Hypertension management in the 21st century: major advances and achievements

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Arterial hypertension: new stakes for the new century

by C. Delles and A. F. Dominiczak, United Kingdom

Cardiovascular diseases are a leading cause of mortality and morbidity worldwide, and hypertension remains one of the most important risk factors for them. For no other cardiovascular risk factor have we seen as many treatment choices emerge as for hypertension. This reflects the importance of the clinical problem, and even more, it demonstrates that treatment of hypertension remains difficult. In fact, the percentage of patients with hypertension whose blood pressure is controlled to target remains low across all nationalities, and the number of premature deaths and individuals with disabilities due to hypertension is enormous, as are the resulting financial implications.

Despite substantial progress over the last few decades, many of the fundamental pathophysiological and clinical challenges of hypertension persist. In these early years of the 21st century, we are still confronted with problems and concepts that were defined in the second half of the preceding century, although our tools to tackle the worldwide epidemic of hypertension have evolved rapidly. The present issue of Medicographia will critically review and dissect the most urgent aspects of hypertension and related cardiovascular diseases, and the timing for this could not be any better. Here we take the opportunity to highlight some of the most urgent tasks for hypertension research in the coming years, and put them into an historical and global context.

Hypertension is a key risk factor for cardiovascular diseases

It was not until the second half of the 20th century that the authors of the Framingham Heart Study recognized high blood pressure as an eminent cardiovascular risk factor. It took another 10 years to robustly demonstrate that treatment of hypertension leads to significant reductions in cardiovascular events. The first Veterans Administration Cooperative Study on Antihypertensive Agents in 1967 included men with diastolic blood pressure of 115 mm Hg to 129 mm Hg. The treatment, comprising hydrochlorothiazide, reserpine, and hydralazine hydrochloride, caused a remarkable average blood pressure reduction of 43/30 mm Hg in the active treatment arm. After only 11 months of follow-up, there were 21 fatal or morbid events in the placebo arm as opposed to 1 event in the active treatment arm; a reason to stop the study prematurely.

A second longer, larger-term Veterans Administration Cooperative Study in patients with milder hypertension impressively confirmed that blood pressure–lowering therapy reduced the incidence of stroke and congestive heart failure. In parallel, other cardiovascular risk factors were discovered, including hypercholesterolemia, obe-
sity, and smoking. While hypertension remains the most important modifiable risk factor for stroke and heart failure, it has been recognized that cardiovascular risk in general is determined by the combined action of several risk factors. The 2003 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines for diagnosis and treatment of hypertension introduced this concept specifically into the management strategy for patients with hypertension. The novel idea was that decisions about hypertension therapy should not be based solely on blood pressure, but also on the presence or absence of other risk factors. A much more holistic view of cardiovascular risk has developed since then, with hypertension being one risk factor among others, and this view has found its way into national and international guidelines.

As a consequence of this development, it has become clear that there is no fixed threshold of blood pressure beyond which treatment is required. More recently, it has been proposed that blood pressure is a quantitative cardiovascular risk factor, and concepts such as “high normal blood pressure” and “prehypertension” have been introduced to highlight the fact that even within a “normal” range, those individuals with lower blood pressure have lower cardiovascular risk and lower risk of progression to hypertension. The 2007 notion of Messerli, Williams, and Ritz that “the time has come to abandon the hypertension/normotension dichotomy and to focus on global risk reduction” clearly sets the scene for hypertension management in the 21st century.

**Treatment of high blood pressure**

In the early 20th century, blood pressure treatment was based on surgical and chemical sympathectomy and a range of pharmaceutical agents with profound side effect profiles that rendered them impractical for widespread clinical use. Better understanding of the pathophysiology of hypertension, including vasoconstriction, vascular remodeling, myocardial function, and renal salt and water handling, led to the development of new antihypertensive principles and agents during the second half of the last century. We have witnessed the introduction of diuretics, β-blockers, calcium channel blockers, and angiotensin-converting enzyme inhibitors into the management of hypertension.

Despite the myriad of treatment options, a number of questions remain unanswered: the optimal target blood pressure for patients with different comorbidities including diabetes and renal disease, the choice of an “ideal” antihypertensive agent for individual patients, and the role of nonpharmacological interventions; all of these still have to be refined. It is evident that in the majority of patients, monotherapy will not reduce blood pressure to target. An important controversy that has to be resolved is whether combination therapy should be initiated early by combining low doses of two or more agents, or later by titrating each agent to its maximum dose before adding another agent. It is almost embarrassing to see that although combination therapy was studied very early in the development of the first mainstream antihypertensive agents half a century ago, we still have not reached a consensus regarding its optimal use.

**Hypertension is a global health problem**

It has taken much longer, however, to recognize that hypertension and cardiovascular diseases are also important health problems in developing countries. In fact, the major burden of cardiovascular diseases worldwide—both from the individual medical point of view and from the financial point of view—is currently seen in the less developed countries. The modification of risk prediction charts—originally developed for use in industrialized countries—to make them suitable for use in countries with limited resources, is an important achievement of the International Society of Hypertension and the World Health Organization. Nevertheless, many aspects of the management of hypertension and associated cardiovascular diseases remain unknown in developing countries.

Existing data indicate, however, that the prevalence of hypertension in developing countries is not hugely different from that in industrialized countries, and that lifestyle changes and urbanization are further aggravating the problem. A number of recommendations for addressing hypertension in the developing world have recently been made by Mittal and Singh, including early detection and primary prevention, education and training of general physicians, increasing the availability of and adherence to antihypertensive treatment, and researching the racial differences in the effectiveness of antihypertensive therapies in developing countries. With the exception of availability of antihypertensive treatment, all of the aforementioned action points are also relevant for developed countries.

**Assessment of blood pressure and target organ damage**

The principles of blood pressure measurement in the 21st century are not much different from those introduced by Korotkoff in 1905. However, we have seen substantial developments in the methodology, with ambulatory blood pressure monitoring, home blood pressure monitoring, and telemedicine being used more and more in clinical practice.

Other areas have also seen major progress. Our ability to noninvasively assess cardiac and vascular structure and function using echocardiography, flow-mediated dilation, pulse wave analysis, pulse wave velocity, and assessment of carotid/intima media thickness can provide us with a very detailed snapshot of early and subclinical target organ damage. In line with the concept of a cardiovascular continuum, these early stages of cardiovascular diseases will normally progress, but they also offer an option to intervene early and in a targeted fashion.
Assessment of organ damage is part of the routine workup of hypertensive patients, but most guidelines focus on investigations for established markers of organ damage, including serum creatinine concentration, direct fundoscopy, and electrocardiography. The degree to which more detailed cardiovascular phenotyping, other emerging biomarkers, and new concepts such as that of a biological vascular age and early vascular aging will improve risk stratification and guide therapy is as yet unclear, but will form part of our agenda for the coming years.13,30

To apply existing knowledge to all patients worldwide
The majority of cardiovascular events occur in individuals in less developed countries, where targeted treatment with established drugs could save millions of lives and prevent disability at an extremely low cost.

To use existing preventative and therapeutic options smartly
The roles of preventative strategies, nonpharmacological intervention, combination therapy, and adherence to treatment in the treatment of patients with high blood pressure have to be examined and defined.

To better understand the pathophysiology of hypertension
Recent discoveries including the relationship between sleep duration and cardiovascular risk, the role of blood pressure variability, novel treatment options such as carotid sinus stimulation and catheter-based renal sympathectomy, and the higher than originally thought prevalence of primary hyperaldosteronism, have to be evaluated in a clinical context.

To use genetic and systems medicine approaches to unravel novel targets for antihypertensive therapy
Recent genome-wide association studies and other genetic and genomic approaches have identified a number of novel candidate genes for hypertension. Future research has to examine how these targets could lead to novel therapeutic strategies. Integration with other systems medicine approaches including proteomics and metabolomics will be one of the central themes in cardiovascular research of the next decade.

To develop better methods for cardiovascular risk prediction
Current models are designed to predict risks of populations, but not necessarily of individual patients. Stratified medicine will take into account additional characteristics of individual patients. These characteristics include a range of factors, from social deprivation to genetic makeup and circulating biomarker profiles.

Table. Hypertension targets for the next decade.

New stakes for the new century and targets for the next decade
It is remarkable that despite enormous progress over the last 50 years, some of the most salient problems in hypertension remain key issues for the coming decades; these range from pathophysiological aspects of hypertension, to management of patients with hypertension in clinical practice.

Recent years have seen exciting developments, particularly in the area of genetics with the identification of robust candidate genes from genome-wide association studies, targeted candidate gene studies involving novel techniques such as re-sequencing of coding and noncoding regions to unravel rare genetic variants. Determination of how these findings will translate into clinical practice remains one of the major challenges for the next few years. Other equally important recent discoveries derive from clinical studies and the identification of new risk factors for hypertension and cardiovascular diseases, including reduced sleep duration, sleep apnea, and blood pressure variability. Again, these new findings require translation into clinical practice. Evidence that it is possible to develop new treatments based on pathophysiological principles is provided by technological advances in carotid sinus stimulation and renal denervation. With regard to the latter, it appears that almost a century after Irvin Page’s description in 1935 of a substance released from the carotid sinus that leads to blood pressure reduction, and Fritz Brüening’s first surgical sympathectomy for hypertension in 1927, better tolerated and widely applicable tools have now become available. Experience with these novel techniques is, however, still limited to extreme cases of resistant hypertension, and it is debatable as to whether use of these invasive procedures will be applicable to mild and moderate hypertension.

It is an ambitious task to identify goals for a whole century. We are much more confident in setting a few targets for the next decade, and these targets are highlighted in the Table. Hypertension and associated cardiovascular diseases remain major causes of morbidity and mortality worldwide, and patients have a right to see clear answers and major progress very soon. We are confident that this issue of MedicoGraphia will not only provide an overview of current concepts, but will also outline a clear program for future research and its translation, to the benefit of patients worldwide.

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Les maladies cardio-vasculaires sont une des principales causes mondiales de mortalité et de morbidité, l’hypertension restant l’un des facteurs de risque les plus importants pour ces pathologies. Aucun autre facteur de risque cardio-vasculaire n’a engendré autant d’options thérapeutiques que l’hypertension, ce qui souligne l’importance du problème clinique et, en plus, démontre que le traitement de l’hypertension reste difficile. De fait, le pourcentage de patients hypertendus traités dont la pression artérielle est abaissée jusqu’aux valeurs cibles reste faible, toutes origines géographiques confondues, et le nombre de décès prématurés et de personnes souffrant d’invalidités dues à l’hypertension reste énorme, comme le sont également les implications financières qui en découlent.

Malgré les progrès importants réalisés au cours des dernières décennies, il persiste un grand nombre de défis physiopathologiques et cliniques fondamentaux concernant l’hypertension. En ce XXIe siècle débutant, nous sommes toujours confrontés à des problèmes et à des concepts définis au cours de la deuxième moitié du siècle précédent, même si nos outils pour affronter l’épidémie mondiale d’hypertension ont connu une évolution rapide. Ce numéro de Medicographia examine de façon critique et minutieuse les aspects les plus urgents de l’hypertension et des maladies cardio-vasculaires qui y sont liées, et le moment ne pouvait pas être mieux choisi. Nous mettrons l’accent sur les objectifs les plus prioritaires des années à venir en ce qui concerne la recherche sur l’hypertension afin de les replacer dans un contexte historique et global.

L’hypertension est un facteur de risque clé pour les maladies cardio-vasculaires

Ce n’est qu’à partir de la seconde moitié du XXe siècle que les auteurs de l’étude de Framingham ont reconnu qu’une pression artérielle élevée constituait un facteur de risque cardio-vasculaire important. Il fallut encore 10 ans pour démontrer de façon solide que le traitement de l’hypertension conduisait à une réduction significative des événements cardio-vasculaires. La première étude, en 1967, la Veterans Administration Cooperative Study on Antihypertensive Agents, avait inclus des sujets de sexe masculin ayant une pression artérielle diastolique comprise entre 115 mmHg et 129 mmHg. Le traitement, à base d’hydrochlorothiazide, de résépine et de chlorhydrate d’hydralazine, permit une remarquable réduction de la pression artérielle moyenne de 43/30 mmHg dans le bras de traitement actif. Après seulement 11 mois de suivi, 21 événements fataux ou morbides étaient constatés dans le bras placebo contre 1 seul dans le bras du traitement actif. Ceci entraîna l’arrêt prématuré de l’étude.
Une seconde étude à plus grande échelle et à plus long terme, la Veterans Administration Cooperative Study, chez des patients ayant une hypertension moins importante, confirme de façon probante que l’abaissement de la pression artérielle réduisait l’incidence des accidents vasculaires cérébraux (AVC) et de l’insuffisance cardiaque.

En parallèle, d’autres facteurs de risque cardio-vasculaires furent découverts, comme l’hypercholestérolémie, l’obésité et le tabagisme. Tandis que l’hypertension reste le facteur de risque modifiable le plus important pour les AVC et l’insuffisance cardiaque, il a été reconnu que le risque cardio-vasculaire dans son ensemble est déterminé par l’association de plusieurs facteurs de risque. Les recommandations de 2003 de l’European Society of Hypertension (ESH)/European Society of Cardiology (ESC) pour le diagnostic et le traitement de l’hypertension introduisirent ce concept de façon spécifique dans la stratégie de prise en charge des patients hypertendus. La nouveauté était que les décisions au sujet du traitement antihypertenseur ne devaient pas être basées seulement sur la pression artérielle, mais également prendre en compte la présence ou l’absence d’autres facteurs de risque. Depuis lors, le risque cardio-vasculaire a été appréhendé de façon beaucoup plus globale, l’hypertension étant considéré comme un facteur de risque parmi d’autres, et ce point de vue a été répercuté dans les recommandations internationales.

Tout ceci contribua à rendre manifeste le fait qu’il n’existe pas de seuil fixe de pression artérielle au-delà duquel il faut traiter. Plus récemment, il a été proposé que la pression artérielle est un facteur de risque cardio-vasculaire quantitatif, et des concepts comme « pression artérielle normale élevée » et « préhypertension » ont été forgés pour faire comprendre que même à l’intérieur de la fourchette des valeurs « normales », les personnes dont la pression artérielle est plus basse ont un risque cardio-vasculaire plus faible et un risque de progression vers l’hypertension moins important. L’idée datant de 2007 de Messerli, Williams et Ritz stipulant « qu’il est temps d’abandonner la dichotomie hypertension/normotension et de se concentrer sur la réduction du risque global » représente ainsi véritablement le point de départ du renouveau de la prise en charge de l’hypertension au XXIe siècle.

L’hypertension est un problème de santé global
Cela a pris encore plus longtemps pour reconnaître que l’hypertension et les maladies cardio-vasculaires étaient aussi des problèmes de santé importants dans les pays en voie de développement. En fait, au plan mondial, la part la plus importante du fardeau des maladies cardio-vasculaires (à la fois du point de vue médical individuel et du point de vue financier) est actuellement supportée par les pays les moins développés. L’adaptation des diagrammes de prédiction du risque cardiovasculaire (établis initialement pour utilisation dans les pays industrialisés), pour qu’ils puissent être utilisés dans des pays aux ressources limitées, a représentée une entreprise majeure pour la Société Internationale d’Hypertension (International Society of Hypertension) et l’Organisation Mondiale de la Santé. Néanmoins, de nombreux aspects de la prise en charge de l’hypertension et des maladies cardio-vasculaires associées restent inconnus dans les pays en voie de développement.

Malgré les innombrables options de traitement, il reste encore un certain nombre de questions sans réponse : (1) Quelle est la pression artérielle cible optimale pour les patients présentant des comorbidités à type de diabète ou de néphropathie ? (2) Comment déterminer le traitement antihypertenseur « idéal » pour chaque patient ? et (3) Quelle est la place des interventions non pharmacologiques ? Il est évident que chez la majorité des patients, une monothérapie ne parviendra pas à abaisser la pression artérielle jusqu’aux valeurs souhaitées. Il reste à résoudre une importante controverse : faut-il commencer très tôt un traitement associant de faibles doses de 2 produits ou plus, ou plus tard en augmentant chaque produit à sa dose maximale avant d’ajouter une autre molécule. Il est presque gênant de constater que bien que le principe des associations thérapeutiques ait été étudié très tôt au cours du développement des premiers antihypertenseurs majeurs il y a un demi siècle, nous n’avons toujours pas atteint de consensus quant à son utilisation optimale.

Traité d’une pression artérielle élevée

Les données disponibles indiquent cependant que la prévalence de l’hypertension dans les pays en voie de développement n’est pas fondamentalement différente de celle des pays industrialisés, et que ce problème est aggravé par les changements de style de vie et l’urbanisation. Mittal et Singh ont récemment formulé un certain nombre de recommandations concernant la prise en charge de l’hypertension dans les pays en voie de développement, comme la détection précoce et la prévention primaire, l’éducation et la formation des généralistes, l’amélioration de l’accès aux médicaments antihypertenseurs, la meilleure adhésion des patients au traitement et la recherche sur les différences raciales dans l’efficacité des traitements.
traitements antihypertenseurs. À l’exception de l’accès au traitement antihypertenseur, tous les points susmentionnés sont aussi pertinents pour les pays industrialisés.

Évaluation de la pression artérielle et des lésions des organes cibles
Les principes de la mesure de la pression artérielle au XXIe siècle ne diffèrent pas énormément de ceux introduits par Korotkoff en 1905. Il y a eu cependant des avancées considérables sur le plan méthodologique, avec un recours de plus en plus large en pratique clinique de la mesure de la pression artérielle ambulatoire, de l’autométrie de la pression artérielle et de la télémédecine.

Des progrès majeurs ont également été faits dans d’autres domaines. Ainsi l’évaluation non invasive des structures et fonctions cardiaques et vasculaires utilisant l’échocardiographie, la vasodilatation médiane par le flux, l’analyse de l’onde de pouls, la vitesse de l’onde de pouls et l’évaluation de l’épaisseur médiale du rapport carotide/intima permet d’obtenir un instantané très détaillé des lésions précoces et infracliniques des organes cibles. Conformément au concept de continuum cardio-vasculaire, ces stades précoces des maladies cardio-vasculaires sont certes appelés à s’aggraver, mais représentent également une opportunité d’intervenir précoce-ment et de façon ciblée.

L’évaluation des lésions des organes cibles fait partie de la prise en charge de routine des patients hypertendus, mais la plupart des recommandations se concentrent sur la recherche des marqueurs des lésions des organes cibles, comme la mesure de la créatinine sémique, l’examen du fond d’œil direct et l’électrocardiographie. Il est encore difficile de dire jusqu’à quel point un phénotype cardio-vasculaire plus détaillé, d’autres biomarqueurs émergents et de nouveaux concepts comme celui d’un âge vasculaire biologique et d’un vieillissement vasculaire précoce pourraient améliorer la stratification du risque et l’orientation du traitement, mais ces aspects feront partie de nos priorités dans les années à venir.

Nouveaux enjeux pour le nouveau siècle et objectifs pour les dix ans à venir
Il est frappant que malgré les progrès énormes de ces 50 dernières années, certains des problèmes les plus fondamentaux de l’hypertension sont justement ceux qui vont tenir le devant de la scène au cours des dix prochaines années, depuis les aspects physiopathologiques de l’hypertension jusqu’à la prise en charge des patients hypertendus en pratique clinique.


Des avancées technologiques dans la stimulation du sinus carotidien et la dénervation rénale fournissent la preuve qu’il est possible de développer de nouveaux traitements basés sur des principes physiopathologiques. En ce qui concerne ces avancées, il semble que presque un siècle après la description de Irvin Page en 1935 d’une libération de substance du sinus carotidien conduisant à la réduction de la pression artérielle, et de la première sympathectomie chirurgicale de Fritz Bruening pour l’hypertension en 1927, nous disposions enfin d’outils mieux tolérés et facilement utilisables. Ces nouvelles techniques invasives sont cependant réservées à des cas extrêmes d’hypertension résistante et il est douteux qu’elles puissent un jour être utilisées dans les hypertensions légères à modérées. Identifier des objectifs pour un siècle entier est une tâche ambitieuse. Nous sommes sur un terrain beaucoup plus sûr en fixant quelques objectifs pour les 10 prochaines années. Ces objectifs sont présentés dans le Tableau (page 9).

L’hypertension et les maladies cardio-vasculaires associées restent une des causes mondiales principales de morbidité et de mortalité, et les patients sont en droit d’espérer des réponses claires et des progrès majeurs dans un avenir très proche. Nous sommes confiants que ce numéro de Médicographia ne passera pas seulement en revue les concepts actuels, mais permettra également de se faire une idée sur le programme que se fixe la recherche future et quels bénéfices en attendre pour les patients du monde entier.

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In recent years, the new concept of early vascular aging (EVA) has emerged as a useful tool to aid understanding of how cardiovascular risk increases in relation to the biological aging process. The core feature of EVA is arterial stiffness, which can be measured as increased pulse wave velocity in relation to a subject’s chronological age and sex. Prevention of EVA should start early in life, as there is evidence that factors acting during fetal life, childhood, and adolescence all contribute to the development of EVA. Improved lifestyle is the first intervention to consider, followed in adults by drug therapy to control risk factors such as hypertension, increased blood pressure variability, hyperglycemia, and hyperlipidemia. Among the antihypertensive drugs to have been found of particular use are classes of agents that block the renin-angiotensin system. These have been shown to produce beneficial results regarding central blood pressure reduction, arterial wall remodeling, and reduction of cardiovascular risk in studies like HOPE (Heart Outcomes Prevention Evaluation), PROGRESS (Perindopril PROtection against REcurrent Stroke Study), ADVANCE (Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation), HYVET (Hypertension in the Very Elderly Trial), ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial), and LIFE (Losartan Intervention For Endpoint reduction in hypertension). Current developments involve attempts to find pathways that can interact with the vascular aging process, including ways to break glycemic linkages or manipulate telomere biology or endothelial function. This holds promise for the future.

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cally, vascular aging. Cardiovascular risk is determined not only by conventional risk factors important in adult life, but also by early life programming arising from intrauterine fetal growth retardation, often followed by rapid catch-up growth patterns. This is called the early life developmental origins of CVD, or sometimes the “mismatch” hypothesis, whereby there is a mismatch between the conditions that the fetus is programmed for in utero, and the environment that the newborn child meets in early postnatal life.

There are several important consequences of this programming effect; it has been shown to influence glucose metabolism through changes in insulin sensitivity and β-cell function, as well as influencing hemodynamic control, neuroendocrine regulation, and kidney function.

In addition, several reports have now documented that vascular structure and function are also to a certain extent determined via programming early in life. This includes several mechanisms that can eventually lead to morphological and functional changes important in the development of adult cardiovascular risk. For example, it has been shown that compared with normal fetal growth, impaired fetal growth is associated with capillary rarefaction, endothelial dysfunction, narrower arterial diameter, and increased aortic-intima-media thickness. In addition, premature birth itself—without growth retardation—is associated with long-term negative consequences for the vascular system.

As has now been documented in numerous studies, one consequence of this impaired development is an increased risk of elevated blood pressure, and later on, overt hypertension. This is accompanied by a tendency to exhibit early arterial changes, as included in the new concept of early vascular aging (EVA) that developed from arterial aging. EVA is also referred to as the EVA syndrome (see Table). One typical clinical example of EVA is the early arterial aging observed in young patients with essential hypertension. Compared with

### Arteriosclerosis
- Arterial stiffness, increased pulse wave velocity and augmentation index, increased wave reflection and central blood pressure

### Endothelial dysfunction
- Impaired vasodilation, impaired nitric oxide production, peripheral inflammation, defects in the microcirculation

### Atherosclerosis
- Increased intima media thickness due to development of atherosclerotic plaques, stenosis and flow disturbances

### Metabolism
- Hyperglycemia, dyslipidemia, decreased insulin sensitivity

### Inflammation
- Localized or general inflammation with increased levels of systemic biomarkers

Table. Core characteristics of the early vascular aging (EVA) syndrome.

age- and gender-matched normotensive individuals, an increased “intrinsic” stiffness of the arterial wall material (Young’s elastic modulus) has been found in younger hypertensive patients, but not in middle-aged and older hypertensive patients. With increasing age, the content of elastin in the arterial wall decreases and the amount of collagen fiber increases, as do cross-linkages between fibers. Several arguments favor an interaction between hypertension and diabetes in the acceleration of vascular aging and increase in cardiovascular risk. One consequence of vascular aging is the development of target organ damage; most notably, left ventricular hypertrophy, microalbuminuria, and retinopathy, but also cognitive decline and peripheral arterial disease. One can also consider arterial stiffness, the core feature of the EVA syndrome, as a tissue biomarker less sensitive to temporary changes than some biomarkers in common use such as serum or plasma biomarkers like lipids, C-reactive protein, fibrinogen, N-terminal pro B-type natriuretic peptide, and others.

**How should EVA be defined?**

Some controversy exists as to how the EVA syndrome should best be defined. One might argue that there is no need for a definition, as this concept is currently more of a
biological model of understanding than a fixed model. Nevertheless, it should be possible to analyze the distribution of pulse wave velocity (PWV) in various age groups, stratified for sex, as a marker of arterial stiffness and EVA. EVA could then be defined as the outliers located above the highest +2 standard deviation of the distribution for a specific population and in relation to age group and sex. This is something that was recently accomplished through European collaboration using an extensive database of PWV measurements. Another way to define EVA would be to analyze the remaining part of PWV that is not explained by conventional cardiovascular risk factors in a multiple regression analysis, with adjustments made for age, gender, blood pressure, hyperlipidemia, smoking, hyperglycemia, and drug treatment.

