could.”

The impresario: Self-proclaimed ‘man of contradictions,’ protean, a hard taskmaster, charismatic, a manipulator of the press, dictatorial, an eye for talent, superstitious, a man whose religion was art. Sergei Pavlovich Diaghilev was born in 1872 into a wealthy family with a town house in Perm (Russia) and a country estate. He studied piano and singing and learned to move with ease among the landed gentry and upper classes. When his father bankrupted the family vodka business, Sergei enrolled at the Faculty of Law in Saint Petersburg, where he took lessons in painting and studied music with a view to becoming a composer, until Rimsky-Korsakov told him he lacked talent.

The impresario:

The legacy: In debt, hounded by creditors, the Ballets Russes disbanded after Diaghilev’s death. Yet their legacy lives on. Serge Lifar restored the reputation of the Paris Opera Ballet, where he was ballet master for a quarter of a century. George Balanchine co-founded in 1948 the New York City Ballet and remained its ballet master for more than 35 years. And Tamara Karsavina was a founder member of the Royal Academy of Dance and helped set up The Royal Ballet, founded by Ninette de Valois, who said that everything she knew about running a ballet company she had learned from Diaghilev.
“In a few months the most elegant neighborhood in Paris will have a new palace: the Théâtre des Champs-Élysées will open its doors to the public... on the Avenue Montaigne... in the quarter of Paris that has become the veritable center of the capital.” Thus did the Ballets Russes herald the new venue for their 1913 season.

Gabriel Astruc, its creator, saw the Théâtre des Champs-Élysées as a rival to state venues that offered the same musical fare to one and all. Resolutely modern in programming and architecture alike, Astruc’s theater allied French taste, English comfort, and German technology.

The theater’s unity of design, from façade to innards, betrays no trace of the ups and downs attendant upon its conception, which evolved over the years through the work of four architects. Aided by Roger Bouvard, Henri Fivaz drew up the initial plans for a site on the Champs-Élysées, but resigned when they were rejected. Shortly afterwards the Paris Town Hall backtracked on its offer of the Champs-Élysées site and a plot was found nearby on the Avenue Montaigne. Walled on three sides by existing buildings, the new site imposed jigsaw-like constraints, but with this limitation came an economic advantage, since the theater would have not four façades, but one.

Bouvard devised new plans with the Avenue Montaigne site in mind. Hired as a consultant, Henry Van de Velde made changes to Bouvard’s designs, with a view to investing the theater with a more contemporary feel. The idea was to use reinforced concrete, for stylistic reasons, of course, but also because of the clayey subsoil and the fact that the River Seine was hard by. With this in mind Van de Velde sought help from the building contractors Auguste and Gustave Perret, who were keen advocates of reinforced concrete. Their role was to erect the theater using the plans worked on by Bouvard and Van de Velde, but the Perrets ended up having a major say in the design. And ever since their name has been indissolubly linked with the architectural planning and construction of the Théâtre des Champs-Élysées.

The artists who worked on the theater—Maurice Denis (frescoes), Henri Lebasque and Édouard Vuillard (paintings), Jacqueline Marval (foyer), Ker Xavier Roussel (stage curtain), René Lalique (glass lamps), Antoine Bourdelle (sculptures)—made no concessions to the outmoded orthodoxy of the traditionalists. Much to the delight of the avant-gardists. Yet the theater gave a nod to tradition with its symmetrical frontage, marble facings within and without, its cornices and sculpted metopes.

Audience comfort was sacrosanct: deep seats with two armrests, a novel heating and ventilation system, elevators and shallow steps between the three floors, a lounge area, a bar. The same norms of convenience, practicality, and elegance were applied to administrative offices, to rehearsal rooms, and to dressing rooms—baths with hot and cold water, sewage disposal toilets, amenities often lacking in the performers’ everyday lives.

Safety, too, was paramount. Time had done little to dim memories of the 1887 inferno at the Opéra-Comique in which 84 people perished. The theater’s design facilitated access by firefighters and the fire risk was lowered by the use of reinforced concrete, fireproof materials, and electricity instead of gas. One century on, the 300,000 concertgoers and thousands of performers who come to the Théâtre des Champs-Élysées each year would doubtless agree with Auguste Perret that “Architecture seizes space, circumscribes, encloses, bounds it. A labor of the mind, it has the privilege of creating magical places.”

Dance, a stone bas-relief (1909) by Antoine Bourdelle (1861-1929), from the frontage of the Théâtre des Champs-Élysées.

© The Bridgeman Art Library.
From the outset Gabriel Astruc and his architects conceived of a single complex with three theaters: the main auditorium for concerts, ballet, and opera, with 1920 seats in a space that could in fact accommodate 3000, to heighten comfort, and two smaller theaters, the Comédie (1200 seats) for drama and the Studio (800) for exhibitions.