Finally, it could be argued that the primary definition of EVA should be the highest quartile or quintile of the distribution of PWV in combination with the corresponding cutoff levels for an inflammatory marker such as C-reactive protein or some other marker of inflammation or endothelial dysfunction. This is something that has not been fully explored yet and is therefore still work in progress. An important element is how PWV or arterial stiffness is measured, as different methods exist (Complior, Sphygmocor, Arteriograph, ultrasound devices) that need to be validated against each other.

Cognitive decline and EVA

A new aspect of EVA to emerge is the link with cognitive decline starting in midlife and with increased risk for dementia later in life, especially that of vascular origin. It has been shown that the burden of vascular risk factors plays an important role in the development of cognitive decline, acting against a background of cognitive reserves shaped by neurocognitive development during early childhood and adolescence. With the help of modern medical devices, it is possible to measure PWV in retinal vessels or the intracranial circulation. This could provide new insights into the connection between vascular pathophysiology and age-related impairment of mental function.

In summary, the EVA syndrome is a useful concept for increasing our awareness of the pathophysiological consequences of a heavy burden of CVD risk factors where the core is arterial stiffness. It is measurable and can be followed over time—for example, through changes in PWV. Broad evaluation and treatment of risk factors is necessary to achieve long-term benefits, as has most visibly been shown in the Steno-2 study in patients with type 2 diabetes. However, the goal for systolic blood pressure in patients with diabetes is still not well defined. It was the subject of extensive discussion following the results of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) blood pressure trial, in which no extra benefit was shown for the primary cardiovascular end point in patients achieving systolic blood pressure of <120 mm Hg compared with controls with <140 mm Hg.

Prevention and treatment of EVA

Ideally, the different components of the EVA syndrome should be prevented early in life; firstly, during the fetal period, but also later on during childhood and adolescence. Normal fetal development and normal physiological and neurocognitive growth during childhood are factors of great importance in the control of vascular risk, and have also long been factors that are addressed in the course of regular maternal and child health care. One important factor is the support of physical activity and neurocognitive development through appropriate diet and mental stimulation. Another component is the prevention of development of obesity with its accompanying insulin resistance and blood pressure elevation.

♦ The role of lifestyle in EVA prevention

The treatment of more established EVA in adult life should start with lifestyle interventions—most importantly, increased physical exercise and cessation of smoking. If possible, the patient should also be encouraged to adopt a healthy pattern of food intake based on what has been referred to as the Mediterranean diet. This includes a large amount of fruit and vegetables, but also fish, poultry, and a restricted amount of red meat. A glass of wine or two forms part of the cultural tradition of this diet. When obesity is a problem, the aim should be for weight stabilization in the first instance, and in some cases, weight reduction—a goal that is hard to achieve and maintain for many people. In selected cases, bariatric surgery can also be an option for weight loss in grossly obese subjects with a body mass index above 35 mg/m².

♦ Drug treatment for prevention of EVA

When it comes to drug therapy in patients with EVA, a multiple risk factor approach is of great importance, and the aim should be to control all of the classic risk factors for CVD. However, special attention should be given to the elevated blood pressure found in these patients, which most commonly engages the central circulation, with increased arterial stiffness and central pulse pressure.

There is emerging evidence that blood pressure variability is an independent CVD risk factor, and it is often linked with vascular properties, arterial stiffness, and aging, as pointed out by Rothwell et al. Furthermore, it is important to gain control of central blood pressure and newer aspects such as the reflected wave in the arterial tree and excess central pressure. In ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial), a higher wave reflection predicted future cardiovascular events independent of conventional risk factors in people with treated hypertension. In an observational study in France, it was shown that it was possible to obtain a large and sustained decrease in aortic stiffness in 97 treated hypertensive patients under conditions of routine clinical practice. These changes likely represent a delayed response to the long-term normalization of blood pressure and cardiovascular risk factors through arterial remodeling.
As there is crosstalk between the central circulation and peripheral circulation, there is also a case for improving the microcirculation. This goal can be achieved by combining different antihypertensive drugs, preferably with therapy based on an agent that blocks the renin-angiotensin system (RAS).

Both angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) seem to be beneficial in blocking RAS, but β-blockers are less useful for arterial stiffness because of the resultant vasoconstriction in the peripheral circulation of the arterioli. In the CAFE (Conduit Artery Function Evaluation) study, treatment with the calcium antagonist amlodipine, often combined with the ACE inhibitor perindopril, was associated with lower central blood pressure compared with β-blocker/thiazide diuretic therapy.

Effective blood pressure control can lead to regression of arterial stiffness and a reduction in PWV—even more than would be predicted on the basis of the blood pressure lowering per se. This supports the notion that long-term risk factor control can reverse aspects of EVA. As the RAS is important in the remodeling of arteries, it is logical to use agents that block the RAS to counteract this process. Often, this is done in combination with the use of statins for lipid control and effective treatment of hyperglycemia in patients with impaired glucose metabolism or type 2 diabetes. Among the RAS blockers, some drugs have accumulated more evidence than others.

Examples are: (i) ramipril in HOPE (Heart Outcomes Prevention Evaluation) and ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial); (ii) perindopril in PROGRESS (Perindopril PROtection aGainst REcurrent Stroke Study), ADVANCE (Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation), and HYVET (Hypertension in the Very Elderly Trial); (iii) losartan in LIFE (Losartan Intervention For Endpoint Reduction in hypertension); and (iv) telmisartan in ONTARGET (vide supra), to name some of the most well known. The aforementioned classic studies were aimed at assessing risk factor control in the first instance and not evaluation of the effect of the drug on arterial stiffness, although such an effect is likely to have contributed to the overall beneficial clinical effect of the drugs. In fact theoretically, differences in effects on arterial stiffness and central blood pressure could contribute to some of the observed variation in the effects of different RAS blockers, but this has still to be proven. In ONTARGET, no difference in clinical effects was observed between patients treated with ramipril or telmisartan, or the combination of these two drugs. This suggests that these two RAS blockers at least are clinically comparable.

It has further been suggested that inflammation plays an important role in hypertension and atherosclerosis, and that inflammatory changes induced even in prehypertensive subjects can lead to increased arterial stiffness. The effects of perindopril on both inflammatory and aortic elasticity markers were tested in 109 hypertensive patients not taking any antihypertensive therapy. Aortic strain, aortic distensibility, aortic stiffness index, and inflammatory markers, including C-reactive protein, interleukin (IL)-1α, IL-1β, and tumor necrosis factor-α, were measured in all patients before and after 20 weeks of perindopril therapy. While aortic strain and distensibility showed statistically significant increases with perindopril therapy, measures on the aortic stiffness index and inflammatory markers were found to decrease. The authors therefore concluded that perindopril therapy resulted in an improvement in aortic elastic properties. There was also an attenuation of the inflammatory status of patients, as reflected by lower inflammatory marker levels compared with pretreatment values.

New drugs for potential treatment of EVA

New drugs are under development for control of hypertension, hyperlipidemia, and diabetes. These drugs should also be tested for their ability to counteract arterial stiffness, endothelial dysfunction, vascular remodeling, and target organ damage.

Examples of such new drugs are: (i) renin antagonists, angiotensin AT1 receptor agonists, and vasopeptidase inhibitors for treatment of hypertension; (ii) cholesteryl ester transfer protein (CETP) antagonists for increasing high-density lipoprotein (HDL) cholesterol; and (iii) the new incretin-acting drugs for treatment of type 2 diabetes. The latter class of drugs is of special interest regarding characterization incretin receptors for glucose-dependent insulinoptive poly-peptide (GIP) and glucagon-like peptide-1 (GLP-1) in the heart and vasculature. Other new drugs are being developed for enhancement of the regular vasodilatory effects of normal endothelium. All these drugs have to be evaluated in randomized control trials, and many such trials are ongoing already.

Other more specific drugs for counteracting EVA and the aging process may be the so-called advanced glycation end product (AGE) modifiers, or AGE-breakers. So far, these have been shown to be more effective in animal studies than in human studies. Research activities are also ongoing regarding manipulation of more complex biological systems such as the Klotho system, and manipulation of telomerase function for regulation of telomere length, or testing of farnesyl transferase inhibitors in patients with Hutchinson-Gilford progeria, a complex disorder involving premature aging, although this is still at present futuristic.

Conclusions

The EVA syndrome has recently been proposed as a new concept in cardiovascular medicine to help better understand the importance of aging of the arterial tree and the CVD risk associated with this. It is important that we gain a better understanding of EVA, and find ways to define it if possible. Broad risk factor intervention is needed in patients at risk; for
example, those with a positive family history of early-onset CVD manifestations. Control of hypertension is a high priority, and based on existing evidence, it appears that agents blocking the RAS are useful for counteracting arterial stiffness and remodeling of the arterial wall. ACE inhibitors and ARBs are now well-proven drugs for achievement of this, one such drug being perindopril, which has shown beneficial results on cardiovascular events and mortality reduction in several intervention trials when combined with indapamide. This approach brings “ADAM” (aggressive decrease of atherosclerosis modifiers) to EVA for risk factor control in subjects at increased risk[13]—and the earlier the better.

References

Keywords: arterial stiffness; cardiovascular disease; EVA (early vascular aging); fetal development; hypertension; pulse wave velocity; renin-angiotensin system; vascular aging

Preventing early vascular aging (EVA) – Nilsson

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Depuis quelques années, le concept de vieillissement vasculaire précoce (EVA, early vascular aging) s’impose comme un outil utile pour comprendre les liens entre l’augmentation du risque cardio-vasculaire et le processus du vieillissement biologique. L’élément central en est la rigidité artérielle, qui se traduit par une vitesse de l’onde de pouls (PWV, pulse wave velocity) augmentée par rapport à l’âge et au sexe du sujet. La prévention du vieillissement vasculaire précoce doit débuter tôt car on sait que les facteurs y contribuant se manifestent dès la vie fœtale, l’enfance et l’adolescence. La première priorité concerne l’amélioration de l’hygiène de vie et, chez l’adulte, le traitement médicamenteux pour contrôler les facteurs de risque comme l’hypertension, l’augmentation de la variabilité tensionnelle, l’hyperglycémie et l’hyperlipidémie. Les antihypertenseurs les plus utiles dans ce contexte sont les agents bloquant le système rénine-angiotensine. Ceux-ci ont des effets bénéfiques sur la réduction de la pression artérielle centrale, du remodelage de la paroi artérielle et du risque cardio-vasculaire, ainsi qu’il en ressort des études HOPE (Heart Outcomes Prevention Evaluation), PROGRESS (Perindopril pROtection aGainst REcurrent Stroke Study), ADVANCE (Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation), HYVET (Hypertension in the Very Elderly Trial), ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial), et LIFE (Losartan Intervention For Endpoint reduction in hypertension). Les approches actuelles se concentrent sur les voies du processus du vieillissement vasculaire, comme par exemple la rupture des liaisons génétiques associées à la glycémie ou la manipulation biologique des téléomères ou des fonctions endothéliales. Toutes ces approches semblent prometteuses pour l’avenir.
The endothelium plays a crucial role in the regulation of vascular tone and structure through production of several substances, the most important of which is nitric oxide. Endothelial dysfunction, a condition characterized by impaired nitric oxide availability, is considered a main promoter of atherothrombosis. An important mechanism determining endothelial dysfunction is the activity of the tissue renin-angiotensin system. In patients with cardiovascular risk factors or coronary artery disease, chronic overexpression of tissue angiotensin-converting enzyme disrupts the angiotensin II/bradykinin balance with a net result of endothelial dysfunction, mainly due to an increased production of oxidative stress and apoptosis. Imbalance between increased endothelial cell apoptosis and decrease in endothelial cell renewal from the bone marrow causes discontinuity of the endothelial layer, favoring the initiation and progression of a biochemical sequence that leads to atherosclerosis, plaque rupture, and eventually acute coronary syndromes. Thus, reversal of vascular functional and structural alterations is crucial to determine whether pharmacological treatment is having a beneficial effect. A large body of scientific evidence indicates that perindopril has a specific efficacy on both the molecular and functional aspects of endothelial dysfunction and arterial stiffness. These effects are important for the prevention of atherosclerosis in patients with cardiovascular risk factors and of clinical events in patients with cardiovascular risk factors or established coronary artery disease.

Since the pioneering report by the 1998 Nobel Prize winner Robert Furchgott on the obligatory role of endothelium in vascular relaxation in response to acetylcholine, an impressive array of evidence has made it possible to state today that vascular endothelium plays a primary role in the control of vascular function and structure through the production of nitric oxide (NO). NO derives from the transformation of L-arginine into citrulline through the activity of the constitutive endothelial enzyme NO synthase (eNOS). NO is produced and released either basally or under the influence of agonists, such as acetylcholine, bradykinin, substance P, serotonin, and others acting on specific endothelial receptors, and by mechanical forces, such as shear stress. Other endothelium-derived relaxing factors include prostacyclin and the production of various endothelium-derived hyperpolarizing factors (EDHFs), which represent a compensatory vasodilating pathway triggered by reduced NO availability. In several pathological conditions, activation of endothelial...
cells can lead to the production and release of prostanoids (thromboxane A₂ and prostaglandin H₂), which are cyclooxygenase-derived endothelium-derived contracting factors (EDCFs) that counteract the relaxing activity of NO, and reactive oxygen species (ROS), which impair endothelial function by causing NO breakdown. Reactive oxygen species (ROS), mainly superoxide anion, trap NO to form substances like peroxynitrite, which are thought to alter vascular function and structure. NO and EDCF not only exert an opposite effect on vascular tone, but NO also inhibits, and EDCF activates, platelet aggregation, vascular smooth muscle cell proliferation and migration, monocyte adhesion, adhesion molecule expression, apoptosis, and cell regeneration, which exert an important role in the genesis of thrombosis and of the atherosclerotic plaque.

**Assessment of endothelial function in humans**

*Vascular reactivity tests*

The autocrine/paracrine activity of endothelial cells makes it very difficult to investigate endothelial function in clinical research. Usually, this requires vascular reactivity studies. It is possible to activate or inhibit endothelial cells in several vascular regions and measure the changes in the vessels induced by experimental manipulation. Endothelial cells respond to agonists acting on specific receptors (acetylcholine, bradykinin...) or by increasing shear stress (flow-mediated dilation (FMD)). In addition, it is possible to block pathways involved in endothelial responses such as NOS activity (by NG-nitro-L-arginine [L-NMMA]), hyperpolarization of vascular smooth muscle cells (by ouabain), cyclooxygenase activity (by indomethacin), or oxidative stress (by antioxidants such as vitamin C). In describing the approach to the evaluation of endothelium-dependent mechanisms in humans, it is crucial to consider the type of vascular bed to be investigated. A distinction should be made between macrocirculation (large arteries) and microcirculation. These two vessel types are subjected to different types of regulation and therefore results obtained in large arteries cannot be extrapolated to the microcirculation. Valuable large arteries include brachial (most frequently), radial, femoral, and epicardial arteries. The microcirculation can be evaluated in peripheral muscle (usually the forearm), subcutaneous tissue, skin, and the coronary circulation.

*Circulating markers of endothelial function*

Use of circulating markers of endothelial function was recently introduced. These include direct products of endothelial cells that change when the endothelium is activated, such as measures of NO biology, inflammatory cytokines, adhesion molecules, as well as markers of endothelial damage and repair.

A promising method for assessing endothelial function by means of circulating markers is to determine the rate of endothelial cell death and regeneration. Imbalance between endothelial apoptosis (death) and renewal from the bone marrow (life) causes discontinuity of the endothelial layer, favoring the initiation and progression of a biochemical sequence that leads to atherosclerosis, plaque rupture, and eventually acute coronary syndromes. Circulating endothelial apoptotic cells or endothelial progenitor cells (CEPCs) can be counted, providing a novel and exciting means of monitoring the determinants of endothelial injury and repair. The expression of surface markers on CEPCs can be measured, but because a wide range of hematopoietic progenitor cells have the potential to adopt an endothelial phenotype, the specificity of these measurements is debated. Other methods to characterize CEPC biology include quantification of the potential to differentiate into an endothelial cell phenotype, as well as determination of functional characteristics, which include migration toward a chemical stimulus, adhesion, formation of vascular tubules, and the ability to attenuate ischemia in animal models.

**Clinical significance of endothelial dysfunction**

In patients with cardiovascular risk factors, endothelial dysfunction is considered as a common mechanism deeply affecting vascular function and structure, including vasomotor function and promotion of atherosclerosis and thrombosis, thereby contributing to cardiovascular events. This is supported by mounting evidence showing the association of endothelial dysfunction with markers of vascular damage and with

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**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADVANCE</td>
<td>Action in Diabetes and Vascular disease: Preteraxand DiamicroN-MR Controlled Evaluation</td>
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<tr>
<td>BANFF</td>
<td>Brachial Artery Normalization of Forearm Function [trial]</td>
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<tr>
<td>BK</td>
<td>bradykinin</td>
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<tr>
<td>CAD</td>
<td>coronary artery disease</td>
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<tr>
<td>CEPC</td>
<td>circulating endothelial progenitor cell</td>
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<tr>
<td>DAPHNET</td>
<td>Diabetes Artery Perindopril Hypertension Normalization Excess (s)Tiffness</td>
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<tr>
<td>EDCF</td>
<td>endothelium-derived contracting factor</td>
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<tr>
<td>EDHF</td>
<td>endothelium-derived hyperpolarizing factor</td>
</tr>
<tr>
<td>ENCORE</td>
<td>Evaluation of Nifedipine and Cervastatin On Recovery of coronary Endothelial function</td>
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<tr>
<td>eNOS</td>
<td>endothelial nitric oxide synthase</td>
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<tr>
<td>EUROPA</td>
<td>EUropean trial on Reduction Of cardiac events with Perindopril in stable Artery coronary disease</td>
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<tr>
<td>FMD</td>
<td>flow-mediated dilation</td>
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<tr>
<td>NO</td>
<td>nitric oxide</td>
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<tr>
<td>PERTINENT</td>
<td>PERindopril—Thrombosis, InflammatioN, Endothelial dysfunction and Neurohormonal activation Trial</td>
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<tr>
<td>PERSPECTIVE</td>
<td>PERindopril’S Prospective Effect on Coronary (a)Therosclerosis byIntraVascular ultrasound Evaluation</td>
</tr>
<tr>
<td>PROGRESS</td>
<td>Perindopril (p)ROtection aGainst REcurrent Stroke Study</td>
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<tr>
<td>RAS</td>
<td>renin-angiotensin system</td>
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<td>ROS</td>
<td>reactive oxygen species</td>
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cardiovascular events, both in patients with essential hypertension and, more generally speaking, in patients with atherosclerotic disease. A recent meta-analysis by Lerman and Zeiher evaluated the available longitudinal studies relating to the prognostic impact of endothelial dysfunction. This meta-analysis included around 2500 patients with atherosclerotic coronary disease or at high cardiovascular risk. The outcomes, evaluated over a wide follow-up range (from 1 to 92 months) included major cardiovascular events. The authors observed that endothelial dysfunction, evaluated either in the coronary territory or in the peripheral circulation, significantly predicted cardiovascular disease or at high cardiovascular risk. The outcomes, analysis included around 2500 patients with atherosclerotic coronary artery disease (CAD).

**Treatment of endothelial dysfunction**

Since impaired endothelium-dependent vasodilation promotes atherosclerosis and cardiovascular events in patients with cardiovascular risk factors, eg, essential hypertension, improving impaired endothelial function is an important treatment target. However, blood pressure lowering with antihypertensive therapy is not sufficient per se to reverse endothelial dysfunction. Thus, antihypertensive compounds, beyond their ability to reduce blood pressure, need to have additional specific properties to restore endothelial function. Diuretics or β-blockers show little evidence of being able to restore endothelial dysfunction in patients with hypertension or CAD. In contrast, renin-angiotensin system (RAS) blockers and calcium antagonists are strongly associated with a beneficial effect on endothelial dysfunction in patients with hypertension or CAD. However, this beneficial effect differs depending on which drug class or vascular district is considered.

**Calcium antagonists**

In patients with hypertension, a wide range of calcium antagonists—including amlodipine, isradipine, lacidipine, lercanidipine, nifedipine, verapamil, and diltiazem—have been shown to improve endothelial function, suggesting that all these agents share a class effect. Schiffrin and Deng found that nifedipine GITs (gastrointestinal therapeutic system) normalized endothelial function as well as the structure of gluteal subcutaneous small arteries. Conversely, use of atenolol in similar patients resulted in equally well-controlled blood pressure, but abnormal endothelial function and thicker small arteries. Taddei et al reported a decrease in circulating plasma lipoperoxides and isoprostanes, an increase in plasma antioxidant capacity, and an improved forearm vasodilator response to acetylcholine in a study in 15 hypertensive patients vs 15 healthy subjects after 3 months of nifedipine treatment.

Investigators have also examined the effects of calcium antagonists on endothelium-mediated vasodilation in patients with CAD. ENCORE I (Evaluation of Nifedipine and Cerivastatin On Recovery of coronary Endothelial function–I) showed a significant reduction in acetylcholine-induced vasoconstriction in patients with CAD receiving nifedipine. However, results are not universally positive, and calcium antagonists failed to improve endothelial function, assessed by measurement of brachial artery FMD, in hypertensive patients or patients with CAD.

**RAS inhibitors: are ACE inhibitors and ARBs equally effective in reversing endothelial dysfunction?**

The possibility that angiotensin-converting enzyme (ACE) inhibitors may improve endothelial function has been raised following reports in the literature from experimental studies showing that the RAS—and in particular angiotensin II—plays a dramatic role in inhibiting NO production and activity, mainly by inducing ROS generation. However, this hypothesis on the role of angiotensin II is not the only explanation for the efficacy of ACE inhibitors regarding endothelial function, since the literature suggests a significant superiority of this drug class vs angiotensin II type 1 (AT1) receptor antagonists, at least in certain clinical situations.

The BANFF study (Brachial Artery Normalization of Forearm Function) compared the effect of drugs belonging to different classes on endothelial function by assessing brachial artery flow-mediated dilation, is improved by chronic treatment with perindopril, whereas other antihypertensive drugs have no effect.

**Figure 1. Effect of antihypertensive drugs on conduit artery endothelial function.**

In hypertensive patients, reduced endothelial function, assessed as brachial artery flow-mediated dilation, is improved by chronic treatment with perindopril, whereas other antihypertensive drugs have no effect.


An important confirmation of these findings derives from a study that enrolled a large population (n=168) of essential hypertensive patients (Figure 1) and compared the effects of...
the principal classes of antihypertensive drugs on peripheral conduit artery endothelial dysfunction (by measuring brachial artery FMD) in essential hypertension.13 The drugs compared in the study were the ACE inhibitor perindopril, the AT1 receptor antagonist telmisartan, the β-blockers atenolol and nebivolol (the latter expected to be effective on endothelium-dependent vasodilation), and the calcium antagonists amlopidine and nifedipine. The only compound able to improve endothelial function was perindopril, while the other drugs, including the AT1 receptor antagonist telmisartan, failed to increase endothelium-dependent vasodilation. In addition to perindopril’s specific ability to improve FMD in the peripheral circulation, its action was also confirmed in coronary epicardial arteries in patients with essential hypertension. In these patients, acute endovenous administration of perindopril restored normal vascular response to endothelial stimuli, thereby determining an increase in coronary flow.21

Under other experimental conditions, AT1 receptor antagonists can improve endothelial function—an effect shared by the ACE inhibitors. However, analysis of the literature indicates that inhibition of converting–enzyme activity has a greater efficacy than blockade of the AT1 receptor.14

![Image of table]

Table I. Evidence-based vascular protection with perindopril

Endothelial and vascular dysfunction: is there a specific role for perindopril?

To date, perindopril is the only compound with documented efficacy on several parameters reflecting vascular dysfunction or structural alterations in the different segments of the arterial tree (Table I).16,21-26 Several hypotheses can be raised to explain perindopril’s specific efficacy.

One such hypothesis concerns the tissue affinity of ACE inhibitors. It is now well documented that vascular homeostasis is regulated by tissue RAS and, therefore, that vascular absorption is crucial for drug efficacy on endothelial function or arterial structural alterations.23 Perindopril is the ACE inhibitor with the greatest documented vascular absorption in comparison with other drugs of the same class, including quinapril, ramipril, enalapril, fosinopril, and captopril.20 This specific characteristic may therefore be one of the possible explanations for perindopril’s unique effects on vascular function and structure.

Another important mechanism, too often forgotten, is the reduction in bradykinin (BK) breakdown determined by ACE blockade.23 BK is an important autacoid with significant effects on endothelium. In addition to the classic stimulation of the NO pathway,21 BK can also release EDHFs,24 which represent an important compensatory mechanism when NO availability is reduced as observed in presence of cardiovascular risk factors, including hypertension.4 EDHFs can not only determine endothelium-dependent vasodilation, but can also positively modulate thrombotic risk by activating endothelial tissue plasmin activator (tPA).22 The ability of BK to stimulate EDHF production in presence of reduced NO availability is not shared by other classic endothelial activators, including acetylcholine.22

The ability of ACE inhibitors to increase BK tissue concentration by blocking its degradation could be an important mechanism for vascular protection, especially in the presence of cardiovascular risk factors or CAD, which cause endothelial dysfunction by NO inactivation. In these patients, chronic overexpression of tissue ACE disrupts the angiotensin II/BK balance, with increased and decreased tissue levels of angiotensin II and BK, respectively, the net result being endothelial dysfunction. The latter is characterized by augmentation of oxidative stress and inflammation with the consequent impairment of NO availability and increase in endothelial damage and apoptosis.23 Apoptosis is an emerging concept in cardiovascular medicine. Thus, endothelium undergoes a life and death cycle, characterized by a programmed cell suicide (apoptosis) associated with subsequent regeneration.23 Imbalance between endothelial apoptosis and regeneration is now considered a promoter of atherosclerosis.23

However, the effect of the different ACE inhibitors on angiotensin II/BK balance and the rate of apoptosis varies markedly. ACE has two different catalytic domains, one cleaving angiotensin I, the other inactivating BK.34 When the ACE inhibitors enalaprilat, perindoprilat, quinaprilat, ramiprilat, and trandolaprilat were tested to compare their binding affinity for the two ACE domains, two major findings emerged. First, all ACE inhibitors have a greater affinity for the BK than for the angiotensin I binding site, supporting the concept that these compounds are primarily inhibitors of BK degradation rather than inhibitors of angiotensin II production.25 Second, perindoprilat has the highest selectivity for the BK binding site while trandolaprilat and enalaprilat had the lowest one (Figure 2).16,34

The effect of the aforementioned ACE inhibitors (enalapril, perindopril, quinapril, ramipril, and trandolapril) on the rate of endothelial apoptosis was assessed in vivo in rats. Apopto-
events in EUROPA, confirming the relevance of endothelial alterations in determining cardiovascular prognosis. One-year treatment with perindopril was able to reduce vWF. In addition, plasma levels of angiotensin II, BK, tumor necrosis factor-α (TNF-α), nitrite/nitrate, and endothelial function at the cellular level by determining protein expression/activity of eNOS and the rate of apoptosis were also measured at baseline and after 1 year of treatment with either perindopril or placebo. At baseline, CAD patients showed decreased BK and increased angiotensin II plasma concentrations, respectively, compared with healthy controls. However, perindopril caused a significant reduction in levels of angiotensin II and an increase in BK, therefore normalizing the BK/angiotensin II ratio. In addition, perindopril also decreased TNF-α and increased nitrite/nitrate (P<0.05 for all). Finally, perindopril upregulated the protein expression/activity ratio of eNOS by 19%/27% (P<0.05) and reduced the rate of apoptosis by 31% (P<0.05) (Figure 3).22

Taken together, these results demonstrate: (i) an excess of angiotensin II and TNF-α (proapoptotic substances by increasing oxidative stress) and a reduction in BK (an antiapoptotic substance) cause endothelial dysfunction and increase apoptosis; (ii) treatment with perindopril restores a normal balance between angiotensin II and BK and reduces inflammation (TNF-α), thereby reversing endothelial dysfunction and preventing apoptosis.

As previously stated, while apoptosis is a marker of endothelial cell death,23 CEPCs are an important marker of endothelial cell regeneration,4 a crucial mechanism to maintain the integrity of the endothelial layer. Thus, to completely prevent endothelial dysfunction, optimal treatment should not only inhibit apoptosis, but also stimulate CEPC production. In experimental conditions, perindopril was shown to increase the number of CEPCs in the spontaneously hypertensive rat

**Figure 2.** Comparative affinity of ACE inhibitors for bradykinin vs angiotensin I binding sites.

The study compares different ACE inhibitors in terms of selectivity for bradykinin vs angiotensin I binding sites. Perindopril has the highest selectivity for bradykinin vs angiotensin I binding sites, and enalapril has the lowest. The resulting greater endogenous concentrations of bradykinin may explain, at least in part, the beneficial vascular effects of perindopril. 

Abbreviations: ACE, angiotensin-converting enzyme; Ang I, angiotensin I; BK, bradykinin.


**Figure 3.** Results from the PERTINENT study. 

Rate of apoptosis in human umbilical vein endothelial cells incubated with in serum from healthy controls or in serum collected from PERTINENT patients at baseline and after 1 year. Perindopril significantly reduces the rate of apoptosis vs placebo.22

Abbreviations: CAD, coronary artery disease; PERTINENT, Perindopril—Thrombosis, Inflammation, Endothelial dysfunction and Neurohormonal activation Trial.

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New evidence for endothelial protection – Taddei
(SHR) with hindlimb ischemia, while losartan has no effect on the number of CEPCs.\textsuperscript{23,37} Perindopril also reverses structural alterations, as shown in the DAPHNET study (Diabetes Artery Perindopril Hypertension Normalization Excess sTiffness),\textsuperscript{25} which found a direct blood pressure–independent effect of perindopril on arterial stiffness. The study enrolled hypertensive patients with type 2 diabetes whose blood pressure values were normalized by perindopril 4 mg daily. Patients were then randomized to continue on the 4-mg daily dose or increase to 8 mg daily while carotid distensibility was measured at baseline and after 7 months of treatment. It was found that, despite similar blood pressure control, only perindopril 8 mg daily reduced carotid stiffness, suggesting a specific effect on vessel structure (Figure 4). This study again underlines that mere blood pressure control is not the only parameter to take into account to determine the efficacy of antihypertensive treatment, and that more specific organ protection can be obtained with higher doses, which should always be used in high-risk patients. With regard to aortic structural changes, a comparative study\textsuperscript{28} showed that perindopril decreased aortic pulse wave velocity, an established marker of aortic stiffness; this effect was also seen with the comparator dihydropyridine calcium-channel blocker, but not with the diuretic or the \( \beta \)-blocker. Finally, in a large population of hypertensive patients, perindopril had a positive effect on aortic elastic properties associated with an attenuation of inflammatory status assessed by the measurement of C-reactive protein, interleukin 1\( \alpha \) and 1\( \beta \), and TNF-\( \alpha \).\textsuperscript{38}

The improvement in functional and structural vascular alterations with perindopril contributes to preventing atherosclerosis, as shown by the PERSPECTIVE study (PERindopril’S Prospective Effect on Coronary aTherosclerosis by IntraVascular ultrasound Evaluation),\textsuperscript{26} another substudy of the EUROPA program. This study evaluated the progression of coronary atherosclerosis by intracoronary ultrasound in coronary segments containing noncalcified or calcified plaques in 118 CAD patients enrolled in EUROPA study. A post hoc analysis assessed the effect of perindopril vs placebo on progression/regression of atherosclerosis based on the degree of calcification. Findings were as follows: (i) coronary plaques with no or little calcium (0\%-25\%) regressed on perindopril, but did not change on placebo (-0.33±1.74 vs -0.03±1.66, respectively; \( P=0.04 \)); (ii) plaques with moderate calcium content (group 25\%-50\%) did not change; and (iii) plaques with high calcium content (group 5\%-100\%) progressed similarly. The important conclusion of the study is that noncalcified plaques may be amenable to regression with perindopril treatment. PERTINENT is the only study to have evidenced the ability of an ACE inhibitor to prevent progression of atherosclerosis in the coronary circulation in vivo.

**Conclusions**

Endothelium plays a central role in the maintenance of vascular homeostasis. Tests have been developed to study endothelial function in humans and assess its changes in relation with subclinical and clinical target organ damage as well as the effect of treatment. Endothelial dysfunction and structural vascular alterations are of particular clinical relevance since they promote atherosclerosis and thrombosis, which are typical complications of hypertension and other cardiovascular risk factors, and thereby play a key role in the occurrence of clinical events.

Not all cardiovascular drugs are able to reverse endothelial and structural dysfunction. Analysis of the literature clearly indicates that perindopril has a unique profile of action, characterized by its effect on both the molecular and functional aspects of endothelial dysfunction and arterial stiffness. This effect has important implications for the prevention of atherosclerosis in patients with cardiovascular risk factors and of clinical events in patients with established CAD. A recent meta-analysis of EUROPA,\textsuperscript{26} ADVANCE (Action in Diabetes and Vascular disease: PreterAx and Diamicron Modified-Release Controlled Evaluation),\textsuperscript{39} and PROGRESS (Perindopril pROtection Against REcurrent Stroke Study)\textsuperscript{40} provides strong evidence in favor of consistent cardiovascular protection with a perindopril-based regimen, by improving survival and reducing the risk of major cardiovascular events.\textsuperscript{31} These specific vascular properties of perindopril may account, at least in part, for the documented superiority of this compound in the prevention of cardiovascular disease.
References


Keywords: ACE inhibitor; angiotensin II; bradykinin; cardiovascular risk factor; coronary artery disease; endothelium; hypertension; large artery, microcirculation; nitric oxide; perindopril
PROTECTION ENDOTHÉLIALE : ACQUISITIONS RÉCENTES

L’endothélium joue un rôle crucial dans la régulation de la structure et du tonus vasculaires par l’intermédiaire de plusieurs substances, dont la plus importante est le monoxyde d’azote. La dysfonction endothéliale, un désordre caractérisé par une altération de la disponibilité du monoxyde d’azote, est considérée comme un des principaux facteurs favorisants de l’athérothrombose. L’activité du système rénine-angiotensine tissulaire est un important mécanisme déterminant la dysfonction endothéliale. Chez les patients ayant des facteurs de risque cardio-vasculaires ou une maladie coronaire, une surexpression chronique de l’enzyme de conversion de l’angiotensine tissulaire rompt l’équilibre angiotensine II/bradykinine entraînant une dysfonction endothéliale, principalement due à une augmentation de production du stress oxydatif et de l’apoptose. Le déséquilibre entre l’augmentation de l’apoptose des cellules endothéliales et la diminution du renouvellement de ces cellules dans la moelle osseuse provoque une discontinuité de la couche endothéliale, favorisant l’amorce et la progression d’une séquence biochimique qui conduit à l’athérosclérose, à la rupture de la plaque et finalement au syndrome coronaire aigu. Ainsi, l’inversion des altérations vasculaires fonctionnelles et structurelles est capitale pour déterminer si le traitement pharmacologique présente un effet bénéfique. De nombreuses études indiquent que le périndopril a une efficacité spécifique à la fois sur les aspects moléculaires et fonctionnels de la dysfonction endothéliale et de la rigidité artérielle. Ces effets sont importants pour la prévention de l’athérosclérose chez les patients ayant des facteurs de risque cardio-vasculaires et pour la prévention des événements cliniques chez les patients ayant des facteurs de risque cardio-vasculaires ou une maladie coronaire établie.
Blood pressure variability (BPV), recognized for many years as being a risk for cardiovascular outcome, has recently become a focus of attention because of a number of studies showing that increased variability predicts cardiovascular outcome, especially stroke, and that different drug classes may affect variability, either beneficially, by reducing it, or detrimentally, by increasing it. The recent literature emphasizes the importance of reducing mean blood pressure levels, as is recommended in all the guidelines; however, physicians are now obliged to consider drugs, such as calcium channel blockers, that have been shown to reduce BPV. Prescribing drugs, such as the older β-blockers, which increase BPV, should be carefully considered in the context of the overall cardiovascular status of the patient. The recent introduction of flexipills containing combinations of drugs, such as amlodipine/perindopril, that reduce both mean blood pressure levels and BPV provides the practicing physician with the option of achieving two desirable targets of treatment. The measurement of short-term BPV can be readily achieved with ambulatory blood pressure measurement, whereas the measurement of long-term visit-to-visit variability is not so easily achieved in routine practice.

In a recent review on blood pressure variability (BPV), Peter Rothwell argues that the management of hypertension has been clouded by the fact that physicians and scientists have been distracted from consideration of variability by giving obsessional attention to mean blood pressure (BP). The hypertension guidelines, which insist on reduction of BP per se and remove BP variability from consideration, may have done science a disservice by obscuring the influence of BPV on cardiovascular outcome. Indeed, though a reduction in BP makes a very valuable contribution to outcome, it does not always account fully for the benefit of therapeutic intervention, which also might be due, in part, to a reduction in BPV. This review will examine the role of BPV, especially for the potential it offers as a new target for treatment.

Blood pressure variability

In discussing BPV, it is important to recognize two forms of variability—short-term BPV, which is the variability of BP over minutes or hours, such as is seen on 24-hour ambulatory blood pressure measurement (ABPM), and long-term BPV, such as is seen with repeated recordings over weeks or months, and which is often called visit-to-visit BPV.
Short-term BPV

The prognostic significance of short-term BPV as a predictor of poor cardiovascular outcome has been documented for many years in different cohorts of initially untreated or treated hypertensive subjects, and in general populations. If standard deviations are used as a measure of BPV, these are usually around 10-15 mm Hg for the daytime and 5-10 mm Hg for the nighttime periods. Studies of the prognostic value of ABPM have been limited by tending to consider only the mean values of BP, or the day-night differences in BP. The results of these studies have often been conflicting, because of the variety of ways in which BPV is expressed, eg, standard deviation or coefficient of variation; the period selected for the assessment of BPV, eg, day, night, or 24-hour periods; and the blood pressure selected, eg, systolic blood pressure (SBP) or diastolic blood pressure (DBP).

As far back as 1987, Parati’s group demonstrated that higher diurnal BPV measured by ABPM over 24 hours was associated with an increased risk of left ventricular hypertrophy. His group has continued to highlight the importance of BPV as a prognostic marker. It has been known for many years that the manifestations of BPV seen during the day and night windows of a 24-hour period, such as nocturnal dipping and the morning surge, are independently related to organ damage and the risk of cardiovascular events. However, in a large population cohort (8938 subjects), though short-term reading-to-reading BPV with ABPM was an independent risk factor, the level of the 24-hour ABPM was the primary BP-related risk factor to be addressed in clinical practice.

Long-term BPV

Data from Framingham showing that cardiovascular events did not appear to be related to BPV drew attention away from variability as a risk over the longer term. However, several randomized controlled trials have shown a strong association of long-term BPV in systolic BP recorded over several visits with stroke and coronary heart disease risk.

Rothwell and his colleagues have recently shown that SBP variation over time and from one visit to the next may be associated with a poor cardiovascular prognosis. Higher visit-to-visit variability in SBP was also associated with stroke and coronary events in treated hypertensive patients enrolled in ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm). BPV between visits and maximum BP reached in 4 cohorts of patients with previous transient ischemic attacks were strong predictors for subsequent stroke. In treated hypertensive patients in ASCOT-BPLA, SBP variation between visits was also a strong predictor of stroke and coronary events, independent of mean clinic BP or ABPM. Variation of ABPM was a weaker predictor overall, but this was related to visit-to-visit variability. Patients with well controlled BP, but high residual variability in SBP had a five times higher risk of stroke than did those with low residual SBP variability in ASCOT-BPLA.

The evidence supporting the influence of BPV on prognosis does not question the importance of lowering BP, as is recommended in all the guidelines, but rather draws attention to BPV as an additional target, which if modified by treatment might confer a benefit above that of reducing BP alone.

The prognostic importance of visit-to-visit BPV has recently received further support from a population-based study in US adults in whom higher visit-to-visit variability in SBP was associated with increased mortality risk over a 14-year follow-up. There was no such association with visit-to-visit variability in DBP. This study has some additional strengths, as observed by Mancia. Firstly, the data analyzed were obtained in a general population distinct from the Rothwell cohorts, which came from clinical trial recruits. Secondly, the study analysis showed that factors, such as female sex, a history of myocardial infarction, diabetes, and several measures of organ damage (albuminuria, estimated glomerular filtration rate, and pulse pressure) also influenced visit-to-visit BPV. Of particular interest, the relationship of visit-to-visit BPV with all-cause mortality was also present in subjects with normal BP, suggesting that visit-to-visit BPV may be a prognostic marker even before BP becomes elevated.

Pathogenic mechanisms of BPV

The main consequence of BPV seems to be its effect on the brain, which is very susceptible to fluctuations in BP. Instability of BP is associated with brain atrophy, subcortical lesions, and cognitive impairment. Several hypotheses have been proposed for mechanisms underlying higher levels of visit-to-visit variability in BP. One of the major factors facilitating BPV may be arterial stiffness. Pulse pressure and older age, which are both directly associated with arterial stiffness, have been shown to be independently associated with higher visit-to-visit variability in SBP. The association of arterial stiffness with BPV is further strengthened by the strong association of the ambulatory arterial stiffness index (AASI) with stroke. The AASI, which is a measure of the dynamic relation between DBP and SBP throughout the entire day, has been shown to predict cardiovascular mortality in a large co-
hort of hypertensive individuals. Furthermore, compared with pulse pressure, the AASI is a stronger predictor of fatal stroke in patients with ambulatory normotension than in patients with hypertension. This important association is similar to the finding of a study in which visit-to-visit BPV predicted all-cause mortality in subjects in whom BP was normal, suggesting that visit-to-visit BPV may be a prognostic marker even before BP becomes elevated. The importance of these remarkable associations is twofold: first, both BPV and the AASI may predict outcome in patients even before BP becomes elevated, thereby providing a means of identifying patients at risk before they develop hypertension, and second, it is possible that the AASI, which is a measure of short-term BPV obtainable for a single ABPM, might be of equal prognostic importance to visit-to-visit BPV, which is only obtainable from repeated BP measurements.

Other mechanisms that might be accountable for increased BPV include baroreflex regulation of BP, inflammation, and heart rate variability. Whereas one study has shown that, in addition to BPV, heart rate variability may also have prognostic significance, other evidence indicates that decreased (not increased) heart rate variability is associated with an increased risk of mortality, suggesting that heart rate variability does not influence the relationship between BPV and mortality.

**How can BPV be measured?**

**Measuring short-term BPV**

ABPM provides numerous values, beyond the arithmetic mean of the measurements, that are not utilized in clinical practice. The reduction in ABPM variability in ASCOT-BPLA almost mirrors visit-to-visit variability, which suggests that it may be possible, by concentrating on the many measures of variability already available within a single ABPM, to identify an index of ABPM BPV that would be equivalent to visit-to-visit BPV. Measures derived from the linear relationship between systolic and diastolic pressures are believed to be associated with mechanical properties of the arteries, especially with stiffening of the arteries with aging.

As has already been mentioned, the AASI provides a readily accessible measurement of both BPV and arterial stiffness. The AASI and its related slope have been shown to predict outcome and target organ damage. However, the value of the AASI as a measure of arterial stiffness has been questioned because of its strong dependence on age, sex, pulse pressure, and nocturnal BP decline. Perhaps more attention should be focused on the prognostic power of the AASI as a measure of BPV rather than on the mechanistic explanation for this association. Various modifications of the AASI have been proposed without much overall advantage over the original index, which is not to say that the incorporation of different mathematical models of the ABPM-derived index will not yield a more robust index. The appropriateness of standard deviation as an index of BPV has been questioned because it only reflects the dispersion of values around the mean and does not account for the order in which BP measurements are obtained. An alternative index, named average real variability, which is based on the total variability concept of real analysis in mathematics, and which is sensitive to the individual BP measurement order, has been proposed. This index of daytime SBP has been shown to be an independent predictor of cardiovascular events in hypertensive patients, whereas a high standard deviation is not.

**Measuring long-term BPV**

It is important to note that regardless of how BP is measured, whatever the associations attributed to long-term BPV, they apply only to systolic BP. No association has been shown between visit-to-visit BPV in DBP and all-cause mortality. For example, in the Honolulu Heart Program, variance of DBP across 4 visits was not associated with subsequent coronary heart disease incidence. In addition, in the UK-TIA (United Kingdom Transient Ischemic Attack) study, the visit-to-visit variability in DBP was not associated with stroke, and an association was present only in the highest deciles in ASCOT-BPLA.

Evidence suggests that visit-to-visit BPV is reproducible and not a random phenomenon. The UK-TIA study and the European Carotid Surgery Trial have shown that reproducibility of visit-to-visit BPV is good. In these studies, BPV was based on a single measurement at each visit; having multiple measurements at each visit results in a higher degree of reproducibility in the level of visit-to-visit BPV. However, the confounding effects of BP-measuring techniques and of BP-lowering treatment call for caution in the interpretation of results. For example, in the NHANES (National Health And Nutrition Examination Survey) study, the first set of BP measurements were obtained during an in-home examination, whereas the latter two sets of measurements were obtained during a medical evaluation conducted in a mobile examination center. Furthermore, whereas the in-home BP measurements were obtained by a research assistant, the clinic BP measurements were obtained by a physician.

In ASCOT-BPLA, BPV in mean daytime SBP on repeated ABPM correlated with visit-to-visit variability in clinic SBP, indicating a contribution from fluctuations in underlying blood pressure. Both within-visit variability in sitting SBP and daytime variability in SBP on ABPM were lower in the amlopidine/perindopril group than in the atenolol/thiazide group, but the latter was a weaker predictor of vascular events than was visit-to-visit variability and accounted less well for the reduced event rate in the amlopidine/perindopril group (Figure 1, page 28). This suggests that the larger variations in BP that are seen from visit to visit better reflect the factor or factors that are causally related to the risk of vascular events. Yet anoth-
er index, the average successive variability index, based on the average absolute difference between successive values, did not predict stroke, and accounted less well for the clinical benefit observed in the amlodipine/perindopril group versus the atenolol/thiazide group than did the standard deviation or coefficient of variation of SBP. It has been suggested that this index measures short-term changes between consecutive BP readings, whereas standard deviation or coefficient of variation from minute to minute (best exemplified as average successive variability on ABPM) does not capture elements of variability that are associated with risk of stroke. However, this index is as yet untested in standardized conditions and its application and the conclusions inferred must be seen as conceptual rather than proven.

How can BPV be treated?

It is clear from a review of the literature that increased BPV, both short-term and long-term, presents a threat for the development of stroke and other cardiovascular events. Hypertension is the most prevalent treatable risk factor for stroke. The current practice of reducing BP levels to normal throughout the day and nighttime periods is not in dispute. However, control of hypertension continues to be inadequate despite the excellent array of effective, well-tolerated medications. Recent data from the US indicates that approximately 28% of Americans with hypertension are unaware of their hypertension, 39% are not receiving therapy, and 65% do not have their BP controlled to levels below 140/90 mm Hg (Figure 2).

In Europe, the situation is even worse, where despite knowing for at least two decades the importance of BP control in preventing stroke and having more than enough drugs available to effectively treat hypertension, the “rule of halves” is operative in most European countries, only half the people in society with hypertension are aware that their BP is elevated; of those identified as having high BP, only half are on BP-lowering drugs; and of those receiving treatment, only half are well controlled. To which might be added, if BP control was achieved in those with undiagnosed hypertension or inadequately treated hypertension, the occurrence of stroke could be halved. In the three EUROASPIRE (EUROpean Action on Secondary and Primary prevention through Intervention to Reduce Events) studies conducted over a decade in specialized centers in Europe, there was no improvement in BP control despite large increases in prescriptions for all classes of antihypertensive drugs, ie, antihypertensive medication is

![Figure 1. Within-visit variability of systolic blood pressure in ASCOT.](image-url)
Stabilization of BPV is a potentially important target for drug development and combination therapy, and new drugs or combinations of drugs that reduce variability even more effectively than calcium channel blockers could greatly reduce the occurrence of stroke. Evidence from recent studies suggests that BPV, whether measured during clinic visits or by ABPM, is predictive of stroke and other cardiovascular events, and that calcium channel blockers—and to a lesser extent thiazide diuretics—are superior to other drugs in reducing BPV and preventing stroke and other vascular events. The evidence also suggests that the older β-blocker atenolol, which increases BPV, should probably only be used as a first-line drug if there are other compelling clinical indications, such as ischemic heart disease. It should be stressed that there is no evidence one way or the other that the newer generation of β-blockers affect BPV.

The recent introduction of what we have termed the “flexipill”—to distinguish it from its predecessor, the “polypill”—is a welcome therapeutic innovation. The pharmaceutical industry has now recognized the need for flexible dose combinations within one tablet allowing a prescribing physician to increase the dosage of the component parts in a single tablet according to BP response. In this regard, we now have flexipill combinations of angiotensin receptor blockers and angiotensin-converting enzyme inhibitors with calcium channel blockers, angiotensin receptor blockers and angiotensin-converting enzyme inhibitors with thiazide diuretics, and β-blockers and renin inhibitors with thiazide diuretics. Triple-drug combinations with flexible dosage options are about to be introduced. Quite apart from the advantages of being able to prescribe low doses of multiple drugs in one tablet—thereby minimizing the adverse effects that might occur with higher doses of the individual components—and the beneficial effects this should have on compliance, the flexipill provides a means of not only lowering BP, but of also reducing BPV by using medication with contrasting modes of action.

Recently, perindopril in combination with amlopidine has been shown to significantly reduce total and cardiovascular mortality as compared with atenolol/diuretic. A greater reduction in BPV, central BP, and specific vascular protective properties of perindopril (improvement in arterial stiffness and endothelial function) might explain these results.

The body of work highlighting the importance of BPV should focus the minds of clinical scientists, the pharmaceutical industry, those interested in BP measurement, and doctors who
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Keywords: ambulatory blood pressure index; blood pressure; cardiovascular outcome; mean blood pressure; treatment of variability

**Stabilisation de la variabilité de la pression artérielle : une nouvelle cible thérapeutique dans l’hypertension**

La variabilité de la pression artérielle (VPA), reconnue depuis de nombreuses années comme représentant un risque d'événements cardio-vasculaires, a récemment attiré l'attention du fait qu'un certain nombre d'études ont montré qu'une augmentation de la variabilité permet la prédictions d'événements cardio-vasculaires, et tout particulièrement les AVC, et que diverses classes de médicaments peuvent influer sur la variabilité, soit de façon bénéfique, en la réduisant, soit de façon négative en l'augmentant. La littérature récente insiste sur l'importance de réduire le niveau de la pression artérielle moyenne, selon les recommandations de toutes les directives ; cependant, les médecins sont maintenant tenus de prendre en compte les médicaments, comme les inhibiteurs calciques, qui réduisent la VPA. Néanmoins, la prescription des médicaments, comme les anciens β-bloquants, qui augmentent la VPA, devrait toujours être étudiée soigneusement dans le contexte de l'état cardio-vasculaire global du patient. L'introduction récente de comprimés flexibles contenant une association de médicaments, comme l'amlodipine/perindopril, qui diminue à la fois la pression artérielle moyenne et la VPA permet au médecin d’obtenir les deux buts souhaités du traitement. La mesure de la VPA à court terme peut être facilement réalisée par la mesure de la PA en ambulatoire, contrairement à la mesure de la variabilité à long terme à chaque visite, dont la mesure ne va pas si facilement de soi en pratique courante.
The skin circulation allows simple, noninvasive, and reproducible assessment of capillary density and endothelial function. There is evidence that capillary rarefaction in the skin may precede the clinical onset of essential hypertension, even in normotensive subjects with a familial predisposition to the disease... For a similar improvement in SBP and DBP, only perindopril/indapamide achieved significant improvement in capillary density and endothelial function, vs treatment with ARBs or β-blockers.”