The roll-call over the years of playwrights and performers at the Comédie includes Paul Claudel, singer and actress Mistinguett, once the highest-paid female entertainer in the world, Jean Cocteau and Darius Milhaud, George Bernard Shaw (Arms and the Man), Louis Jouvet, and Jean Giraudoux (three plays premiered). More recently, Yasmina Reza’s play Art premiered here, winning two Molière awards.

Centenary season
In the Spring of 2013, the Théâtre des Champs-Élysées celebrated its centenary by reliving some of the great events that marked its first one hundred years, notably a performance of The Rite of Spring with Vaslav Nijinsky’s original choreography, reconstructed by the music historians Millicent Hodson and Kenneth Archer. The centenary season also included concert versions of the operas Benvenuto Cellini by Berlioz and Pénélope by Fauré, and a homage to another major event in the theater’s history—the first Paris appearance in October 1925 of Josephine Baker, the American ‘Queen of the Wild Dance,’ in La Revue Nègre, with a jazz band from New York. The watchword of the Théâtre des Champs-Élysées over the last hundred years has been continuity. A spectator from the 1920s or the 1950s would not feel out of place if he were to return to a concert this very evening. Continuity, plus diversity and modernity. Three heartfelt principles of the man who one hundred years ago on a rainswept night stood on the Avenue Montaigne before his dream made real, the Théâtre des Champs-Élysées. The man whose single-mindedness and acumen made everything possible. Gabriel Astruc.
Instructions for authors

General instructions
- Manuscripts should be provided by e-mail (judit.siklosi@fr.netgrs.com) or by 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 portrait 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.
- Figures and Tables. Figures should be of good quality or professionally prepared, numbered according to their order, with proper orientation indicated (eg, “top,” or “left”). Figures may be provided as pdf files (printing resolution = 300 dpi scans, on CDrom, or via e-mail; screen resolution = 72 dpi scans acceptable only if large-sized format [A4]). Provide fully explicit legends, not repetitive of text. All abbreviations used should be explained in the legends. As figures and graphs may need to be reduced or enlarged, all absolute values and statistics should be provided. Illustrations will be reproduced in full color only when clearly necessary, eg, images from nuclear medicine or histology. Provide each table on a separate sheet, with title above and description below. All figures and tables should be cited in the text, with distinct numbering for figures and tables.
- Note that Editorials and Abstracts will be published in English and French. Translations into French will be provided by the Publisher’s Editorial Department.
- Include Headings using a consistent style for the various levels of headings, to highlight key points and facilitate comprehension of the text. The Editorial Department reserves the right to add or delete headings when necessary.
- Abbreviations should be used sparingly and expanded at first mention. A list of selected abbreviations and acronyms should be provided (or will be prepared by the Editorial Department) where necessary.
- Use Système International (SI) units.
- Use generic names of drugs.
- All references should be cited in the text and numbered consecutively using superscript arabic numerals. Presentation of the references should be based on the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Ann Intern Med. 1997; 126:36-47 (“Vancouver style”). The author-date system of citation is NOT acceptable. In press references are to be avoided. In the bibliography, titles of journals should be abbreviated according to the Index Medicus. All authors should be listed up to six; if there are more, only the first three should be listed, followed by “et al.” Where necessary, references will be styled by the Editorial Department to Medicographia copyediting requirements. Authors bear total responsibility for the accuracy and completeness of all references and for correct text citation. Example of style for references:

Specific formats
- Editorial: 1500 words. No abstract or illustrations should be included. A French translation of the Editorial will be provided by the Editorial Department and submitted to the author.
- Theme - Focus - Update - Therapeutic outlook article - Touch of France: Abstract: 200-230 words. Main text: 2800-3200 words. References: their number should not exceed 50. Illustrations (figures and tables): their number should not exceed 5 unless clearly necessary.
- Interview: Abstract: 200-230 words. Main text: 2000-2500 words. Headings are the questions posed at the interview. References, if cited, should in no case exceed 10. No illustrations.
- Replies to the Controversial Question: 400-600 words. No abstract or illustrations should be included. References, if cited, should in no case exceed 6.

Editorial processing
- Editorial style: All contributions to Medicographia will be styled by the Editorial Department according to the specifications of the current edition of the American Medical Association Manual of Style, Williams & Wilkins.
- Page proofs and editorial queries will be sent to the corresponding author for approval. Corrections should be returned within 48 hours by e-mail, and fax or express mail. If this deadline is not met, changes made by the Editorial Department will be assumed to be accepted by the author. Authors are responsible for all statements made in their work, including changes made by the Editorial Department and authorized by the author. Articles and abstracts will be edited to required length or returned to the author if specific requirements are not complied with.

Copyright
- Copyright of articles will be transferred to the Publisher of Medicographia. The Copyright Transfer Agreement must be signed by the main author and all coauthors and returned to the Publisher.