Improvement of the coronary microcirculation: a desirable goal helping to reduce the incidence of coronary events

In hypertensive patients, there is a large body of evidence suggesting the presence of severe alterations in microvascular structure and function that are mainly characterized by capillary rarefaction, endothelial dysfunction, and decreased vasodilation reserve. Abnormal microcirculation contributes to the impairment of tissue perfusion and, thus, to end organ damage. Reversal and prevention of microvascular damage are thus potentially important clinical goals. Cutaneous circulation has emerged as an accessible and representative vascular bed that could enable the study of the mechanisms of microcirculatory function and dysfunction. Increased skin capillary density and cutaneous endothelial function have both been observed in successfully treated essential hypertensive patients compared with untreated hypertensive patients, suggesting a tight relationship between blood pressure and capillary density. Furthermore, hypertensive patients controlled on a perindopril/indapamide combination exhibit significantly greater capillary density and endothelial response to endothelial stimulation than blood pressure-controlled patients receiving non-ACE (angiotensin-converting enzyme) inhibitor treatment. ACE inhibitors inhibit the degradation of bradykinin and contribute to the accumulation of bradykinin and nitric oxide, both of which may be beneficial to diseased hearts. Finally, ACE inhibitors are also involved in hypoxia-induced neovascularization and could participate in the protection of target organs against ischemic damage. Vascular endothelial growth factor exerts a variety of pleiotropic effects, which include an acute protective effect. The pleiotropic effects of ACE inhibitors may be related to the results of a meta-analysis that showed that, out of the 19 major hypertension trials of the last decade, only 2, ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial), with amlodipine/perindopril vs atenolol/bendroflumethiazide, and ADVANCE (Action in Diabetes and Vascular disease: PreterAx and Diamicron-MR Controlled Evaluation), with perindopril/indapamide vs placebo, demonstrated a significant reduction in coronary events as well as in cardiovascular and total mortality.

Medicographia. 2012;34:32-38 (see French abstract on page 38)
A primary function of the microcirculation is to optimize nutrient and oxygen supply within tissues in response to variations in metabolic demand. The microcirculatory bed is also the site where the earliest manifestations of cardiovascular disease—in particular, inflammatory processes—occur.

The microcirculation is widely taken to encompass vessels <150 µm in diameter, which include arterioles, capillaries, and venules. The microcirculation largely determines tissue perfusion and hemodynamic vascular resistance. The small arteries, the main site of hemodynamic peripheral resistance, are named “resistance arteries.” However, there is no universally accepted anatomical definition of these resistance vessels. A definition based on arterial vessel physiology rather than diameter or structure has therefore been proposed, depending on the response of the isolated vessel to increased internal pressure. According to this definition, all those arterial vessels that respond to increasing pressure by a myogenic reduction in lumen diameter are included in the microcirculation, as well as the capillaries and venules. This definition includes the smallest arteries and arterioles in the microcirculation, and is in line with recent evidence that the small arterial and arteriolar components should be considered a continuum rather than distinct sites of resistance control.

In hypertension, the structure and function of the microcirculation are altered in at least three ways.
- First, the mechanisms regulating vasomotor tone are abnormal, leading to enhanced vasoconstriction and/or reduced vasodilator responses.
- Second, there may be anatomical alterations to the structure of individual precapillary resistance vessels, such as an increase in the wall-to-lumen ratio of conduit arteries and larger arterioles.
- Finally, there may be changes at the microvascular network level, involving a reduction in the density of the smaller resistance arterioles and capillaries within the vascular beds of various tissues (eg, muscle and skin). This is called vascular rarefaction.

In several tissues, capillary density was found to be inversely correlated with blood pressure in both hypertensive and normotensive subjects. While it has been known for many years that increased wall-to-lumen ratio of arteries and microvascular rarefaction can be secondary to a sustained elevation of blood pressure, there is also evidence that abnormalities in the microcirculation may precede high blood pressure, and thus may be one of its causal components. Microvascular rarefaction, similar in magnitude to the rarefaction observed in patients with established hypertension, can even be demonstrated in subjects with mild intermittent hypertension and in normotensive subjects with a genetic predisposition to high blood pressure. Moreover, in hypertensive subjects, capillary rarefaction in muscles was shown to be able to predict an increase in mean arterial pressure over a period of two decades (Figure 1). Similarly, in a prospective population-based study of normotensive middle-aged persons, a smaller retinal arteriolar diameter was shown to indicate hypertension and predict its development. Thus, it seems likely that microvascular abnormalities can both result from, and contribute to, hypertension, and a “vicious cycle” may exist, in which the microcirculation maintains or even amplifies an initial increase in blood pressure.

In arterial hypertension, several mechanisms reduce the formation and number of microvessels. Impaired formation of microvessels (impaired angiogenesis) and microvascular rarefaction can, on the other hand, contribute to increased peripheral resistance and raise blood pressure.

**SELECTED ABBREVIATIONS AND ACRONYMS**

- **ACE**: angiotensin-converting enzyme
- **ADVANCE**: Action in Diabetes and Vascular disease: PreterAx and DiamicroN-MR Controlled Evaluation
- **Ang II**: angiotensin II
- **ARB**: angiotensin receptor blocker
- **ASCOT**: Anglo-Scandinavian Cardiac Outcomes Trial
- **BK**: bradykinin
- **DBP**: diastolic blood pressure
- **NO**: nitric oxide
- **per/ind**: perindopril/indapamide
- **REASON**: PREterax in regression of Arterial Stiffness in a controlled double-blind study
- **SBP**: systolic blood pressure
Coronary microcirculation and myocardial perfusion in hypertension

Hypertension is an established risk factor for ischemic coronary disease as well as for myocardial infarction and its complications (heart failure, rupture, sudden death, and arrhythmias). Animal and clinical studies have shown that the major conduit coronary arteries are enlarged in pressure-overloaded, hypertrophied ventricles. This enlargement is accompanied by an increase in media-to-lumen ratio (hypertrophy) and in the extracellular component of the medial wall (fibrosis). Decrease in capillary density and the resulting increase in diffusion distance have been observed in many forms of hypertrophy, especially in the subendocardium. Myocardial pO₂, which reflects oxygen consumption and oxygen supply, also depends on capillary density, radius, and permeability. Under chronic overload conditions, which result in adaptive cardiac hypertrophy, the increase in capillary density with increasing oxygen consumption presumably occurs to meet the additional metabolic demand. In hypertrophied failing hearts, the decrease in relative capillary density with increasing diastolic pressure may be explained by a compression of the capillary bed due to intraventricular blood pressure. In the normal and hypertrophied myocardium, there is a strong relationship between the intercapillary distance and the pO₂ and pH of the interstitial tissue (Figure 2).

In most tissues, especially in the myocardium, the maximum distance for oxygen diffusion does not exceed 100 μm.6,0 Thus, capillary rarefaction may contribute to both altered tissue perfusion and altered oxygen supply to the myocardial cells. Finally, in the presence of hypertension and hypertrophy, autoregulation is impaired, especially in the subendocardium. The mechanism of angina in patients with hypertension with normal coronary angiograms has been linked to impaired vasodilator reserve, which is likely to be related to microvascular dysfunction and capillary rarefaction in the hypertrophied ventricle.

Microcirculation and treatment of hypertension

It is likely that the relative contributions of the macrovascular and microvascular networks will be different in different vascular beds and may vary between different forms and models of hypertension. Indeed, increased capillary density was reported in effectively treated essential hypertensive vs untreated hypertensive patients, suggesting a cause-and-effect relationship between blood pressure and capillary density.11
It is actually possible to discern a historical shift in the focus of antihypertensive therapy between these different mechanisms. Initially, antihypertensive therapy was directed mainly toward altering vasomotor tone and promoting vasodilation (with pure vasodilator drugs such as hydralazine, α-blockers, and then calcium blockers).

More recently, the focus was directed toward reducing or reversing the changes in resistance vessel structure (with the angiotensin-converting enzyme [ACE] inhibitors and the antagonists of angiotensin [Ang] II receptors), and in the last few years there has been a further evolution toward reducing or reversing microvascular network rarefaction (with the ACE inhibitors).

Antihypertensive agents that also have an effect on microvascular remodeling may thus provide significant clinical benefits. Although some classes of antihypertensive agents, such as the diuretics, are believed to have little beneficial action on the microcirculation, experimental and clinical studies suggest that others, such as the ACE inhibitors, improve microvessel structure and network density.12-15

Interestingly, addition of a blood volume-lowering agent, such as a thiazide-like diuretic, to an ACE inhibitor appears to confer additional benefits.16 Perindopril (per) and indapamide (ind) are both well-established, effective agents; the per/ind combination increased the capillary density in the ischemic tissue of spontaneously hypertensive rats and in the myocardium of stroke-prone hypertensive rats.17 In normotensive rats, the per/ind combination also induced an early and sustained effect on the postischemic revascularization process.18

The skin circulation is a unique site allowing simple, noninvasive, and reproducible assessment of capillary density and endothelial function and could be a valuable model of the overall microcirculation.19 There is evidence that capillary rarefaction in the skin may precede the clinical onset of essential hypertension, even in normotensive subjects with a familial predisposition to the disease.

Previous exploratory clinical studies showed that, in newly diagnosed patients with essential hypertension, per/ind improved coronary vasodilator reserve and myocardial blood flow.20 Similarly, coronary reserve increased after 12 months of treatment with perindopril.21

### Capillary density and endothelial function in treated hypertensive patients

A meta-analysis has showed that the ACE inhibitors are effective in treating ischemic and nonischemic heart failure,22 making them one of the standard drugs for the treatment of heart failure as well as essential hypertension. ACE is known to produce Ang II, which can cause potent coronary and systemic vasoconstriction. Thus, Ang II may worsen the extent of ischemic and nonischemic myocardial damage. In the hypertrophied hypertensive heart, ACE inhibitors reduce left ventricular hypertrophy, attenuate myocardial fibrosis, and prevent ventricular remodeling, thus contributing to cardioprotection. ACE catalyzes the conversion of Ang I to Ang II and the breakdown of bradykinin (BK) into inactive peptides. Hence, the pharmacological effect of ACE inhibitors may be in part mediated via the inhibition of Ang II formation but also via BK accumulation. BK is generated from the action of kallikreins on their substrate, kininogen, and acts through at least two receptor subtypes, B₁ and B₂. The B₂ receptor is constitutively expressed in various tissues and is responsible for the majority of BK effects. In contrast, B₁ has a higher affinity for kinin metabolites and its expression is induced in pathological conditions. Activation of the B₂ receptor leads to release of nitric oxide (NO) and prostacyclin, which modulate numerous biological functions, including vasodilation and sprouting of new capillaries.23

In addition to mediating the generation of NO through B₂-receptor activation and limiting the production of Ang II, BK also directly causes coronary vasorelaxation via B₂-receptor ac-

![Figure 3. Systolic (SBP) and diastolic blood pressure (DBP) in control, treated, and untreated hypertensive patients. Based on data from reference 27.](image-url)
Capillary density was significantly greater in controlled-per/ind and existing treatment:27

- Controlled hypertensive patients treated with per/ind (controlled-per-ind).
- Controlled hypertensive patients treated with agents other than ACE inhibitors or diuretics, ie, mostly angiotensin receptor blockers (ARBs) or β-blockers (controlled-other).
- Uncontrolled hypertensive patients treated with agents other than ACE inhibitors or diuretics (uncontrolled-other).
- Untreated normotensive subjects.

Capillary density was significantly greater in controlled-per/ind patients (99±12 capillaries/mm²) than in all the other groups (P<0.05). Controlled per/ind patients also showed significantly better endothelial function than patients from all the other groups (P<0.05). Although similar brachial systolic blood pressure (SBP) and diastolic blood pressure (DBP) values were obtained both in the controlled-per/ind group and the controlled-other group (Figure 3, page 35), capillary density and endothelial function were significantly improved only with per/ind treatment (Figures 4 and 5).

Altogether, the findings of this study highlight the fact that equivalent blood pressure control is not synonymous with equivalent microvascular benefits, therefore suggesting different long-term results for end organ damage. Most of the controlled-other patients were being treated with an ARB (48%) or a β-blocker (26%). β-Blockers do not have a clear effect on the vaso-motor tone of arterioles or on endothelial relaxation. Although ARBs have been shown to improve the microcirculation in some studies, several studies reported that they do not increase coronary flow reserve. The effects of per/ind on the microcirculation are likely to be attributable to both perindopril and indapamide. As an ACE inhibitor, perindopril downregulates the renin-angiotensin system, which is expressed both systemically and in the tissues, and contributes to low-grade inflammation. Ang II stimulates the expression of inflammatory cytokines such as interleukin-6 and monocyte chemoattractant protein--1. Thus, downregulation of Ang II synthesis through inhibition of ACE suggests a mechanism by which perindopril decreases inflammation-related damage to the microcirculation. The mechanism by which indapamide contributes to the normalization of the microcirculation, however, is less clear, although in at least one study, indapamide normalized the cross-sectional area of vessel walls and attenuated the rightward shift of the stress-strain curve in spontaneously hypertensive rats. These data are consis-
tent with those recorded in animal models, where microvascular benefits of per/ind treatment were accompanied by im-
provements in blood pressure and cardiac hypertrophy, and
with the data from REASON (PREterax in regression of Arter-
ial Stiffness in a controlEld double-blind study), the large clin-
ic study in which 1 year of treatment with per/ind decreased
brachial and central SBP and pulse pressure as well as left
ventricular ejection time and aortic augmentation index.

Conclusion

The experimental, clinical, and epidemiological results re-
ported in the present review are in favor of a paradigm shift in
 cardiovascular medicine, with the development of strategies
aiming to identify the hypertensive patients at higher risk of
ischemic end organ damage and the use of treatments able
to normalize blood pressure levels, the microcirculatory net-
work, and tissue perfusion. This could be linked to the evi-
dence provided by a recent meta-analysis,28 which showed
that only 2 out of the 19 major hypertension trials of the last
decade: ASCOT (Anglo-Scandinavian Cardiac Outcomes Tri-
al), with amloidipine/perindopril vs atenolol/bendroflumethia-
ze and ADVANCE (Action in Diabetes and Vascular disease:
PreterAx and Diamicron-NR Controlled Evaluation), with pe-
rindopril/indapamide vs placebo, demonstrated a significant
reduction in coronary events and cardiovascular and total
mortality.

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Keywords: ACE inhibitor; capillary density; coronary disease; endothelial dysfunction; hypertension; myocardial perfusion
AMÉLIORATION DE LA MICROCIRCULATION CORONAIRE : 
UN OBJECTIF SOUHAITABLE POUR CONTRIBUER À LA RÉDUCTION DE L’INCIDENCE DES ÉVÉNEMENTS CORONAIRES

La littérature s’accorde largement sur l’existence, chez les patients hypertendus, d’altérations de la structure et de la fonction microvasculaires, principalement caractérisées par une raréfaction capillaire, une dysfonction endothéliale et une diminution de la réserve de vasodilatation. Ces anomalies de la microcirculation contribuent à une diminution de la perfusion tissulaire favorisant de possibles lésions des organes cibles. La correction et la prévention des anomalies microvasculaires sont donc des buts cliniques potentiellement importants. La circulation cutanée est un lit vasculaire facilement accessible et représentatif des autres lits vasculaires ; l’analyse de la microcirculation cutanée pourrait permettre de mieux appréhender les dysfonctions microcirculatoires. Une normalisation de la densité capillaire diminuée et de la fonction endothéliale cutanées ont été observées chez des patients traités avec succès pour une hypertension essentielle par rapport à des patients hypertendus non traités, ce qui suggère une relation étroite entre la pression artérielle et la densité capillaire. De plus, chez les patients contrôlés par une association péridopril/indapamide on retrouve une densité capillaire et une réponse endothéliale significativement plus importantes que chez les patients dont la pression artérielle est efficacement contrôlée par un traitement qui ne comprend ni inhibiteur de l’enzyme de conversion (IEC), ni diurétique. Les IEC inhibent la dégradation de la bradykinine et contribuent à son accumulation ainsi qu’à une augmentation de la synthèse de monoxyde d’azote ; ces effets étant bénéfiques pour les patients souffrant de pathologies cardiovasculaires. Enfin, les IEC sont aussi impliqués dans la néo-vascularisation induite par l’hypoxie et pourraient ainsi participer à la protection des organes cibles contre les lésions ischémiques. Les effets pléiotropes des IEC pourraient être à l’origine des résultats rapportés dans une méta-analyse qui a montré que, parmi les 19 grandes études des 10 dernières années sur l’hypertension, seules 2, ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial), avec l’amlodipine/péridopril vs aténolol/bendrofluméthiazide, et l’étude ADVANCE (Action in Diabetes and Vascular disease : PreterAx and Diamicron-MR Controlled Evaluation), avec péridopril/indapamide vs placebo, pouvaient se prévaloir d’une diminution significative des événements coronaires et de la mortalité cardiovasculaire et totale.
In patients with arterial hypertension and coronary artery disease (CAD), mortality remains high despite the positive decreasing trend observed over the last few decades. This article will examine options to further improve the pharmacological management of hypertension in contemporary, optimally treated patients with stable CAD, taking into consideration lessons from recent clinical trials and analyses. Specific therapy for hypertension in the presence of CAD is chosen based on pathophysiological mechanisms common to both, such as overactivation of the renin-angiotensin-aldosterone system (RAAS) and early vascular aging, which mediate damage to target organs, including coronary vessels and the myocardium. One should also note that our traditional beliefs about blood pressure (BP) goals, as well as about the accuracy of “usual” BP in predicting the risk of cardiovascular (CV) events, have been challenged. In addition to brachial BP reduction, the reduction of other key BP parameters—BP variability, 24-hour BP, and central BP—has been shown to be important if we are to improve the quality of antihypertensive therapy to improve outcomes in populations at high CV risk. Inhibitors of the RAAS, especially angiotensin-converting enzyme (ACE) inhibitors, with a proven efficacy to improve prognosis and with proven dosages, should be considered as first-line treatment for hypertension, particularly in the presence of CAD. The results of some recent large trials have supported the rationale for combining ACE inhibitors and calcium channel blockers (CCBs) in hypertensive patients, including those with stable CAD.

Medicographia. 2012;34:39-47 (see French abstract on page 47)
This coexistence of hypertension and CAD also determines specific treatment objectives and approaches, because both hypertension and CAD are vascular diseases with common pathophysiological mechanisms. These mechanisms lead to the development of the diffuse atherosclerosis seen in hypertension, the more patchy atherosclerotic lesions of epicardial CAD, and the remodeling of conduit and resistant arteries, as well as medium and small coronary arteries. Prevention and reversal of these processes are major goals of therapy in hypertension and CAD.

Common pathophysiological relationships between mechanisms in hypertension and CAD

- **Blood pressure** and blood flow are the most important physical forces influencing cardiac and vascular structure and function. Increased myocardial oxygen demand and diminished coronary blood flow or, at least, diminished coronary flow reserve, are common features of hypertension and CAD.
  - When systolic blood pressure (SBP) is elevated, there is an increase in both left ventricular (LV) output impedance and intramyocardial wall tension, which increases myocardial oxygen demand.
  - Diminished coronary flow reserve is a complex function of plaque-related occlusive CAD, remodeling of medium and small coronary arteries, and, if diastolic pressure is low enough, a decrease in coronary perfusion pressure.

- **Early vascular aging** is commonly seen in patients with hypertension. Vascular aging, an inescapable fact of life, is drastically accelerated by elevated BP.5
  - Hypertension prompts degenerative vascular changes and endothelial dysfunction, leading to increased arterial rigidity. Systolic hypertension with enhanced pulse pressure is one of the clinical manifestation of early vascular aging.6

- **Oxidative stress** is another critical feature in both hypertension and atherogenesis. Excess generation of reactive oxygen species provokes a low-grade, self-perpetuating vascular inflammatory process, damages endothelial and muscle cells, helps perpetuate the ongoing atherosclerotic process, and leads to acute and chronic changes in CV structure and function.9,10

- **Renin-angiotensin-aldosterone system (RAAS)** hyperactivity is among the mechanisms responsible for the initiation and maintenance of hypertension and CAD. Angiotensin II elevates BP and promotes target-organ damage, including atherosclerosis, by a large variety of mechanisms. Angiotensin II has a direct effect on vasoconstriction, aldosterone synthesis and release, enhancement of sympathetic stimulation from the brain, and facilitation of catecholamine release from the adrenal glands and peripheral sympathetic nerve terminals.11,12 Angiotensin II promotes cardiac and vascular smooth muscle cell hypertrophy directly via activation of the angiotensin II type 1 receptor, and indirectly by stimulating the expression of a number of growth factors and cytokines. Finally, there is a link between RAAS activation and fibrinolysis,13 as well as evidence of a link between the RAAS and dyslipidemia, in which the RAAS stimulates the accumulation of low-density lipoprotein cholesterol in the arterial wall.14 Therefore, antihypertensive drugs may exert at least some of their beneficial effects on the vasculature by actions that are independent of BP lowering alone. In addition, RAAS inhibitors have been shown to block the activation of reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, thus limiting the degree of oxidative processes in the vasculature. This finding further supports the concept that RAAS blockers may have vasoprotective effects beyond BP lowering alone.15

- **Calcium** is also one of the crucial elements in the pathogenesis of hypertension and CAD. Calcium ions are major intracellular mediators of vascular smooth muscle cell contraction, as well as of inotropic and chronotropic functions of the heart. In addition to these acute regulatory functions, increased in-
tracellular calcium has atherosclerosis-promoting effects.\textsuperscript{16} Absence of coronary artery calcification has been associated with a favorable prognosis.\textsuperscript{17} The presence of coronary artery calcification increases the risk of cardiac events and all-cause mortality in CAD patients and in hypertensive patients at high CV risk who are still free of CAD, as does the extent of coronary artery calcification.\textsuperscript{18} Calcium channel blockers (CCBs), particularly dihydropyridine CCBs, are widely used in the treatment of high blood pressure and CAD (angina), because they are highly selective for arterial/arteriolar tissue, including the coronary arteries, where they cause vasodilation.

\textbullet \textbf{Elevated heart rate} has been proposed as an emergent CV risk factor by the latest hypertension guidelines.\textsuperscript{19} Heart rate is one of the major determinants of myocardial oxygen consumption, and, consequently, heart rate reduction is one of the cornerstones of angina prevention and treatment. Despite this, evidence for the benefit of reducing heart rate in patients with stable CAD was not available until recently, with the publication of the BEAUTIFUL (morBidity-mortality EvAlUaTion of the I\textsubscript{i} inhibitor iMibradine in patients with coronary disease and left ventricuLar dysfunction) trial results. In the placebo arm of BEAUTIFUL,\textsuperscript{20} we found that in CAD patients with heart rates \( \geq 70 \) beats/minute (bpm), there were significant increases in CV death (8%), admission to hospital for heart failure (HF) (16%), and coronary revascularization (8%) for every 5 bpm increase in heart rate. Further analyses from the LIFE (Losartan Intervention For Endpoint reduction in hypertension) trial\textsuperscript{21} and ONTARGET/TRANSCEND (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessements Study in ACE iNTolerant subjects with cardiovascular Disease) trial populations also identified a systematic increase in CV events among patients with a baseline heart rate >70 bpm vs those with a baseline heart rate \( \leq 70 \) bpm.\textsuperscript{22} Thus, findings on the prognostic importance of heart rate are consistent and should be considered in the management of stable CAD patients, including those with hypertension.

\textbf{New insights: expanding our knowledge of the relationship between BP and CV risk}

Effective BP control is indispensable to successful antihypertensive therapy.\textsuperscript{23} However, new clinical trial results and the latest analyses of older trials, which appeared in 2010, have challenged two traditional beliefs in hypertension management. The findings have raised major questions about the appropriateness of aggressive BP lowering in high-risk patients (systolic BP \(< 120 \) mm Hg)—which has been thought to be beneficial in high-risk patients for the past several decades—as well as about our exclusive reliance on “usual” BP (based on brachial tonometry readings) to guide clinical decisions and assess prognosis.

The debate over the benefits of a “the lower, the better” approach to BP management in patients with established CAD or those at risk of CAD, and the BP J-curve, has been going on since 1979, when Stewart demonstrated that among patients with severe arterial hypertension, the relative risk of myocardial infarction (MI) was over 5-fold higher in individuals whose DBP had fallen below 90 mm Hg than in those with a BP in the 100-109 mm Hg range.\textsuperscript{24} We still cannot definitively answer all the questions relating to this effect, although today,\textsuperscript{25} hypertension specialists agree that there is a lowest BP value (the so-called “nadir”) below which the maintenance of life would be impossible. This constitutes the basis for the J-curve phenomenon and might reflect the physiological range of arterial BP. The absence of significant benefit in CV disease outcomes other than stroke in the ACCORD (Action to Control Cardiovascular Risk in Diabetess) trial\textsuperscript{26} is consistent with post hoc analyses of other outcome trials published in 2009.
The risk of CV events also has a long history. Evidence collected during the last decade suggests that standard brachial blood pressure measurements are not adequate, and may even be misleading for the evaluation of CV risk. Data and analyses from the Stroke Prevention Research Unit at Oxford in the UK have shown a particularly striking relationship between within-individual variability in SBP and the risk of stroke and coronary events, independent of mean SBP.

These data are important because variability in home and ambulatory BP readings, and transient fluctuations in BP in response to specific stimuli (such as stress, pain, or postural changes), are not generally thought to predict future CV events, and treatment is normally the same as that for elevation in usual BP. However, patients with arterial hypertension have greater arterial stiffness, which leads to decreased arterial elasticity, loss of arterial buffering capacity, and, ultimately, greater BP variability.

An important analysis of data from major trials of antihypertensive treatments—including the ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm), MRC (Medical Research Council), and UK-TIA (United Kingdom Transient Ischemic Attack) trials—supports the hypothesis that treatments effecting the greatest reductions in BP variability are associated with the greatest reductions in risk of stroke, coronary events, and mortality, independent of mean SBP reduction (Figure 1).

Indeed, in the latest megatrials investigating additional benefits of antihypertensive therapy, a systematic link between the magnitude of BP reduction and reduction in CV outcomes and mortality was not always observed. For example, in the TRANSCEND trial (in high-risk patients, 76% of whom were hypertensive), a 4 mm Hg greater reduction in mean SBP with an angiotensin receptor blocker (ARB) vs placebo did not translate into greater reduction in CV outcomes and mortality.

Similar observations have been made in other trials, such as SCOPE (Study on Cognition and Prognosis in the Elderly) and ProFESS (Prevention Regimen For Effectively avoiding Second Strokes), which compared the effect of an ARB vs placebo in hypertensive patients. A statistical adjustment analysis of the ASCOT-BPLA study showed that the difference in brachial BP (mean ∆ SBP, 2.7 mm Hg) would only partially account for the superiority of amlodipine-perindopril vs atenolol-bendroflumethiazide in reducing CV events and mortality in ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial). There was still a significant residual difference in events, which was totally accounted for after the results were further adjusted for the reduction in BP variability.

and 2010. An observational subgroup analysis of the 6400 participants in INVEST (International Verapamil SR/trandolapril Study) who had both diabetes and CAD showed little difference in CV disease outcomes between those who maintained tight BP control and those with usual control. Moreover, patients with SBP <110 mm Hg had increased risk of all-cause mortality. Similarly, a retrospective analysis of outcomes in 25,588 high-risk participants in ONTARGET revealed no relationship between in-trial SBP reduction and risk of MI, HF, and CV mortality. In addition, the analysis defined a J-shaped curve with a nadir ≈130 mm Hg for the relationship between achieved SBP and risk for all outcomes, except stroke.

There is also the opinion that in an era when BP management is not particularly effective, drawing attention to the J-curve issue might have a negative impact, by disposing physicians to aim for less strict control of BP.

At this point, it is worth noting yet another important aspect associated with the J-curve and pulse pressure (PP). As SBP and DBP lowering are closely linked, a problem may arise in patients with high PP, in whom SBP is high and DBP is low. The current position of the majority of experts is that SBP is the main focus of hypertension treatment, yet caution is advisable to avoid excessive lowering of both SBP (to <110-120 mm Hg) and DBP (to <70 mm Hg) in patients with CAD.

The question about the accuracy of mean BP in predicting the risk of CV events also has a long history. Evidence collected during the last decade suggests that standard brachial blood pressure measurements are not adequate, and may even be misleading for the evaluation of CV risk. Data and analyses from the Stroke Prevention Research Unit at Oxford in the UK have shown a particularly striking relationship between within-individual variability in SBP and the risk of stroke and coronary events, independent of mean SBP.
Apart from BP variability, other key BP parameters, such as central BP and 24-hour BP, have also been demonstrated to be superior to peripheral BP as indicators of CV disease prognosis.41,42 The European Society of Hypertension has acknowledged this phenomenon in the latest guidelines.19

**Treatment strategy to further improve prognosis**

The treatment objectives in stable CAD and hypertension are to prevent CV complications and death, as well as minimize or abolish symptoms. Lifestyle changes and drug treatment play a vital role in halting the progression, or inducing the regression, of coronary atherosclerosis. Reducing all key blood pressure parameters, as well as inflammatory vascular abnormalities, endothelial dysfunction, and prothrombotic disorders, is critical to minimize CV complications. In certain circumstances, such as in patients with severe lesions in coronary arteries that supply a large area of jeopardized myocardium, revascularization may improve prognosis by improving existing perfusion or by providing alternative routes of perfusion.19,43,44

Today, through the united efforts of the medical establishment, programs for secondary prevention measures in CV disease have been implemented. The rationale and benefits of lipid-lowering and antiplatelet therapy, as well as of reperfusion measures, have been discussed elsewhere.43,44 In light of new evidence-based lessons in hypertension management, the potential of RAAS inhibitors to further improve prognosis in hypertensive patients with CAD will be reviewed here. The results of some recent large trials support the benefits of combining ACE inhibitors and CCBs in patients with high CV risk, whether stable coronary patients or hypertensive patients.

The four trials that tested the use of ACE inhibitors in secondary prevention in CAD patients are, in order of appearance in the literature, QUIET (QUinapril Ischemic Event Trial), HOPE (Heart Outcomes Prevention Evaluation), EUROPA (EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease), and PEACE (Prevention of Events with Angiotensin-Converting Enzyme inhibition) (Figure 2).45-48 Although all the trials tested a similar hypothesis, they came to quite different conclusions. While QUIET did not show a prognostic benefit for ACE inhibition with quinapril 20 mg/day,45 HOPE showed a significant prognostic benefit with ramipril 10 mg/day in high-risk patients, including those with CAD.46 Next, EUROPA extended the use of ACE inhibitors to all-risk populations, showing a prognostic benefit with perindopril tert-

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**Figure 2. Primary outcomes of the four major ACE inhibitor trials (QUIET, HOPE, EUROPA, PEACE) in stable coronary artery disease.**

**Abbreviations:** CI, confidence interval; CV, cardiovascular; EUROPA, European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease; HOPE, Heart Outcomes Prevention Evaluation; MI, myocardial infarction; PEACE, Prevention of Events with Angiotensin-Converting Enzyme inhibition; QUIET, QUinapril Ischemic Event Trial; RR, relative risk; y, years.

butylamine at a target dose of 8 mg/day (corresponding to perindopril arginine 10 mg) in a population with stable CAD. Finally, and very surprisingly, PEACE did not find a prognostic benefit for trandolapril 4 mg/day in a population that was very similar to that in EUROPA.

A meta-analysis of HOPE, EUROPA, and PEACE that included data from nearly 30 000 patients found that ACE inhibition was systematically better than placebo and significantly reduced the risk of total and CV mortality, fatal and nonfatal MI, HF, revascularization, and stroke in patients with atherosclerosis without evidence of HF or LV dysfunction. The results of this meta-analysis left no doubt that CAD patients should receive ACE inhibitors.

![Table I. Effects of perindopril on markers of endothelial function in patients with stable coronary artery disease.](image)

<table>
<thead>
<tr>
<th>Table I. Effects of perindopril on markers of endothelial function in patients with stable coronary artery disease.</th>
<th>Baseline</th>
<th>1 year</th>
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<tr>
<td>Markers</td>
<td>Placebo</td>
<td>Perindopril</td>
</tr>
<tr>
<td>Placebo</td>
<td>Perindopril</td>
<td>Placebo</td>
</tr>
<tr>
<td>(n=44)</td>
<td>(n=43)</td>
<td>(n=44)</td>
</tr>
<tr>
<td>eNOS expression (arb.units/mg protein)</td>
<td>7.4±2.9</td>
<td>7.1±2.5</td>
</tr>
<tr>
<td>eNOS activity (pmol/min/mg protein)</td>
<td>2.5±1.0</td>
<td>2.4±0.9</td>
</tr>
<tr>
<td>Apoptosis (%)</td>
<td>7.8±2.9</td>
<td>6.8±1.9</td>
</tr>
<tr>
<td>Angiotensin II (pg/mL)</td>
<td>15.8±7.7</td>
<td>17.1±6.4</td>
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<tr>
<td>Bradykinin (pg/mL)</td>
<td>12.4±6.0</td>
<td>14.8±6.2</td>
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<tr>
<td>TNF-alpha (pg/mL)</td>
<td>27.7±4.4</td>
<td>27.1±4.4</td>
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Although one mechanism of action is BP reduction, this may not be the only one. The degree of BP reduction was very similar in the four trials. In fact, BP reduction alone could not be the sole explanation for the results of EUROPA: the effect of perindopril was independent of BP at entry and was even recorded in patients in whom there was no reduction in brachial BP. It might also be due to a greater reduction in other important BP parameters that are more closely related to coronary events than BP measured in the brachial artery, and to the effects of perindopril on central BP and BP variability, which have been demonstrated clinically.

Another explanation is that ACE inhibitors have BP-independ ent effects, such as endothelial protection that arrests or impairs the process of atherosclerosis, as seen in the EUROPA trial. In CAD patients participating in the EUROPA trial, we measured markers of endothelial function, including endothelial nitric oxide synthase (eNOS), the rate of apoptosis, and the level of von Willebrand factor (vWF), and we have clinical results showing that perindopril normalizes the angiotensin II/bradykinin balance, reduces inflammation, and prevents endothelial apoptosis (Table I). It also appears that perindopril may be able to reverse new atherosclerotic plaque formation if it occurs. A higher rate of apoptosis vs regeneration disrupts endothelial continuity, which in turn leads to pathological sequelae, such as the onset of atherosclerosis, and plaque erosion and rupture. A post hoc analysis of the PERSPECTIVE (PERindopril’s proSPective Effect on Coronary aTherosclerosis by IntraVascular ultrasound Evaluation) substudy of EUROPA found that perindopril was able to reduce the size of noncalcified plaques compared with placebo. Moreover, there is accumulating preclinical evidence for the absence of a class effect for ACE inhibitors, including evidence that they have differences in their effects on eNOS and on the rate of endothelial apoptosis. These differences appear to be related to tissue affinity, penetration of atherosclerotic plaque, and affinity for the target enzyme.

In this context, current European guidelines for stable angina recommend prescription of ACE inhibitors at doses with proven efficacy. ACE inhibitors are recommended for CV event prevention in hypertension. ARBs are also recommended, despite this being a matter of controversy after the publication of results from the latest large-scale trials, ONTARGET and TRANSCEND. These two trials were conducted with the same inclusion criteria: populations with stable vascular disease and hypertension (around 2/3 of patients). In ONTARGET, the ARB telmisartan showed no benefit in preventing CV events or mortality vs the ACE inhibitor ramipril; in TRANSCEND, the same ARB failed to demonstrate superiority vs placebo. Evidence-based medicine currently considers RAAS inhibitors and CCBs to be among the best components of an antihypertensive combination. The reappraisal of the hypertension guidelines highlights ACE inhibitor/CCB combinations as being supported by the strongest evidence, from ACCOMPLISH (Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension) and, particularly, ASCOT. ASCOT was considered a breakthrough in hypertension management due to the reduction in all-cause mortality seen in hypertensive patients treated with a combination of amlodipine and perindopril—a first for a modern antihypertensive treatment. Moreover, recent trials, such as ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation) and HYVET (Hypertension in the Very Elderly Trial), have confirmed the ASCOT finding that antihypertensive treatment that includes perindopril reduces all-cause mortality.
Combination of ACE inhibitors and CCBs would also fulfill important therapeutic objectives in CAD. Further reductions in cardiac outcomes and mortality were found in the recent EUROPA analysis in stable CAD patients when perindopril was added to long-term CCB treatment. Among study participants who received CCB at every visit in the perindopril arm vs placebo arm of EUROPA (perindopril/CCB, n=1022; placebo/CCB, n=1100), the total mortality was reduced by 46% (P<0.01 vs placebo) and the primary end point (a composite of CV mortality, nonfatal MI, and resuscitated cardiac arrest) was reduced by 35% (P<0.05 vs placebo) with perindopril/CCB (Figure 3).

This finding suggests clinical synergy between an ACE inhibitor and a CCB leads to both antihypertensive and cardioprotective effects (Table II).

Indeed, in hypertensive patients from the ASCOT study, this combination effectively reduced brachial BP and had favorable effects on BP variability, central BP, and nighttime/24-hour BP; new research indicates that these are key BP parameters for determining the impact of treatment on CV risk and mortality.

Additionally, a preliminary report of a meta-analysis of clinical trials in hypertension indicates that strategies including perindopril (combined with amlodipine or indapamide) further reduce mortality. This meta-analysis looked at 19 randomized controlled RAAS inhibitor trials conducted during the last decade. Trials in HF, acute MI, stroke, post cardiac surgery, or trials with less than 66% of hypertensive patients were excluded. Only 3 trials—ASCOT, ADVANCE, and HYVET—including 34,242 patients, demonstrated significant reduction in all-cause mortality (13% when pooled; 95% confidence interval [CI], 0.81 to 0.93; P<0.0001). When these three trials were excluded, the treatment effect of other RAAS inhibitors in the remaining 16 trials was neutral (hazard ratio, 0.99; 95% CI, 0.95 to 1.01; P=0.21).

Table II. Modes of action of angiotensin-converting enzyme (ACE) inhibition with perindopril and calcium channel blockade (CCB) with amlodipine.

<table>
<thead>
<tr>
<th>Perindopril</th>
<th>Amlodipine</th>
<th>Clinical advantage of synergy</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ Vasodilation</td>
<td>↑ Vasodilation</td>
<td></td>
</tr>
<tr>
<td>↓ Vasoconstriction</td>
<td>↑ Reflex vasodilation</td>
<td></td>
</tr>
<tr>
<td>↑ Antioxidant effect (eNOS expression, NO)</td>
<td>↑ Antioxidant effect (NO)</td>
<td>↑↑↑ Enhanced BP lowering</td>
</tr>
<tr>
<td>↑ Antiremodeling effect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ Endothelial function</td>
<td>↑ Activation of sympathetic nervous system</td>
<td></td>
</tr>
<tr>
<td>↑ Increased postcapillary vasodilation</td>
<td>↑ Increased precapillary vasodilation</td>
<td>↓ Decreased lower limb edema</td>
</tr>
<tr>
<td>↑ t-PA activity</td>
<td>↑ t-PA activity</td>
<td>↑ Improved fibrinolytic balance</td>
</tr>
<tr>
<td>↓ PAI-1 levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ SMC growth, proliferation and migration</td>
<td>↓ SMC proliferation</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BP, blood pressure; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; PAI-1, plasminogen activator inhibitor 1; SMC, smooth muscle cell; t-PA, tissue plasminogen activator.

Conclusion
Common pathophysiological mechanisms of arterial hypertension and CAD prompt degenerative vascular changes and endothelial dysfunction, leading to acceleration of atherosclerosis and target-organ damage. Lessons from recent clinical trials and analyses have challenged some of the traditional beliefs in hypertension management and seem to be particularly useful to further improve prognosis in hypertensive patients with stable CAD:

- Clearly, effective reduction in systolic BP remains the objective of hypertension treatment, yet caution is advisable to avoid excessive lowering of both SBP (to <110-120 mm Hg) and DBP (to <70 mm Hg) in patients with CAD.
- In addition to brachial BP reduction, reduction of BP variability, 24-hour BP, and central BP seem to improve quality of antihypertensive therapy and thus, improve prognosis in populations at high CV risk.
- ACE inhibitors with proven efficacy and at proven dosages are indispensable for effective management of contemporary hypertensive patients with stable CAD to further reduce CV events and mortality.
- Combination antihypertensive therapy with ACE-inhibitors, such as perindopril, and CCBEs, such as amlodipine, is supported by the results of recent clinical trials in hypertensive patients, including those with stable CAD.

References
Protection des patients hypertendus ayant une maladie coronaire stable: nouvelles données d'études

Chez les patients porteurs d’hypertension et de maladie coronaire (MC), la mortalité reste élevée malgré la tendance à la diminution observée ces dernières années. Nous examinons dans cet article les options permettant une amélioration supplémentaire de la prise en charge pharmacologique de l’hypertension chez des patients actuels ayant une maladie coronaire stable, traités de façon optimale, en prenant en compte les enseignements générés par les analyses et études cliniques récentes. Le traitement spécifique de l’hypertension en présence de MC se détermine sur la base de mécanismes physiopathologiques communs aux deux pathologies, comme la suractivation du système rénine-angiotensine-aldostérone (SRAA) et le vieillissement vasculaire précoce qui ralentit les organes cibles comme les vaisseaux coronaires et le myocarde. Il faut noter aussi que nos convictions traditionnelles sur les objectifs de pression artérielle (PA) ainsi que sur la fiabilité de la PA « habituelle » dans la prévision du risque d’événements cardio-vasculaires (CV) ont été remises en question. En plus de la réduction de la PA brachiale, la réduction des autres paramètres clés de la PA (variabilité de la PA, PA des 24 h et PA centrale) s’est montrée essentielle dans l’amélioration du traitement antihypertenseur pour de meilleurs résultats dans des populations à risque élevé. Les inhibiteurs du SRAA, en particulier les IEC (inhibiteurs de l’enzyme de conversion), dont l’efficacité dans l’amélioration du pronostic et dont les posologies ont été prouvées, doivent être considérés comme le traitement antihypertenseur de premier choix, surtout en présence de MC. Quelques grandes études récentes soutiennent l’argumentaire en faveur d’une association d’IEC et d’AC (antagonistes calciques) chez les hypertendus, y compris chez ceux ayant une MC stable.

Keywords: arterial hypertension; calcium channel blockers; cardiovascular outcome; renin-angiotensin system inhibitors; stable coronary artery disease

Évaluation de la question hypertensive et de la survenue d’événements cardio-vasculaires lors du traitement par perindopril dans le protocole CROWN.


Reducing both microalbuminuria and cardiovascular events: how easy is it to reach this target?

by J. A. García-Donaire and L. M. Ruilope, Spain

Microalbuminuria is an indicator of impaired renal function and an accepted risk marker for cardiovascular events and mortality. Coexistence of type 2 diabetes and arterial hypertension significantly increases the risk of cardiorenal disease and the development of cardiovascular events, and potentially augments mortality. This has led to the recommendation of use of albuminuria as a therapeutic target. Overactivity of the renin-angiotensin-aldosterone system (RAAS) has been implicated in the deterioration of renal function in patients with diabetic nephropathy. Increases in microalbuminuria are attenuated by BP reduction using inhibitors of the RAAS. In spite of a high number of well-designed controlled, randomized trials, controversies remain regarding optimal antihypertensive therapy in diabetic patients—including whether drugs acting on the RAAS have specific renal protective properties—and the relationship between renal and mortality end points. Moreover, most hypertensive diabetic patients need combinations of two or more antihypertensive drugs, which may complicate the interpretation of the evidence. Results of the published trials provide inconsistent evidence, by showing that the effects of treatment can vary widely among different renal, cardiovascular, and mortality end points. Also combinations of antihypertensive drugs differ in their ability to prevent major renal and cardiovascular events, even if they produce similar reductions in BP. And finally, simply adding further antihypertensive drugs may not improve renal and mortality outcomes, even if it produces further reductions in BP. Furthermore, in most antihypertensive treatment trials—but not all—in patients with type 2 diabetes, a reduction in microalbuminuria was consistently associated with evidence of renal protection. In this article, we review further evidence on the extent to which treatment-induced changes in proteinuria reflect cardiovascular risk modifications in patients with type 2 diabetes.

Persistent microalbuminuria has been increasingly recognized not only as an early predictor of nephropathy, but also as a risk marker for cardiovascular (CV) events and CV and all-cause mortality in patients with diabetes mellitus as well as in nondiabetic patients.1-3 This has led to the recommendation of more widespread urine testing for microalbuminuria and the use of albuminuria as a therapeutic target.4 The presence of hypertension in patients with diabetes mellitus substantially increases the risk of renal and other organ damage, and leads to much greater incidence of cardiac events and mortality. Chronic kidney disease (CKD) is highly preva-
lent in people with diabetes. A recent analysis of NHANES (National Health And Nutritional Examination Survey) data found that 39.6% of people with diagnosed diabetes, 41.7% of those with undiagnosed diabetes, and 17.7% of those with prediabetes had CKD. A recently published collaborative meta-analysis of general population cohorts, which pooled data of all-cause and CV mortality involving more than 1 million participants, concluded that an estimated glomerular filtration rate (GFR) <60 mL/min/1.73 m² and an albumin-to-creatinine ratio ≥1.1 mg/mmol (≥10 mg/g) were independent predictors of mortality risk in the general population. Both parameters were associated with an increased risk of mortality without any evidence of interaction. These data have confirmed that GFR 60 mL/min/1.73 m² and the lower limit of high-normal albuminuria (1.1 mg/mmol [10 mg/g]) are adequate limits for risk assessment and for the definition and staging of CKD.

Overactivity of the renin-angiotensin system has been implicated in the deterioration of renal function in patients with diabetic nephropathy. There is evidence that RAAS blockers may have specific renal protective properties, and such agents are preferred both for monotherapy and as components of combination therapy. Early detection and treatment with blood pressure (BP)-lowering drugs, especially drugs acting on the RAAS, has been shown to at least delay, and possibly even prevent, development of end-stage renal disease in patients with diabetes and macroalbuminuria/proteinuria.

However, several controversial points remain regarding optimal antihypertensive therapy in diabetic patients. Evidence of simultaneous reductions in BP, microalbuminuria, renal impairment, and CV and all-cause mortality were demonstrated in the ADVANCE trial (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation). More recently, in the ROADMAP trial (Randomized Olmesartan And Diabetes Macroalbuminuria Prevention) and in ORIENT (Olmesartan Reducing Incidence of Endstage Renal Disease in Diabetic Nephropathy Trial), reduction in BP values in patients with type 2 diabetes was associated with improved renal outcomes, while no reduction in risk of CV outcomes could be observed in active treatment groups. In this article, we review and evaluate recent evidence from landmark trials with renal end points regarding the extent to which treatment-induced changes in proteinuria reflect CV risk modification in the management of hypertension in type 2 diabetes.

**Microalbuminuria as a cardiovascular risk marker**

Parving et al first described the association of essential hypertension and microalbuminuria in 1974. They observed that the presence of elevated levels of urinary excretion of albumin in unsatisfactorily treated hypertensive patients was directly correlated with BP values and tended to be reduced if a better control of BP was obtained. These results were later confirmed by other trials.

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**SELECTED ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
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<tr>
<td>ARB</td>
<td>angiotensin receptor blocker</td>
</tr>
<tr>
<td>CKD</td>
<td>chronic kidney disease</td>
</tr>
<tr>
<td>CV</td>
<td>cardiovascular</td>
</tr>
<tr>
<td>GFR</td>
<td>glomerular filtration rate</td>
</tr>
<tr>
<td>IMT</td>
<td>intima-media thickness</td>
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<tr>
<td>UACR</td>
<td>urinary albumin-to-creatinine ratio</td>
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**SELECTED STUDY ACRONYMS**

<table>
<thead>
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<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACCOMPLISH</td>
<td>Avoiding Cardiovascular events through COMBination therapy in Patients Living with Systolic Hypertension</td>
</tr>
<tr>
<td>ACCORD</td>
<td>Action to Control CardiOvascular Risk in Diabetes</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>Action in Diabetes and Vascular disease PreterAx and DiamicroN MR Controlled Evaluation</td>
</tr>
<tr>
<td>ASCOT-BPLA</td>
<td>Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure–Lowering Arm</td>
</tr>
<tr>
<td>DIRECT</td>
<td>Diabetic Retinopathy Candesartan Trials</td>
</tr>
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<td>HARVEST</td>
<td>Hypertension and Ambulatory Recording VPnetia Study</td>
</tr>
<tr>
<td>HOPE</td>
<td>Heart Outcomes Prevention Evaluation</td>
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<tr>
<td>HYVET</td>
<td>Hypertension in the Very Elderly Trial</td>
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<tr>
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<td>Irbesartan type 2 Diabetic Nephropathy Trial</td>
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<tr>
<td>IMT</td>
<td>intima-media thickness</td>
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<tr>
<td>IRMA-2</td>
<td>Irbesartan type 2 diabetic nephropathy trial</td>
</tr>
<tr>
<td>LIFE</td>
<td>Losartan Intervention For Endpoint reduction in hypertension</td>
</tr>
<tr>
<td>MICRO-HOPE</td>
<td>Microalbuminuria, Cardiovascular and Renal Outcomes–Heart Outcomes Prevention Evaluation</td>
</tr>
<tr>
<td>ONTARGET</td>
<td>Onngoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial</td>
</tr>
<tr>
<td>PHARAO</td>
<td>Prevention of Hypertension with the Angiotensin-converting enzyme inhibitor Ramipril with high-normal blood pressure</td>
</tr>
<tr>
<td>PROGRESS</td>
<td>Perindopril pR0tection aGainst REcurrent Stroke Study</td>
</tr>
<tr>
<td>RAAS</td>
<td>renin-angiotensin-aldosterone system</td>
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<tr>
<td>RENAAI</td>
<td>Reduction of Endpoints in NIDDM (non-insulin dependent diabetes mellitus) with the Angiotensin II Antagonist Losartan</td>
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<tr>
<td>SHEP</td>
<td>Systolic Hypertension in the Elderly Program</td>
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<tr>
<td>STAR</td>
<td>Study of Trandolapril/verapamil SR And insulin Resistance</td>
</tr>
<tr>
<td>TRANSCEND</td>
<td>Telmisartan Randomized AssessemeNT Study in ACE iNtolerant subjects with cardiovascular Disease</td>
</tr>
<tr>
<td>TROPHY</td>
<td>Trial Of Preventing Hypertension</td>
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</table>
Microalbuminuria, defined as a urine albumin:creatinine ratio of 30 to 300 mg/g, is an accepted marker of CV risk,\(^\text{16,17}\) and is detectable in almost 40% of the hypertensive type 2 diabetes population, predominantly in those patients not controlled adequately on medical treatment. The prevalence of microalbuminuria is associated with the duration and severity of hypertension.\(^\text{18}\) In a large series of non-diabetic treated and nontreated hypertensive patients, the presence of microalbuminuria was significantly greater in patients with coronary artery disease, left ventricular hypertrophy, stroke, and peripheral vascular disease.\(^\text{16}\) HARET (Hypertension and Ambulatory Recording VENetia Study) examined the association between the urinary albumin-to-creatinine ratio (UACR) and office and ambulatory BP and their relationship with other recognized CV risk factors in stage I middle-aged hypertensive patients.\(^\text{19}\) An association between microalbuminuria and target-organ damage has been reported previously. Biesenbach et al described a higher prevalence of coronary artery disease and hypertensive retinopathy in a group of hypertensive patients.\(^\text{19}\) Moreover, Bigazzi et al reported an increased thickness of the intima and media layers of the common carotid artery in a group of patients with essential hypertension and microalbuminuria; this suggests a greater degree of vascular remodeling.\(^\text{20}\) Pontremoli et al reported that patients with microalbuminuria are characterized by signs of diffuse vascular and organ damage (ie, a higher incidence of major ECG abnormalities and vascular retinal changes) supporting the statement that microalbuminuria is a marker of early end-organ and CV damage in patients with essential hypertension.\(^\text{21}\) The presence of microalbuminuria in patients with essential hypertension has been systematically interpreted as a sensitive marker of intrarenal vascular dysfunction, characterized by an impairment of renal function. Several studies have shown an increased intima–media thickness (IMT) of the carotid artery in patients with microalbuminuria.\(^\text{22}\) CKD can be considered based on the finding of a decreased GFR, an elevation of serum creatinine, or an elevated urinary excretion of albumin.\(^\text{24}\) While an elevated serum creatinine concentration points to a reduced GFR, an increased rate of albumin points to a derangement in the glomerular filtration barrier. Microalbuminuria could constitute the renal expression of a generalized disorder characterized by increased endothelial permeability, abnormalities of the fibrinolytic and coagulation pathways, and activation of the inflammatory process,\(^\text{25}\) explaining the link between microalbuminuria and CV risk. In essential hypertension, microalbuminuria can be considered as a predictor of progressive deterioration of renal function.\(^\text{26,27}\) Although it has been argued that BP lowering is the primary reason for the prevention of, or decrease in, microalbuminuria, this has only been demonstrated to be the case in studies using RAAS inhibitors.\(^\text{28–31}\)

RAAS inhibition in patients at cardiovascular risk and with diabetes

The first evidence of a beneficial effect of lowering BP below 150/85 mm Hg, (which was considered as “tight BP control” in the early 1990s) with angiotensin-converting enzyme (ACE) inhibitors in patients with diabetes mellitus came from UKPDS-38 (UK Prospective Diabetes Study).\(^\text{32}\) Then came MICRO-HOPE (Microalbuminuria, Cardiovascular and Renal Outcomes–Heart Outcomes Prevention Evaluation), a sub-analysis of a diabetic population (n=3577) from the hugely influential HOPE trial. MICRO-HOPE involved high-risk patients with a history of vascular disease or diabetes plus one other CV risk factor who were randomized to receive the ACE inhibitor ramipril or placebo for approximately 4.5 years. Among patients with diabetes, reduction in BP with ramipril, relative to placebo (2.4/1.0 mm Hg) was even smaller than in the total study population (approximately 3/2 mm Hg), but the risk reductions tended to be slightly larger, with reductions in the primary outcome of 25%, CV death by 37%, and all-cause death by 24%. There was also a reduction in the incidence of overt nephropathy by 24%.\(^\text{33}\) The HOPE trial was soon followed by PROGRESS (Perindopril pROjection aGainst REcurrent Stroke Study),\(^\text{34}\) which was primarily a study in secondary prevention of stroke, but which had important implications for subsequent trial design, especially regarding combination therapies. Patients (N=6105) with a history of stroke or transient ischemic attack were randomized to active treatment with perindopril, with or without the addition of the thiazide-like diuretic indapamide, or placebo, and mean follow-up was 3.9 years. Overall, active treatment produced a reduction of 28% in stroke and 26% in major vascular events; the benefits were similar in hypertensive and nonhypertensive patients. Approximately 42% of patients were treated with perindopril alone and 58% with the perindopril+indapamide combination. BP was reduced by 5/3 mm Hg by perindopril alone, and by 12/5 mm Hg by the perindopril+indapamide combination. Results in patients receiving the perindopril+indapamide combination were dramatic, with risk reductions of 43% in stroke and 40% in major vascular events. Subsequent analysis in the 761 patients with diabetes at baseline indicated a nonsignificantly larger treatment effect in diabetic compared with non-diabetic patients, with risk reductions for stroke of 38% and 28%, respectively,\(^\text{35}\) and diabetic patients who received perindopril + indapamide showed a dramatic 46% reduction in stroke risk. The results of these trials validated the benefits of ACE-inhibitor therapy, a point reinforced by subsequent guidelines, and made a strong case for their use in control groups in later trials.

Another study from the early 2000s, LIFE (Losartan Intervention For Endpoint reduction),\(^\text{36}\) compared treatment based on the angiotensin II receptor blocker (ARB) losartan and the β-blocker atenolol (addition of a thiazide diuretic was allowed in both arms) in 9193 patients with left ventricular hypertro-
Hypokalemia may lead to diminished pancreatic function and hypertension (mean baseline BP 174/98 mm Hg), with a mean follow-up of 4.8 years. The risk of the primary end point was reduced by 13% in the losartan group, with a significant decrease in risk of stroke of 25%, relative to atenolol-based treatment. CV and all-cause mortality were not significantly different between the treatment groups. In the subgroup of patients with diabetes at baseline, losartan was associated with a reduction of 24% in the primary end point, and significant reductions of 37% in CV and 39% in all-cause mortality.10 Albuminuria decreased more with losartan than with atenolol, and significant reductions in CV and all-cause mortality with losartan were found only among patients in the quartile of baseline microalbuminuria.10 Further robust evidence of parallel reduction in microalbuminuria and CV and all-cause mortality was prospectively demonstrated in ADVANCE, discussed below.10

**RAAS inhibition and development of diabetes**

The results of the LIFE trial have been the subject of considerable discussion, and a systematic review concluded that the β-blockers studied (principally atenolol) had no effect on coronary artery disease and all-cause mortality compared with placebo and had only a weak beneficial effect on stroke.27,39 In ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial), which enrolled 14,120 nondiabetic patients, the risk of new-onset diabetes was substantially lower with an amiodarone±perindopril regimen than with atenolol±thiazide (hazard ratio [HR], 0.66; 95% CI, 0.59-0.74). In a network meta-analysis of 22 trials, the odds ratios of new-onset diabetes with RAAS inhibitors, relative to diuretics, were 0.57 for ARBs and 0.67 for ACE inhibitors.41 Several mechanisms for “thiazide-induced dysglycemia” have been proposed, and hypokalemia has been widely implicated. In nondiabetic patients in SHEP (Systolic Hypertension in the Elderly Program), the incidence rate of diabetes was more than doubled with chlorthalidone compared with placebo and had only a weak beneficial effect on stroke.27,39

Results showed a mean systolic BP reduction greater by 2.8 mm Hg with valsartan vs placebo, and a lower cumulative incidence of diabetes of 33.1% in the valsartan group vs 36.8% in the placebo group (P<0.001). Valsartan did not significantly reduce the incidence of CV outcomes, CV or all-cause mortality compared with placebo.46

**RAAS inhibitors, nephropathy, and mortality**

Patients with type 1 or type 2 diabetes mellitus are at high risk for chronic kidney disease, which usually manifests with the onset of microalbuminuria, followed by nephropathy28,47 and steeply increasing risk of CV death (Figure 1).47 The complex interactions between CV disease, CKD, and diabetes are becoming more widely appreciated, if not fully understood.49 Blockade of the RAAS is widely acknowledged as beneficial in terms of renal outcomes, and a series of meta-analyses have indicated that ACE inhibitors can prevent new-onset microalbuminuria, progression to macroalbuminuria, and reduce all-cause mortality in patients with diabetic nephropathy, and that ARBs have only renoprotective properties.50

IDNT (Irbesartan in Diabetic Nephropathy Trial) and the RENAAL trial (Reduction of Endpoints in NIDDM [non–insulin dependent diabetes mellitus] with the Angiotensin II Antagonist Losartan) included patients with type 2 diabetes and nephropathy. In both trials, randomized treatments were given in addition to standard hypertensive therapy, which excluded ACE inhibitors, ARBs, and in the case of IDNT, calcium-channel blockers. IRMA 2 (Irbesartan in Microalbuminuria, type 2 diabetic nephropathy trial) was a smaller study that compared two doses of irbesartan with placebo in patients with type 2 diabetes and persistent microalbuminuria, who could

![Figure 1. Annual risk of cardiovascular (CV) death in patients with type 2 diabetes mellitus and different degrees of nephropathy in the UKPDS (United Kingdom Prospective Diabetes Study).](image-url)
receive other antihypertensive drugs apart from ARBs and ACE inhibitors. The level of urinary albumin excretion was reduced by 38% in the irbesartan 300-mg group compared with a reduction of 2% in the placebo group (P<0.001). Other data have concluded that ARBs offer no renal benefit in ACE-intolerant people at high vascular risk, but without macroalbuminuria.\textsuperscript{2} Evidence from the ROADMAP trial in 4500 patients with type 2 diabetes without microalbuminuria showed that target BP achievement in patients treated with olmesartan 40 mg was associated with increased time to onset of microalbuminuria. There was no significant difference in renal function between the two study groups (a doubling of the serum creatinine level occurred in approximately 1% of the patients in each study group). Although the analysis is markedly underpowered for CV end points, fatal CV events occurred in more patients in the olmesartan group than in the placebo group—15 (0.7%) vs 3 (0.1%) (P=0.01).\textsuperscript{11} This difference could be explained in part by a higher number of deaths from CV causes among patients with preexisting coronary heart disease. However, this was also discussed as a possible CV safety signal together with a similar signal from the ORIENT trial (566 patients with type 2 diabetes and overt nephropathy), despite reduction in BP values and improved renal outcomes with the same RAAS-blocking agent.\textsuperscript{12}

An analysis of 19 randomized trials\textsuperscript{13} in predominantly hypertensive patients since 2000 showed that only 3 trials (ASCOT-BPLA [Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure–Lowering Arm],\textsuperscript{14} ADVANCE,\textsuperscript{15} and HYVET [Hypertension in the Very Elderly Trial])\textsuperscript{16} had a significant reduction in all-cause mortality. The successful treatments in these three studies were amlopidine (± perindopril), perindopril + indapamide, and indapamide (± perindopril), respectively.

### Specific combinations

Many hypertensive patients in clinical practice receive more than one antihypertensive drug, and the use of combination therapy is widely recommended in hypertension guidelines.

In the very large ONTARGET trial (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial),\textsuperscript{56} telmisartan and the combination of telmisartan and ramipril were compared with ramipril alone in patients with CV disease or diabetes with end-organ damage. There were no significant differences between the telmisartan and ramipril groups for any renal, CV, or mortality end point. However, the combination was more effective than ramipril alone in preventing new-onset microalbuminuria and progression of preexisting microalbuminuria. On the other hand, the primary renal end point, the composite of doubling of serum creatinine, dialysis or death, occurred significantly more frequently with the combination than with ramipril (P<0.0001). Thus, addition of telmisartan to ramipril reduced the incidence of proteinuria, but caused a more rapid decline in GFR, increased the incidence of major renal events, and showed no benefit in terms of CV events or mortality.

ADVANCE is the largest trial performed in diabetics, involving 11 140 patients. It compared a fixed-dose combination of perindopril and the thiazide diuretic indapamide with placebo in patients with type 2 diabetes and a history of major CV disease or at least one other CV risk factor.\textsuperscript{10,57} Combination therapy reduced the composite renal end point (new-onset microalbuminuria, new-onset nephropathy, doubling of serum creatinine, or end-stage renal disease) by 21% (HR, 0.79; P<0.0001). There were also significant reductions in new-onset microalbuminuria (21%) and progression from microalbuminuria to macroalbuminuria (31%). In contrast to the trials of ARBs described in the previous section, the renal benefits of the perindopril + indapamide combination were accompanied by significant reductions in all-cause mortality (by 14%, P=0.025), CV death (by 18%, P=0.027) and coronary events (by 14%, P=0.020). At least three further features of the ADVANCE trial are notable. Firstly, almost all other antihypertensive treatments were allowed (including RAAS inhibitors in 73% of patients of the control group, a first in these trials), except that thiazide diuretics were not permitted. Regression of albuminuria by at least one stage was observed in 50.2% of patients in the placebo group; nonetheless, active treatment provided a further benefit of 16% in the incidence of regression (P=0.0017). Secondly, significant reductions in renal events were seen in all subgroups of patients defined by baseline BP, including those with starting BP below 125/75 mm Hg. Indeed, the lowest risk for renal events was observed in patients with achieved BP levels below 110 mm Hg systolic or 65 mm Hg diastolic. Thirdly, a recent analysis has shown that the relative risk of all-cause mortality was reduced to a similar extent in patients with or without nephropathy, and whatever their CKD stage at baseline. One issue not resolved by ADVANCE was whether the observed benefits were independent of BP reduction, because the BP achieved was lower in the active treatment group by an average of 5.6 mm Hg systolic and 2.2 mm Hg diastolic. However, since the majority of diabetic patients with hypertension in clinical practice do not reach their target BP,\textsuperscript{18} the greater antihypertensive efficacy of the perindopril + indapamide combination could be regarded as an additional positive result.

The third trial in this group is ACCOMPLISH (Avoiding Cardiovascular Events through COMbination therapy in Patients Living with Systolic Hypertension),\textsuperscript{58} which compared two fixed-dose combinations, benazepril + amlodipine and benazepril + hydrochlorothiazide, in patients with hypertension and a history of CV disease or diabetes; approximately 60% of randomized patients had diabetes. The primary end point was the composite of CV events and CV death, and the trial was halted prematurely due to a significant reduction in this end point in the benazepril + amlodipine group (HR, 0.80; P<0.001). There was a significant reduction in the compo-
ite of all CV events (17%; \(P=0.002\)), but the reductions in all-cause death (10%), CV death (20%), and stroke (16%) did not reach statistical significance. The primary renal end point, the composite of doubling of serum creatinine and end-stage renal disease, was almost halved in the benazepril + amlodipine group (HR, 0.52; \(P<0.0001\), due mainly to a 49% reduction in doubling of serum creatinine (\(P<0.0001\)). As in the ADVANCE trial, dialysis was infrequent, performed in 7 patients in the benazepril + amlodipine group and 13 patients in the benazepril + hydrochlorothiazide group (NS). Despite the marked reduction in later-stage renal events with benazepril + amlodipine, the proportion of patients with baseline microalbuminuria who regressed to normoalbuminuria was substantially lower in this group (41.7%) than with benazepril + hydrochlorothiazide (63.3%, \(P=0.0016\)). The systolic BP level in the two treatment groups differed by less than 1 mm Hg.

Of note, both the perindopril + indapamide and the benazepril + amlodipine combinations have been investigated extensively in additional studies, and have shown specific beneficial actions, additional to BP lowering, that were greater with the combination than with the individual components. For example, perindopril + indapamide has been shown to improve the microcirculation in humans, with increased myocardial capillary density and improved coronary perfusion.\(^{50}\)

**Intensive therapy—more is not always better**

The recent ACCORD study (Action to Control Cardiovascular Risk in Diabetes)\(^{61}\) evaluated the benefit of intensive BP lowering to a target of <120 mm Hg systolic compared with standard therapy with a target of <140 mm Hg in type 2 diabetics. The study treatments used in both groups were at the discretion of the individual investigators. The mean number of antihypertensive drugs taken at 1 year was 3.4 in the intensive group and 2.1 in the standard therapy group, and by the end of the study 41% of patients in the intensive group were taking drugs from ≥4 classes (including RAAS inhibitors). Achieved BPs averaged 119/64 mm Hg in the intensive group and 134/71 mm Hg with standard therapy. There was a significant reduction in the occurrence of macroalbuminuria in the intensive group (6.6% vs 8.7%, \(P=0.009\), but elevated serum creatinine was reported more frequently with intensive (23.8%) compared with standard therapy (15.5%; \(P<0.001\)). There was no benefit from intensive therapy in the primary end point (the composite of myocardial infarction, stroke, or CV death), or in all-cause and CV mortality, or in the frequency of end-stage renal disease or the need for dialysis. On the other hand, there was a marked reduction in the frequency of stroke with intensive therapy (HR, 0.59; \(P=0.01\)). For a summary of results of trials with renal end points in patients with diabetes mellitus, see Table I.\(^{50}\)

![Table I. Summary of results of large randomized trials with renal end points including patients with diabetes mellitus.](Image)

Results should be interpreted line by line, in comparison with a control group specific to the trial. More extensive assessment is available in reference 62.

Abbreviations: *renal events; **urinary albumin/creatinine ratio; † urinary albumin excretion rate; ‡ doubling serum creatinine; NS, not significant; RRR, relative risk reduction.

Study acronyms: refer to the Study Acronyms box on page 49.
Conclusions

Antihypertensive drugs and combinations differ widely in their effects, particularly regarding their capacity to reduce mortality, and the differences may be especially important in diabetic patients. The near-universal use of more than one drug class to achieve target BP in diabetic patients has important implications for clinical trial design and interpretation. Beneficial and adverse effects of one drug may be accentuated or minimized by concomitant therapies, but the types and doses of background therapies are often not standardized in trials. Finally, the strategy of simply adding additional drugs to patients already receiving two or more drugs in an effort to drive BP to ever-lower levels may be counterproductive.

A lack of concordance among different renal end points and between renal and mortality end points emerged clearly from this review, and is consistent with concerns expressed over the use of proteinuria as a surrogate for kidney disease progression. Ultimately, all-cause and CV mortality are the most reliable trial end points, and so far only few and limited subgroups of trials have demonstrated simultaneous reduction of micro-albuminuria and mortality. Finally today, the ADVANCE trial (conducted with the perindopril + indapamide combination versus a control group including RAAS inhibitors) is the first main trial to have shown unequivocal renal and mortality benefits in a large population of diabetic patients.

References

34. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-
Reducing both microalbuminuria and cardiovascular events – García-Donaire and Ruilope

Keywords: angiotensin-converting enzyme inhibitor; cardiovascular event; chronic kidney disease; hypertension; microalbuminuria; renin-angiotensin-aldosterone system inhibitor; type 2 diabetes mellitus
La microalbuminurie est un indicateur de l’atteinte de la fonction rénale ainsi qu’un marqueur de risque reconnu pour les événements cardio-vasculaires et la mortalité. La coexistence d’un diabète de type 2 et d’une hypertension artérielle augmente de façon significative le risque de pathologie cardio-rénale et le développement d’événements cardio-vasculaires et, de façon potentielle, la mortalité. Ces faits ont conduit à la recommandation d’utiliser l’albuminurie comme cible thérapeutique. L’hyperactivité du système rénine-angiotensine-aldostérone (SRAA) a été invoquée pour expliquer la détérioration de la fonction rénale chez les patients présentant une néphropathie diabétique. Les augmentations de la microalbuminurie sont atténuées en parallèle avec la réduction de la pression artérielle obtenue avec les inhibiteurs du SRAA. En dépit d’un nombre élevé d’essais thérapeutiques contrôlés et randomisés bien conçus, des incertitudes existent pour définir le traitement antihypertenseur optimal chez les patients diabétiques, en particulier en ce qui concerne l’existence ou non de propriétés réno-protectrices spécifiques des inhibiteurs du SRAA, ainsi que sur la relation entre les critères de jugement rénaux et de mortalité. En outre, la plupart des patients diabétiques hypertendus nécessitent des associations thérapeutiques comprenant deux ou plus médicaments antihypertenseurs, ce qui peut compliquer l’interprétation des faits. Les résultats des études publiées ne concordent pas tous, en montrant des variations substantielles dans les effets du traitement selon les différents critères de jugement, qu’ils soient rénaux, cardio-vasculaires ou de mortalité. Les associations d’antihypertenseurs diffèrent également dans leur capacité à prévenir les événements rénaux et cardio-vasculaires majeurs, même si leurs effets sur la réduction de la pression artérielle sont similaires. Enfin, dans la plupart des études utilisant les antihypertenseurs – même si ce n’est pas le cas pour toutes – réduction de la microalbuminurie et protection rénale sont étroitement associées. Cet article examine dans quelle mesure les modifications de la protéinurie liées au traitement correspondent à une modification du risque cardio-vasculaire chez les patients ayant un diabète de type 2.
Hypertension is prevalent in and remains an important risk factor in the elderly and very elderly. Randomized controlled outcome trials have shown the benefit of antihypertensive treatment in patients with systolic-diastolic hypertension and in patients with isolated systolic hypertension, aged 60 years and over. More recently, a benefit has also been shown in octogenarians with hypertension. The results of a meta-analysis of 1670 patients 80 years and over, who were included in trials in the elderly, suggested a benefit of treatment for cardiovascular events, stroke and heart failure, but not for mortality in these very old patients. The properly designed HYVET (HYpertension in the Very Elderly Trial) randomly assigned 3845 patients who were 80 years of age or older to receive either the diuretic indapamide or matching placebo. The ACE inhibitor perindopril, or matching placebo, was added if necessary to achieve the target blood pressure of 150/80 mm Hg. Active treatment was associated with a 30% reduction in the rate of stroke (P=0.06), a 21% reduction in the rate of death from any cause (P=0.02), and a 64% reduction in the rate of heart failure (P<0.001). In the HYVET-COG substudy (HYpertension in the Very Elderly Trial–COGNitive function), incident dementia tended to be 14% lower in the active treatment group; when combined with the results from other placebo-controlled trials of antihypertensive treatment, the combined risk reduction became significant (13%, P=0.045). In the fracture substudy, Cox proportional hazards regression analysis, with adjustment for baseline characteristics, indicated that incident fracture risk was 42% (P=0.05) lower in the active treatment group. Based on HYVET results, recent guidelines for the management of hypertension recommend that antihypertensive treatment should be extended to hypertensive patients aged 80 years or above.

Epidemiological studies show that blood pressure increases with age. Whereas systolic blood pressure continues to rise with age, diastolic blood pressure plateaus in the sixth decade of life and may even decrease thereafter. This results in a wider pulse pressure at higher age, mainly attributed to structural alterations of the arterial wall with aging, leading to increased stiffness of the aorta and elastic arteries due to loss of elasticity; in addition, atherosclerosis may contribute to the process. Therefore, hypertension is common in the elderly, with a large prevalence of isolated systolic hypertension, and high blood pressure remains an important cardiovascular risk factor in the elderly and very elderly, respectively defined as aged ≥60 years and aged ≥80 years.
Blood pressure as a risk factor at older age

The Prospective Studies Collaboration analyzed the age-specific relevance of usual blood pressure to vascular mortality in a meta-analysis of individual data for one million healthy adults from 61 prospective studies. The study showed that systolic and diastolic blood pressure are strongly and directly related to stroke mortality, mortality from ischemic heart disease, and other vascular mortality, and that this was the case in each decade of age, including in the elderly and very elderly. For example, age-specific hazard ratios for stroke mortality, associated with a 20 mm Hg lower usual systolic blood pressure, amounted to 0.43 (95% confidence interval [CI], 0.41-0.45) at ages 60-69 years, 0.50 (0.48-0.52) at ages 70-79 years, and 0.67 (0.63-0.71) at ages 80-89 years. Controlling for blood cholesterol, diabetes, weight, alcohol consumption, and smoking at baseline did not materially alter the estimated hazard ratios. Results were similar in men and women and were also observed for ischemic heart disease mortality and other vascular mortality. However, these observational data do not necessarily mean that lowering blood pressure by use of antihypertensive drugs would improve prognosis in these patients.

Benefit of antihypertensive treatment in the elderly

**Systolic-diastolic hypertension**

As early as 1992, Thijs et al reported a meta-analysis of 6 randomized controlled outcome trials of antihypertensive drug treatment in patients with systolic-diastolic hypertension, aged 60 years and over. In trials including younger as well as elderly patients, only the subgroups above the age of 60 years were considered. The analysis included a total of 8420 elderly patients, of whom 4253 were in the control groups and 4169 in the intervention groups. The percentage of women ranged from 45% to 70% in these trials. The analysis was restricted to mortality. Whereas all-cause mortality tended to decrease by 9% (95% CI, -1 to 18), cardiovascular, cerebrovascular, and coronary mortality decreased significantly in the active treatment groups compared with the control groups, by 22% (10-32), 33% (9-50), and 26% (9-40), respectively. Furthermore, the significant overall decrease in cardiovascular, cerebrovascular, and coronary mortality was not caused by any particular study. There was no significant influence on noncardiovascular mortality (+11%; 95% CI, –6 to 31). Notably in these older trials, first-line treatment consisted of a diuretic or a β-blocker, with a variety of additional blood pressure-lowering drugs for better blood pressure control, such as reserpine, methyldopa, hydralazine, nifedipine, and clonidine. Blood pressure was lower in the intervention group than in the control group of these trials, by on average 5 to 22 mm Hg for systolic blood pressure and by 2 to 10 mm Hg for diastolic blood pressure. The authors of the meta-analysis concluded that pharmacological treatment of elderly patients with combined systolic and diastolic hypertension decreased cardiovascular mortality, whereas the incidence of fatal noncardiovascular end points was not significantly affected.

**Isolated systolic hypertension**

Isolated systolic hypertension is quite prevalent in subjects older than 60 years and is rare at younger ages. In 1999, Staessen et al published a meta-analysis of 3 placebo-controlled outcome trials on antihypertensive drug treatment of this disorder. Entry systolic blood pressure was at least 160 mm Hg in all trials, whereas the upper diastolic blood pressure was less than 90 mm Hg in SHEP (Systolic Hypertension in the Elderly Program), and less than 95 mm Hg in the Syst-Eur trial (Systolic Hypertension in Europe) and in the Syst-China trial (Systolic Hypertension in China). Average ages were 72, 70 and 67 years, respectively, and the percentage of males 43%, 33% and 64%. A total number of 11825 patients were included in the meta-analysis. All-cause mortality was reduced by 17% (P<0.01) and cardiovascular mortality by 25% (P=0.005). All fatal and nonfatal cardiovascular events, strokes, and coronary events were reduced by 32% (P<0.001), 37% (P<0.001), and 25% (P<0.005), respectively. Active treatment, in SHEP, was started with the diuretic chlorthalidone, with the possible addition of atenolol or reserpine; in Syst-Eur and Syst China, active treatment commenced with the calcium channel blocker nifedipine, with the possible addition of enalapril and/or hydrochlorothiazide. Mean net effects of active treatment on blood pressure ranged from 6.9 to 11.5 mm Hg for systolic blood pressure and from 2.3 to 4.1 mm Hg for diastolic blood pressure. The authors concluded that the pooled results of the 3 placebo-controlled trials in older patients with isolated systolic hypertension prove that antihypertensive treatment is beneficial if, on repeated measurements, systolic pressure is 160 mm Hg or higher.

**Benefit of antihypertensive treatment in the very elderly**

**The INDANA meta-analysis**

A number of the randomized controlled trials on the benefit of antihypertensive treatment in the elderly included patients aged 80 years and over. The INDANA (INdividual Data ANalysis of Antihypertensive...
sis of Antihypertensive drug intervention) working group took
the initiative to meta-analyze the results in these octogenarians.14,15 The meta-analysis included data from 4 trials on di-
astolic hypertension6-8,16 and 2 on systolic hypertension.11,12
The very elderly subgroups represented about 15% of the
participants in the various trials and involved 1670 subjects
between 80 and 98 years of age (mean age, 83 years), of
whom 76% were women. First-line treatment consisted of a
diuretic, a β-blocker, or a calcium channel blocker in the in-
cluded trials. As shown in Figure 1,13 all-cause and cardiovas-
cular mortality were not significantly different between active
treatment and control. However, there was a 22% (P=0.01)
reduction in the incidence of major cardiovascular events, a
34% (P=0.01) reduction in fatal and nonfatal strokes, and a
39% (P<0.05) reduction in heart failure in the active treatment
groups. There was only a nonsignificant tendency for a reduc-
tion in major coronary events (23% reduction). Overall, the re-
sults suggest a significant benefit of treatment in very old pa-
tients for cardiovascular events, stroke, and heart failure, but
not for mortality. In the overall analysis, all-cause mortality
tended to increase by 6% (P=0.30) on active treatment, but
the increase amounted to 14% (P=0.05) in the double-blind
trials,6,8,11,12 which was a reason for concern. The authors also
noted that the apparent beneficial results were not robust,
because of the relatively small number of subjects, and that
confirmation would be needed through a properly designed
trial in very old people aged 80 years or more.

◆ The HYpertension in the Very Elderly Trial pilot study
Before embarking on the main HYpertension in the Very Eld-
erly Trial (HYVET), the HYVET investigators performed a pi-
lot study to test the trial administration, obtain a preliminary
estimate of the rate of recruitment, test the techniques of
measurement and recording, determine the safety of active
treatment, and obtain a rough estimate of any treatment ef-
fects.17 In this multicenter international open trial, 1283 pa-
tients aged over 80 years and having sustained blood pres-
sures of 160-219/90-109 mm Hg were allocated randomly
to 1 of 3 treatments—a diuretic-based regimen, an ACE in-
hibitor regimen, or no treatment. The protocol permitted dos-
es of the drug to be titrated and slow-release diltiazem to be
added to active treatment. Target blood pressure was <150/
80 mm Hg and mean follow-up was 13 months. In the com-
bined actively treated groups, the reduction in the relative haz-
ard rate (RHR) for stroke events was 0.47 (95% CI, 0.24-0.93;
P<0.02). However, the estimate of total mortality supported
the possibility of excess deaths with active treatment (RHR 1.23; 95% CI, 0.75-2.01; 
P<0.42). The preliminary results suggested that
treatment of 1000 patients for one year may reduce stroke
events by 19, but may be associated with 20 extra nonstroke
deaths, and supported the need for the main HYVET trial.

◆ The main HYVET trial
In the meantime, the results of the main HYVET
have become available.18,19 In the trial, 3845 patients
aged 80 or above, with sustained systolic blood pres-
sures between 160 and 199 mm Hg, were ran-
domly assigned to receive either the diuretic indis-
perindopril (2 to 4 mg), or
matching placebo, to which the angiotensin-converting-enz-
yme (ACE) inhibitor perindopril (2 to 4 mg), or
matching placebo, could be added if necessary
to achieve the target blood pressure of 150/80
mm Hg. At the start of the trial, in the year 2000,
the mean diastolic blood pressure had to be 90 to 109 mm Hg;
but in 2003, a protocol amendment allowed the inclusion of
patients with isolated systolic hypertension. At 2 years, 73.4% of
actively treated patients were on combination treatment,
and 85.2% of the patients were on placebo. Patient age av-
eraged 83.6 years and the mean sitting blood pressure was
173.0/90.8 mm Hg at baseline. At 2 years, blood pressure
was 150/6.1 mm Hg lower in the active treatment group than
in the placebo group. The incidence of the primary end point,
that is, fatal and nonfatal stroke, was reduced by 30% (95% CI,
1 to 51; P=0.06), and the rate of fatal stroke was reduced by
39% (95% CI, 1-62; P<0.05).

Table I (page 60)19 summarizes the effects on other end points.
The significant 21% reduction in the rate of all-cause mortal-
ity is remarkable in view of the concern raised by the pilot
trial and the INDANA meta-analysis. In the meta-analysis,
the significant reductions in stroke and heart failure were
associated with a significant increase in mortality in the double-
blind trials, although not in the overall analysis. In HYVET,
there were no significant differences between the groups with re-
gard to changes in serum potassium, uric acid, glucose, and
creatinine, and there were fewer serious adverse events in
Angoulvant et al. noticed that results of randomized controlled trials on antihypertensive treatment in very old patients are consistent in showing reduced rates of stroke, heart failure, and cardiovascular events, but inconsistent with regard to the effect on total mortality. An updated meta-analysis including HYVET confirmed the beneficial effect on stroke, heart failure, and cardiovascular events, but the overall relative risk for total mortality was not significant (RHR, 1.06; 95% CI, 0.89-1.25). It should be noted that there was significant heterogeneity for mortality between HYVET and the other trials, which could be due to methodological aspects, the study population, type and dose of antihypertensive treatment, and the achieved difference in blood pressure. The authors concluded that the heterogeneity could not be explained by the double-blind character of HYVET, differences in the follow-up duration between trials, the health condition of the various study populations, and the use of long-acting thiazide (like) diuretics as first-line therapy. However, exploratory meta-regression analysis suggested possible associations between an increase in total mortality and higher intensity of antihypertensive treatment. A similar association was observed between the increase in total mortality and higher intensity of antihypertensive treatment as first-line therapy. Nevertheless, the HYVET findings, when included in a meta-analysis with other trials, might support antihypertensive treatment to reduce incident dementia. Finally, the effects of antihypertensive therapy on cognitive function in controlled trials have been conflicting and meta-analyses of the trials have not provided clear evidence of whether antihypertensive treatment reduces dementia incidence. Participants in HYVET had no clinical diagnosis of dementia at baseline. In the HYVET-COG substudy (Hypertension in the Very Elderly Trial—COGnitive function), cognitive function was assessed at baseline and annually thereafter in all participants, using the Mini Mental State Examination (MMSE); cases of dementia were identified by various means during follow-up. There were 263 incident cases of dementia in the 3336 HYVET participants with at least one follow-up assessment, a prerequisite for inclusion in the substudy. The rates of incident dementia were 38 per 1000 patient-years in the placebo group and 33 per 1000 patient-years in the treatment group. There was no significant difference between treatment and placebo groups (RHR, 0.86; 95% CI, 0.67-1.09). However, when these data were combined in a meta-analysis with other placebo-controlled trials of antihypertensive treatment, the combined risk ratio favored treatment (RHR, 0.87; 95% CI, 0.76-1.00; P=0.045). The authors concluded that antihypertensive treatment in the very elderly patients included in HYVET does not statistically reduce incidence of dementia. This negative finding might have been due to the short follow-up, owing to early termination of the trial, or to the modest effect of treatment. Nevertheless, the HYVET findings, when included in a meta-analysis with other trials, might support antihypertensive treatment to reduce incident dementia. Finally, the mean change in MMSE score in HYVET at 2 years was –1.1 points (standard deviation (SD)=3.9) in the placebo group versus 0.7 points (SD=4.0) in the active treatment group (P=0.08).

### Table 1. Main fatal and nonfatal end points in the intention-to-treat analysis in HYVET (Hypertension in the Very Elderly Trial).


<table>
<thead>
<tr>
<th>End point</th>
<th>Rate per 1000 patient-years</th>
<th>Unadjusted hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal or nonfatal</td>
<td>12.4</td>
<td>17.7</td>
<td>0.70 (0.49-1.01)</td>
</tr>
<tr>
<td>Death from stroke</td>
<td>6.5</td>
<td>10.7</td>
<td>0.61 (0.38-0.99)</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From any cause</td>
<td>47.2</td>
<td>59.6</td>
<td>0.79 (0.65-0.95)</td>
</tr>
<tr>
<td>From noncardiovascular or unknown causes</td>
<td>23.4</td>
<td>28.9</td>
<td>0.81 (0.62-1.06)</td>
</tr>
<tr>
<td>From cardiovascular cause</td>
<td>23.9</td>
<td>30.7</td>
<td>0.77 (0.60-1.01)</td>
</tr>
<tr>
<td><strong>Fatal or nonfatal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any heart failure</td>
<td>5.3</td>
<td>14.8</td>
<td>0.36 (0.22-0.58)</td>
</tr>
<tr>
<td>Any cardiovascular event*</td>
<td>33.7</td>
<td>50.6</td>
<td>0.66 (0.53-0.82)</td>
</tr>
</tbody>
</table>

* Any cardiovascular event was defined as death from cardiovascular causes or stroke, myocardial infarction or heart failure.

**HYVET substudies**

* **Incident dementia and cognitive function**

Observational epidemiological studies have shown a positive association between hypertension and risk of incident dementia; however, the effects of antihypertensive therapy on cognitive function in controlled trials have been conflicting and meta-analyses of the trials have not provided clear evidence of whether antihypertensive treatment reduces dementia incidence. In conclusion, HYVET provided unique evidence that antihypertensive treatment in the very elderly, based on sustained-release indapamid and the possible addition of perindopril, with the goal of achieving a target blood pressure of 150/80 mm Hg, is beneficial and safe, and is associated with reduced risks of death from stroke, death from any cause, and heart failure. Whether treatment of patients with grade 1 hypertension, and whether further reduction of blood pressure would be more beneficial still needs to be established. Finally, it would be premature to extrapolate the results from HYVET to patients in this age group who are frailer.

**An updated meta-analysis**

After the publication of the results of the HYVET trial, Bejan-Angoulvant et al. noticed that results of randomized controlled trials on antihypertensive treatment in very old patients are consistent in showing reduced rates of stroke, heart failure, and cardiovascular events, but inconsistent with regard to the effect on total mortality. An updated meta-analysis including HYVET confirmed the beneficial effect on stroke, heart failure, and cardiovascular events, but the overall relative risk for total mortality was not significant (RHR, 1.06; 95% CI, 0.89-1.25). It should be noted that there was significant heterogeneity for mortality between HYVET and the other trials, which could be due to methodological aspects, the study population, type and dose of antihypertensive treatment, and the achieved difference in blood pressure. The authors concluded that the heterogeneity could not be explained by the double-blind character of HYVET, differences in the follow-up duration between trials, the health condition of the various study populations, and the use of long-acting thiazide (like) diuretics as first-line therapy. However, exploratory meta-regression analysis suggested possible associations between an increase in total mortality and higher intensity of antihypertensive treatment. A similar association was observed between the increase in total mortality and the achieved systolic blood pressure reduction. The authors concluded that the most reasonable strategy in octogenarians is the one proposed by the HYVET trial, ie, a thiazide-like diuretic as first-line therapy and maximal antihypertensive therapy with two drugs in low doses.

**HYVET substudies**

* **Incident dementia and cognitive function**

Observational epidemiological studies have shown a positive association between hypertension and risk of incident dementia; however, the effects of antihypertensive therapy on cognitive function in controlled trials have been conflicting and meta-analyses of the trials have not provided clear evidence of whether antihypertensive treatment reduces dementia incidence. Participants in HYVET had no clinical diagnosis of dementia at baseline. In the HYVET-COG substudy (Hypertension in the Very Elderly Trial—COGnitive function), cognitive function was assessed at baseline and annually thereafter in all participants, using the Mini Mental State Examination (MMSE); cases of dementia were identified by various means during follow-up. There were 263 incident cases of dementia in the 3336 HYVET participants with at least one follow-up assessment, a prerequisite for inclusion in the substudy. The rates of incident dementia were 38 per 1000 patient-years in the placebo group and 33 per 1000 patient-years in the treatment group. There was no significant difference between treatment and placebo groups (RHR, 0.86; 95% CI, 0.67-1.09). However, when these data were combined in a meta-analysis with other placebo-controlled trials of antihypertensive treatment, the combined risk ratio favored treatment (RHR, 0.87; 95% CI, 0.76-1.00; P=0.045). The authors concluded that antihypertensive treatment in the very elderly patients included in HYVET does not statistically reduce incidence of dementia. This negative finding might have been due to the short follow-up, owing to early termination of the trial, or to the modest effect of treatment. Nevertheless, the HYVET findings, when included in a meta-analysis with other trials, might support antihypertensive treatment to reduce incident dementia. Finally, the mean change in MMSE score in HYVET at 2 years was –1.1 points (standard deviation (SD)=3.9) in the placebo group versus 0.7 points (SD=4.0) in the active treatment group (P=0.08).
In a subsequent paper, Peters et al. modeled dynamics of cognition in relation to treatment of hypertension to see if treatment effects might be better discerned by a model that included baseline measures of cognition and consequent mortality. They observed that the probability of maintaining cognitive function, based on baseline function, was slightly higher in the actively treated group and that people treated with antihypertensives may maintain their cognitive health state for longer. However, the authors concluded that these findings need to be confirmed by additional studies.

**Fracture risk**

Fractures may have serious implications in an elderly individual. In view of the fact that thiazide diuretics and indapamide reduce urinary calcium and may increase bone mineral density, a fracture substudy was designed to investigate whether or not the HYVET antihypertensive treatment would reduce the fracture rate in very elderly hypertensive subjects. In the trial, considerable care was taken to ascertain any fractures and to identify risk factors for fracture. Incident fractures were validated and analyzed based on time to first fracture. Among 102 reported fractures, there were 90 validated first fractures, 38 in the active group and 52 in the placebo group. When the treatment groups were compared using a Cox proportional hazards regression model, the group receiving antihypertensive treatment tended to be favored, with a hazard ratio of 0.69 (95% CI, 0.46-1.05; P=0.086). Adjusting for the baseline factors that were indicated as potentially impacting on subsequent fracture (age, gender, and previous use of β-blockers) resulted in a hazard rate of 0.58 (95% CI, 0.33-1.00; P=0.0498). The authors concluded that despite the lowering of blood pressure, treatment with a thiazide-like diuretic and an ACE inhibitor does not increase, and may in fact decrease, fracture rate.

**Impact of HYVET on hypertension guidelines**

The 2007 ESH/ESC (European Society of Hypertension/European Society of Cardiology) guidelines regretted that, although there was overwhelming evidence of the benefits of pharmacological lowering of blood pressure in the elderly, this evidence was inconclusive for patients aged 80 years or above, in whom only a meta-analysis of a limited number of patients from various trials and the HYVET pilot study were available, suggesting beneficial effects for morbidity, but not for mortality. In the meantime, this gap has been filled with the publication of the HYVET results, which indicate that even in the very elderly stratum of the population, antihypertensive treatment is well tolerated and not only prevents cardiovascular morbidity events, but also translates into prolongation of life. However, because hypertensive patients were generally in good physical and mental condition, with a low rate of cardiovascular disease, the extent to which the results can be extrapolated to more fragile octogenarians is uncertain. In addition, the premature interruption of the trial made its duration so short (1.8 years) as to leave unanswered the question of whether the benefit of antihypertensive treatment persists for several years. Finally, only a small fraction of the participants was more than 85 years old, which leaves open the question of whether the benefit extends to older ages.

On the basis of the important evidence provided by HYVET, and within the context of its limitations, the reappraisal of the European hypertension guidelines published in 2009 recommended that antihypertensive treatment should be extended to hypertensive patients aged 80 years or above. An evidence-based general recommendation was given to prescribe antihypertensive treatment to octogenarians with systolic blood pressure above 160 mm Hg, with the target to lower it below 150 mm Hg. However, due to differences in the general health of very elderly patients, the decision to treat should be taken on an individual basis, and blood pressure lowering should be in any case gradual and carefully monitored. The optimal blood pressure goal for reducing cardiovascular events and mortality is not known.

More recently, the ACCF/AHA (American College of Cardiology Foundation/American Heart Association) 2011 Expert Consensus Document on Hypertension in the Elderly stated that the HYVET results provide clear evidence that blood pressure lowering by drugs is associated with definite cardiovascular benefits in patients aged 80 years or above, and that previous guidelines, which avoided firm recommendations on drug treatment in octogenarians because of questionable benefit, should be modified accordingly.

**References**


11. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive

**Keywords:** antihypertensive treatment; dementia; elderly; fractures; hypertension; mortality; octogenarians; prognosis

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**Le défi de l’abaissement de la pression artérielle chez les personnes très âgées**

Chez les personnes âgées et très âgées, l’hypertension est très répandue et reste un important facteur de risque. Des études contrôlées randomisées ont montré le bénéfice du traitement antihypertenseur chez des patients atteints d’hypertension systolo-diastolique et chez ceux ayant une hypertension systolique isolée, âgés de 80 ans et plus. Un bénéfice a également été démontré plus récemment chez des octogénaires hypertendus. Les résultats d’une méta-analyse de 1 670 patients de 80 ans et plus, inclus dans des études sur les personnes âgées, ont montré un bénéfice du traitement pour les événements cardio-vasculaires, les accidents vasculaires cérébraux (AVC) et l’insuffisance cardiaque, mais pas pour la mortalité chez ces patients très âgés. La bien-nommée étude HYVET (Hypertension in the Very Elderly Trial) a inclus 3 845 patients de 80 ans ou plus sélectionnés au hasard pour recevoir soit l’indapamide, un diurétique, soit un placebo. Un inhibiteur de l’enzyme de conversion, le périndopril, ou un placebo d’aspect identique, était ajouté si nécessaire pour atteindre la pression artérielle cible de 150/80 mmHg. Le traitement était dit actif quand il s’associait à une réduction du taux d’AVC de 30 % (p = 0,06), une réduction du taux de décès toutes causes de 21 % (p = 0,02) et une réduction du taux d’insuffisance cardiaque de 64 % (p < 0,001). Dans la sous-étude HYVET-COG (Hypertension in the Very Elderly Trial–COGNitive function), l’incidence de la démence était plus faible de 14 % dans le groupe de traitement actif ; en associant les résultats d’autres études de traitement antihypertenseur contrôlées contre placebo, la diminution du risque associé devenait significatif (13 %, p = 0,045). Dans la sous-étude sur les fractures, l’analyse de régression du risque proportionnel de Cox, avec ajustement pour les caractéristiques initiales, a indiqué que le risque de fracture incidente était plus faible de 42 % (p = 0,05) dans le groupe de traitement actif. Se basant sur les résultats de l’étude HYVET, les directives récentes pour la prise en charge de l’hypertension recommandent que le traitement antihypertenseur soit élargi aux hypertendus de 80 ans et plus.
International surveys are consistent in showing that only a minority of hypertensive people get their blood pressure (BP) controlled to recommended targets. Trial data show that most hypertensive patients require at least two agents to reach BP targets. The latest European and American guidelines recommend that a large proportion of hypertensive patients should start treatment with two antihypertensive agents. In 2006, British guidance prioritized two combinations of therapy – “A + C” or “A + D” where “A” is an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), “C” is a calcium channel blocker and “D” is a diuretic. These combinations represent four of the five combinations recommended in the 2009 reappraisal of the European guidelines. In ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial), amlodipine plus perindopril (“A + C”) was shown to be superior to a β-blocker and a diuretic (“B + D”) in terms of preventing major cardiovascular events. More recently, the ACCOMPLISH (Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension) trial compared benazepril and amlodipine (“A + C”) with benazepril and thiazide (“A + D”). Despite very similar BP lowering, the “A + C” combination was significantly superior to the “A + D” combination in terms of the primary composite cardiovascular end point. Based on current trial evidence, it seems reasonable to conclude that the best evidence-based combination of antihypertensive medication is “A + C.” Consequently in 2011, the NICE guidelines from the UK recommend only “A + C” as the best drug combination. Then, if further BP-lowering is needed, a thiazide-like diuretic, such as indapamide or chlorthalidone, is recommended as step 3 therapy.

by N. R. Poulter, United Kingdom

The results from ASCOT highlight the potential importance of differences between BP-lowering regimens other than those attributable to clinic BP differences. The 34% reduction in the rate of new-onset diabetes associated with the amlodipine ± perindopril regimen compared with atenolol ± thiazide is a very good example of what is probably a BP-independent difference between two pairs of antihypertensive agents.”

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Hypertension management in the 21st century: major advances and achievements

Combination therapy in the management of hypertension: which one for which patient?

National and international surveys are consistent in showing that only a minority of hypertensive people get their blood pressure (BP) controlled to the currently recommended targets. Survey data from around the world show a wide range in awareness, treatment, and control of raised BP, and, with the exception of the USA, that only a minority of patients with a prior diagnosis of hypertension are receiving antihypertensive medication. Furthermore, in most countries, it is clear that only a minority of treated patients achieve BP control.

However, large improvements in BP management have been reported over relatively short time periods in several parts of the world. Reasons for these improvements are not definitively established, but include effective guideline dissemination,
better patient/doctor education, increased use of nondrug treatments, a pay-for-performance approach to management, and increased antihypertensive drug use. In representative samples of the English population, BP control rates rose from 6% to 28% between 1994 and 2006. In 2006, 61% were receiving two or more drugs to treat raised BP, compared with only 40% in 1994. Due to this improvement in management, more than half of treated patients had their BP under control in 2006, compared with 35% in 1994. The mean BP reductions achieved in randomized controlled trials (RCTs) serve to demonstrate that even in a context where patients and doctors are more likely to be motivated to achieve better BP control, systolic targets are achieved only by a minority of participants while, on average, diastolic targets are almost always achieved (Figure 1).
Among patients with type 2 diabetes and those with chronic renal failure, the lower BP targets that pertain to these groups (<130/80 mm Hg) are even less frequently achieved in RCTs. Indeed, the systolic target of <130 mm Hg had never been achieved in a morbidity/mortality hypertension trial in diabetic patients until the ACCORD trial (Action to Control Cardiovascular Risk in Diabetes) was published in 2010.

Guideline recommendations

Both the latest European guidelines (European Society of Hypertension [ESH]-European Society of Cardiology [ESC] 2007), which were reappraised in 2009, and American guidelines (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [JNC 7]) recommend that, for some hypertensive patients, therapy should be initiated with two drugs. While these two sets of guidelines are not consistent in terms of the specific population for which two-drug combinations are recommended, in both guidelines the recommendations apply to a significant proportion of the hypertensive population despite no RCT data being currently available to support the preferential use of this approach.

Which antihypertensive drug combinations should be used?

Guidelines around the world vary considerably in their recommendations for first-line antihypertensive agents. Thus, it is not surprising that the same guidelines also differ regarding optimal pairs of agents!

JNC 7—as shown in Figure 2—is not specific regarding which drug combinations to use, but does suggest that “thiazide-type” diuretics should usually be one of the components. This reflects the fact that all the RCT data supporting the use of diuretics have been based on either high-dose thiazides (usually with a potassium-sparing component), chlorthalidone, or indapamide. Contrary to popular belief, these last two agents are not thiazides. In the three trials in which low-dose thiazides have been used alone or as part of a combination and compared with another agent (ANBP2 [Second Australian National Blood Pressure Study], 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]), the thiazide was inferior to its comparator in terms of preventing major cardiovascular (CV) events. Nevertheless, low-dose thiazides are recommended in several sets of guidelines around the world and are commonly used as monotherapy and in combination therapy. This practice reflects cost issues rather than RCT-based evidence. Figure 3 shows the
ESH-ESC (2007) recommendations for optimal drug combinations. Unfortunately, it recommends combinations that have not been formally tried and tested in RCTs (eg, calcium channel blockers [CCB] plus β-blockers) and others that seem illogical due to some mechanistic overlap (eg, CCB plus thiazide diuretic). However, the combination of CCBs and β-blockers was used by a significant number of those in the ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial) trial who were randomized to the CCB (amlodipine) group. The combination of a CCB and a diuretic was used in the VALUE trial (Valsartan Antihypertensive Long-term Use Evaluation) in comparison with an angiotensin receptor blocker (ARB) (valsartan) plus a thiazide diuretic. However, although both drugs promote natriuresis—which presumably is responsible for at least part of the BP-lowering efficacy of these agents—this combination of drugs is quite commonly used in contemporary practice (at least in England!). This may, in part, reflect the fact that both classes of drugs have been shown to be effective as monotherapy in the elderly in trials such as Syst-Eur (Systolic Hypertension in Europe) and SHEP (Systolic Hypertension in the Elderly Program) and/or because diuretics (albeit ill-advisedly from a theoretical viewpoint) are often used to try to offset the ankle edema induced by dihydropyridine CCBS! One glaring error in Figure 3 is the use of “thiazide diuretics” as part of the hexagon. As described above, the RCT evidence for the benefits of true thiazides (at least at a low dose) on CV events is nonexistent and thus, this point on the hexagon should be labeled “diuretics” or “thiazide-like diuretics.”

In the 2009 reappraisal of the ESH-ESC guidelines, five combinations are recommended for priority use (Table I); the use of β-blockers plus CCBS is cited later on. In essence, there seems to be very little progress in the European recommendations between 2007 and 2009. Figure 4 summarizes the British Hypertension Society (BHS)/National Institute for Health and Clinical Excellence (NICE) recommendations of 2006.

This simple “A/CD” algorithm is based on the fact that, on average, younger people (excluding black people of African origin) have higher renin levels and respond better (in terms of BP reduction) to “A” drugs (angiotensin-converting enzyme [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” or “D” drugs (CCBs or diuretics, respectively). The “A/CD” algorithm published in 2006 began life as the “AB/CD” algorithm that was included in the BHS guidelines of 2004, and in which β-blockers were recommended as first-line agents for younger patients.

However, by 2006, the BHS along with NICE decided that β-blockers should be demoted to fourth-line therapy. The rationale for making that decision was based on four issues:
- Meta-analyses, including one from the Cochrane Collaboration, showed that β-blockers are less effective in preventing major CV events than the other major drug classes.
- Increasing data confirmed that β-blockers exert an adverse effect on the incidence of new-onset diabetes.
- The ASCOT-BPLA trial showed that the combination of a β-blocker and a thiazide was inferior to the combination of a CCB and an ACE inhibitor in terms of preventing CV events.
- Cost-effectiveness analyses showed β-blockers to be the least cost-effective drug class.

In 2011, following the usual rigorous systematic review approach, NICE modified its recommendations on drug sequencing as shown in Figure 5. The key changes are:
- Diuretics are demoted to 3rd-line agents except where there is intolerance to CCBS or when there is a high risk of heart failure.
- “A+C” is the only combination recommended in light of the results of the ACCOMPLISH trial (see below).
- The “Ds” recommended are either indapamide or chlorothalidone. Thiazides are specifically no longer recommended.

<table>
<thead>
<tr>
<th>Table I. Priority antihypertensive drug combinations (European guidance 2009).</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>ACE inhibitor plus diuretic</em></td>
</tr>
<tr>
<td><em>ARB plus diuretic</em></td>
</tr>
<tr>
<td><em>CCB plus diuretic</em></td>
</tr>
<tr>
<td><em>ACE inhibitor plus CCB</em></td>
</tr>
<tr>
<td><em>ARB plus CCB</em></td>
</tr>
</tbody>
</table>

**Figure 4. NICE/BHS 2006 recommendations.**

Abbreviations: BHS, British Hypertension Society; NICE, National Institute for Health and Clinical Excellence. A = ACE inhibitor (consider angiotensin-II receptor antagonist if ACE inhibitor–intolerant); C = calcium channel blocker; D = thiazide or thiazide-type diuretic.


**Table of Abbreviations**

- ACE: angiotensin-converting enzyme
- ARB: angiotensin receptor blocker
- CCB: calcium channel blocker
- A: ACE inhibitor
- AB: β-blocker
- D: thiazide diuretic
- CCB: calcium channel blocker
- β-blocker
- Step 1: Younger than 55 years
- Step 2: 55 years or older or black patients of any age
- Step 3: Add further diuretic therapy or β-blocker or α-blocker
- Step 4: Consider seeking specialist advice
several RCTs suggests that the use of ACE inhibitors may be "benefits beyond BP reduction." A meta-analysis of the effects precludes the possibility that certain agents may exert equally effective at preventing CV events. However, this implication that, for the same level of BP reduction, all drug classes are directly related to the degree of BP reduction.22 This implies that, for the same level of BP reduction, all drug classes are equally effective at preventing CV events. However, this implication precludes the possibility that certain agents may exert "benefits beyond BP reduction." A meta-analysis of the effects of ACE inhibitors on coronary heart disease (CHD) events in several RCTs suggests that the use of ACE inhibitors may be associated with CHD benefits beyond BP lowering.23 Similarly, an analysis of the impact of CCBs on stroke appears to suggest that CCBs generate benefits in terms of stroke prevention beyond BP effects.23

It is also clear that different antihypertensive agents exert different effects on other non-BP determinants of CV outcomes, including glucose, lipids, pulse rate, body weight, left ventricular hypertrophy, etc. It is therefore not too difficult to believe that for the same level of clinic BP reduction, different agents may generate different effects on CV protection.

Very few trials other than ASCOT [Anglo-Scandinavian Cardiac Outcomes Trial] have compared the CV effects of completely different pairs of antihypertensive agents. Most early trials compared single agents (± an unstructured assortment of add-on drugs) with placebo or with another single agent (± an unstructured assortment of add-on drugs). More recently, trials have usually specified the add-on agents, and the second sec-

The ASCOT trial
This trial included over 19,000 patients with hypertension and three or more other common CV risk factors, but without established CHD. It compared the effect of a standard antihypertensive regimen (β-blocker plus low-dose thiazide) versus a newer regimen (CCB plus ACE inhibitor).21 The newer regimen induced significantly lower average BPs than the standard regimen throughout the trial—although particularly in the first few months. The newer regimen was clearly superior in terms of preventing CV events overall and significantly so for most of the end points considered in the trial. The trial was stopped early because of significant beneficial effects on all-cause mortality associated with allocation to the amlodipine ± perindopril regimen. Such an effect on total mortality is a relatively unique finding in hypertension trials (see Table II page 68 to put these findings in perspective). However, it had the effect of generating insufficient power to allow evaluation of the primary end point effectively.

Subsequent analyses suggested that the CV benefits associated with the newer regimen were unlikely to be the result of superior BP reduction alone.25 Other possible contributors to the superior effects of the newer regimen included body weight, glucose, high-density lipoprotein cholesterol, triglycerides, creatinine, and potassium. Indeed, only changes in pulse rate did not favor the newer regimen. These ASCOT results highlight the potential importance of differences between BP-lowering regimens other than those attributable to clinic BP differences. The 34% reduction in the rate of new-onset diabetes associated with the amlodipine ± perindopril regimen compared with atenolol ± thiazide is a very good example of what is probably a BP-independent difference between two pairs of antihypertensive agents.25 These ASCOT findings are compatible with several previous trials that showed diuretics and β-blockers to have adverse effects on the incidence of new-onset diabetes, whereas other more recent trials have suggested a modest protective effect associated with renin-angiotensin system (RAS) blockade.27,28

After the main publication of the ASCOT-BPLA results,11,25 the findings of the CAFE (Conduit Artery Function Evaluation) substudy of ASCOT were published.23 This substudy, which measured central and brachial BP in a subgroup of trial participants, suggested that those receiving the amlodipine ± perindopril regimen had significantly lower central BPs compared with the atenolol ± perindopril group, while brachial BP differences were negligible. The authors concluded that these differential effects on central BP of the two antihypertensive regimens may be, in part at least, responsible for the differential effects on CV outcomes. More recently, two sets of analyses including...
ASCOT data have shown that long-term BP variability is a strong predictor of CV outcomes and that the amlodipine ± perindopril regimen generated much less BP variability than the atenolol ± thiazide regimen. Furthermore, these analyses suggested that the differential effects of the two regimens on BP variability were the likely mechanisms whereby differential effects on CV events were generated. Based on those findings, the NICE 2011 guidelines recognized BP variability as an independent risk factor for CV events and recommended the best-available treatment for suppressing BP variability.

Other trials of combinations of antihypertensive agents

The LIFE trial essentially compared β-blocker plus thiazide vs ARB plus thiazide. While achieving very similar effects on BP, the ARB-based regimen produced significantly better reductions in the composite CV primary end point. Interestingly, breakdown of this end point into its component parts revealed that the benefits were actually all due to superior stroke prevention with, if anything, marginally less effective CHD prevention.

The relative benefits of ACE inhibitors and ARBs have been controversial since the launch of the first ARB, losartan. The results of the ONTARGET trial (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) were eagerly awaited because this trial of 25,588 high-risk people compared the effects of an ACE inhibitor (ramipril) with an ARB (telmisartan) and the combination of both drugs. Overall, neither agent was superior to the other, nor to the combination. The ARB was nonsignificantly inferior to the ACE inhibitor in terms of preventing CHD events (hazard ratio [HR], 1.07 [0.94-1.22]) and the ARB was nonsignificantly superior to the ACE inhibitor in terms of stroke events (HR, 0.91 [0.79-1.05]).

### Table II. Effects of primary end point and mortality in the main clinical trials from the last decade, conducted among hypertensive and/or at-risk patients.

<table>
<thead>
<tr>
<th>Trial vs placebo</th>
<th>Comparators</th>
<th>Death from any cause (control arm), rate per 1000 patient-years</th>
<th>Primary end point</th>
<th>Cardiovascular mortality</th>
<th>All-cause mortality</th>
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<tbody>
<tr>
<td>ADVANCE</td>
<td>Perindopril/indapamide vs placebo on top of standard therapy</td>
<td>19.6</td>
<td>-9</td>
<td>0.041</td>
<td>-18</td>
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<td>HYVET</td>
<td>Indapamide/perindopril vs placebo</td>
<td>59.6</td>
<td>-30</td>
<td>0.06*</td>
<td>-23</td>
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<tr>
<td>TRANSCEND</td>
<td>Telmisartan vs placebo</td>
<td>24.9</td>
<td>-8</td>
<td>0.22</td>
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<tr>
<td>PROFESS</td>
<td>Telmisartan vs placebo</td>
<td>29.1</td>
<td>-5</td>
<td>0.23</td>
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<tr>
<td>NAVIGATOR</td>
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<td>-14</td>
<td>&lt;0.001</td>
<td>+9</td>
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<td>CHARM-Overall</td>
<td>Candesartan vs placebo</td>
<td>79.2</td>
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<td>0.005</td>
<td>-12</td>
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### Trials vs active treatment

<table>
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<tr>
<th>Trial</th>
<th>Comparators</th>
<th>Death from any cause (control arm), rate per 1000 patient-years</th>
<th>Primary end point</th>
<th>Cardiovascular mortality</th>
<th>All-cause mortality</th>
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</thead>
<tbody>
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<td>ALLHAT</td>
<td>Lisinopril vs chlorthalidone</td>
<td>17.3</td>
<td>-1</td>
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<td></td>
<td>Amlodipine vs chlorthalidone</td>
<td>17.3</td>
<td>-2</td>
<td>0.65†</td>
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<td>LIFE</td>
<td>Losartan/HCTZ vs atenolol/HCTZ</td>
<td>19.6</td>
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<td>0.009</td>
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<td>ANBIP-2</td>
<td>Enalapril vs HCTZ</td>
<td>17.1</td>
<td>-11</td>
<td>0.05</td>
<td>-1</td>
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<td>INVEST</td>
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<td>+1</td>
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<td>ASCOT</td>
<td>Amlodipine/perindopril vs β-blocker/HCTZ</td>
<td>15.5</td>
<td>-10</td>
<td>0.11**</td>
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<td>JIKEI</td>
<td>Valsartan add-on vs non-ARB</td>
<td>6.3</td>
<td>-39</td>
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<td>ONTARGET</td>
<td>Telmisartan vs ramipril</td>
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<td>+1</td>
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<td>Telmisartan + ramipril vs ramipril</td>
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<td>+10</td>
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<td>ACCOMPLISH</td>
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<td>&lt;0.001</td>
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<td>KYOTO</td>
<td>Valsartan vs non-ARB</td>
<td>7.2</td>
<td>-45</td>
<td>0.00001</td>
<td>-34</td>
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</table>

*Stopped prematurely due to survival benefits with indapamide/perindopril
**Stopped prematurely due to survival benefits with amlodipine/perindopril
†data not shown

**Abbreviation:** ARB, angiotensin receptor blocker; CV, cardiovascular; HCTZ, hydrochlorothiazide; NS, nonsignificant; RRR, relative risk ratio; SR, sustained release.

nonsignificant trends supported previous hypotheses of differential effects on specific end points, but perhaps most importantly from a practical viewpoint, the overall CV effects were not different. One of the equally interesting findings of the ONTARGET trial was that although the combination of the ACE inhibitor and the ARB induced significant additional BP reduction compared with the ACE inhibitor alone, no additional CV benefits were attributable to the combination of drugs compared with either single drug.

Importantly, and in stark contrast with the expectations of some, the combination of ARB and ACE inhibitor induced a significant increase in hard renal end points despite significant improvement in proteinuria. The obvious conclusion is that the beneficial effects on proteinuria are not necessarily mirrored (at least within the confines of a trial of up to 5 years’ duration) by benefits in hard renal or CV events.

The HYVET trial (Hypertension in the Very Elderly Trial) investigated the effect of placebo-controlled BP lowering using indapamide and perindopril, in those ≥80 years of age. The trial was stopped early due to the benefits on all-cause mortality associated with active treatment. As a result of early closure of the trial, the primary end point of stroke was not significantly improved. However, the merit of active intervention is compelling in light of the significant all-cause mortality effects, the large benefits in all CV events, and improved well-being.

The ACCOMPLISH trial set out to compare the CV effects of an “A + C” combination with an “A + D” combination (where “A” stands for an ACE inhibitor or an ARB, “C” stands for a CCB and “D” stands for a diuretic). This trial included 11 506 hypertensive patients at high risk for CV events, the majority of whom were diabetic. The trial was particularly relevant to the 2006 BHS/NICE guidance because the two combinations of drugs being compared were those recommended in these guidelines. BP was reduced very effectively in both treatment arms and to a similar extent, but not at the cost of serious postural hypotension. The effects on the primary outcome of the trial—a composite of CV events—and the individual CV end points, were in favor of the “A + C” combination (Figure 6). The beneficial effects of the “A + C” combination were almost identical among those with and without type 2 diabetes and in all other subgroups. Consequently, it seems reasonable to conclude that, pending any further contradictory data, “A + D” is an inferior combination compared with “A + C” in terms of preventing CV events. These data supported by the metabolic data from the STAR trial (Study of Trandolapril/verapamil SR And insulin Resistance) provide compelling support for the selection of the “A + C” combination in preference to any other.

The VALUE trial compared the effects of an ARB-based regimen with a CCB-based regimen (adding a thiazide to both groups as second-line therapy) among 15 245 hypertensive patients at high CV risk. Unfortunately, the results were at least in part confounded by superior BP lowering achieved in the CCB-based group, particularly in the first 6 months of the trial. The CCB-based regimen tended to be better than, or at least as good as, the ARB-based regimen in terms of preventing most CV events. Various post hoc analyses implied that these differences in CV prevention were induced by the dif-

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**Table 1. Effects on primary and other end points.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite death from cardiovascular causes and cardiovascular events</td>
<td>0.80 (0.72-0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>0.80 (0.62-1.03)</td>
<td>0.08</td>
</tr>
<tr>
<td>Myocardial infarction (fatal or nonfatal)</td>
<td>0.78 (0.62-0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Stroke (fatal or nonfatal)</td>
<td>0.84 (0.66-1.08)</td>
<td>0.17</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>0.75 (0.50-1.10)</td>
<td>0.14</td>
</tr>
<tr>
<td>Coronary revascularization procedure</td>
<td>0.86 (0.74-1.00)</td>
<td>0.05</td>
</tr>
<tr>
<td>Resuscitation after sudden cardiac arrest</td>
<td>1.75 (0.73-4.17)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

---

**Figure 6. ACCOMPLISH: Effects on primary and other end points.** Only the first event in an individual patient was counted in the analysis of the primary end point. For the subsequent analysis of the component end points, if a patient had events in more than one category, one event per category was counted.

**Abbreviations:** ACCOMPLISH, Avoiding Cardiovascular events through COMBination therapy in Patients Living with SysTole; Hypertension; ACE, angiotensin-converting enzyme; CCB, calcium channel blocker; CI, confidence interval; HCTZ, hydrochlorothiazide; HR, hazard ratio.

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M A J O R A D V A N C E S A N D A C H I E V E M E N T S
fential BP effects. In the largest trial of patients with type 2 diabetes—ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation)—over 11,000 patients who did not necessarily have raised BP at baseline, but had a high CV risk were randomized to receive either a combination of perindopril/indapamide or placebo. The resultant differential effect on BP of 5.6/2.2 mm Hg was associated with improved effects on CV mortality and thereby on all-cause mortality and on the primary end points of combined macro- and microvascular events. These unusual benefits on mortality were independent of baseline BP with the implication that additional BP lowering with the type of regimen used in ADVANCE may be appropriate add-on therapy for all patients with type 2 diabetes, irrespective of BP level.

Summary and conclusions
The worsening threat of raised BP to global health, demands more assertive action. Although not mentioned hitherto, improved diets and lifestyle are a critical component of preventing raised BP and associated CV events, and should be encouraged in all populations, hypertensive or not. For those who also need antihypertensive medication, enhanced efforts to lower BP must be made. Currently, while not being completely based on definitive RCT evidence, the 2011 NICE recommendations for drug sequencing are based on the best currently available evidence (Figure 5). The simplified rationale for why I use these drug choices is as follows:

- **Step 1.** Ideally one should start with the agent most likely to produce the most effective BP lowering and which has proven benefits on CV morbidity and mortality in one or more RCTs. For the reasons outlined above, “A” drugs for younger patients and CCBs for older patients are evidence-based choices. Furthermore given that “A + C” is apparently the best 2-drug combination, it is logical to start with “A” and “C” as first-line agents.

- **Step 2.** The ACCOMPLISH trial supports the ASCOT-BPLA trial and currently provides the best evidence for “A + C” as the most effective drug combination for CV prevention.

- **Step 3.** Patients who are insufficiently responsive to two antihypertensive agents are increasingly likely to be “water-retainers” and therefore the use of a diuretic is recommended. In light of the RCT evidence discussed, nonthiazide diuretics are chosen and the more metabolically friendly profile of indapamide compared with chlorthalidone, makes the former drug my personal preference.

- **Step 4.** In ASCOT-BPLA, doxazosin gastrointestinal therapeutic system was used as the common third-line add-on agent for both of the BP-lowering treatment regimens. Based on data from over 11,000 patient-years of follow up, doxazosin was shown to lower BP by 12/7 mm Hg on average. Of importance, and in contrast to the results of the ALLHAT trial, there was no sign of any increase in heart failure associated with the use of doxazosin. There were, however, small, but significant, beneficial effects on lipid profiles and the drug was well tolerated. Hence, doxazosin is a logical choice as a fourth-line agent.

- **Step 5.** In the ASCOT-BPLA trial, spironolactone was used as a fourth-line add-on agent by over 1400 patients. Among this large cohort of users—who by definition could be considered to have “resistant” hypertension—BP was reduced by 22/10 mm Hg on average. At the low doses used (average 42 mg/day) the drug was well tolerated with only 6% stopping the drug due to side effects. I therefore use spironolactone as a fifth agent. Should a patient complain of gynecomastia, eplerenone can be used instead, but larger doses (on a mg for mg basis) are required to achieve the same BP-lowering effect.

It has to be admitted that, once the second agent has been selected, there are no robust RCT data to inform best drug sequencing. However, the data from ASCOT-BPLA described above—albeit observational—are the best available data to support the use of any third- or fourth-line agents. In clinical practice these five steps will control the BP of the vast majority of hypertensive patients. Meanwhile, for those who do require two or more agents to control their BP to current targets, the increased use of single-pill combinations of drugs (often inaccurately called “fixed-dose combinations”) seems a logical step for the reasons summarized in Table III.

| Table III. A summary comparison of the relative benefits of monotherapy and combination therapy provided as two pills or a single pill for the management of hypertension. Abbreviation: BP, blood pressure. After: Poulter N. Combination Therapy in Hypertension. © Nova Professional Media, UK, 2010. |
|---|---|---|
| Response rate | Low | High |
| Dosage simplicity | Simple | Complex |
| Titration flexibility | High | High |
| Tolerability | Medium | Medium |
| Compliance | Medium | Medium |
| Cost | Medium | Medium |
| Overall BP control | Low | Medium/high |
| **Combination therapy** | | |
| “Free” | | |
| Single pill | | |

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ASSOCIATIONS MÉDICAMENTEUSES DANS LA PRISE EN CHARGE DE L’HYPERTENSION :
QUEL TRAITEMENT POUR QUEL PATIENT ?

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  More information is available on the ESM Web site: www.esmicrocirculation.eu

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  The 2011 Servier/UIP fellowship was awarded to Gyozo Szolnoky (Hungary) at the World Congress of the UIP in 2011 (Prague, Czech Republic).

  The next grant will be awarded at the World Congress of the UIP in 2013 (Boston, Massachusetts, USA).

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Antihypertensive treatment was classically initiated with monotherapy, uptitrating the dosage and adding on therapy as required. The latest European guidelines state that “in the vast majority of patients effective BP control can only be achieved by combination of at least two antihypertensive drugs” and that initiating treatment with drug combinations “may also offer advantages... in patients at high cardiovascular risk in which early BP control may be desirable.” Are you finding these new guidelines helpful in your daily practice?

When and in which patients would you initiate antihypertensive treatment with a fixed combination?

1. H. R. Black, USA
2. I. E. Chazova, Russia
3. J. Dalal, India
4. H. Elghetany, Egypt
5. Z. Gaciong, Poland
6. Ö. Kozan, E. E. Özcan, Turkey
7. G. Latkovskis, Latvia
8. J. Polónia, Portugal
9. Y. Sirenko, Ukraine
10. C. Tsioufis, Greece
11. P. N. Vinh, Vietnam
When and in which patients would you initiate antihypertensive treatment with a fixed combination?

In the 1960s, the most popular initial treatment for hypertension was a fixed-dose combination (FDC) of three drugs: hydrochlorothiazide, reserpine, and hydralazine (Ser-ApEs®). With the development of newer antihypertensives came a choice between two basic approaches when initiating therapy. One, “step care,” recommends starting with one drug, increasing it to the highest tolerated dose, before adding agents of a different class in a stepwise fashion, until the treatment goal is reached. The alternative, “sequential monotherapy,” recommends starting with a drug of the class expected to be most effective based on demography, pathophysiology, comorbidity, and other risk factors, and titrating that drug until the highest tolerated and appropriate dose is reached. Should the patient not achieve the goal, or if the first choice was poorly tolerated, then rather than add a drug of a different class, the recommendation would be to stop the first drug and start one of a different class—also at the lowest dose—and titrate.

The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) offered both choices, but JNC 7 dropped the recommendation for sequential monotherapy, as it became clear that most hypertensives, perhaps as many as 75%, needed two or more drugs to reach goal BP, and based on results from the VALUE trial (Valsartan Antihypertensive Long-term Use Evaluation), the time duration to get to that goal was also recognized as important. Sequential monotherapy may simply take too long, but stepped care can also be a lengthy process involving multiple dose titrations before the right regimen is achieved.

JNC 7, and later, European guidelines, recommended that initial treatment for hypertensives with systolic BP ≥160 mm Hg and/or diastolic BP ≥100 mm Hg (and some with systolic BP ≥140-159 mm Hg and/or diastolic BP ≥90-99 mm Hg) begin with two drugs. The rationale was that high-risk hypertensives—determined on the basis of BP, target organ damage, diabetes mellitus, and other risk factors (lipid profile or smoking)—needed to be aggressively treated to get their BP to goal promptly.

If treatment with two or more drugs would ultimately be required, why not start treatment with two drugs? In addition to the more robust BP reduction, combining agents with different mechanisms of action broadens the treatment spectrum and can reduce the metabolic and clinical adverse reactions seen with either or both drugs individually.

But what about starting treatment with an FDC if the compounds in that combination match what the clinician wants to use? Combining drugs in a pharmacokinetically and phama-codynamically calibrated FDC assures that the doses and timing of treatment is appropriate. Using FDCs may improve treatment adherence and reduce the pill burden for patients on multidrug regimens. FDCs are usually less expensive than each element separately, since there is a single charge rather than one for each prescription. But there are disadvantages. The desired combination may not be available. The dose titration schedule may not be possible with the FDCs available. And dose-independent adverse events such as angioedema, or cough with angiotensin-converting enzyme (ACE) inhibitors, may occur if the drugs are used in fixed combination rather than as a two-drug combination separately.

The wise clinician will start therapy with an FDC in a high-risk patient for whom they feel getting BP to goal promptly is necessary. In such patients, starting with an FDC is appropriate, if the right combination is available and affordable.

If we are to manage the worldwide cardiovascular epidemic and burden that hypertension places on our health care systems, we must improve the quality of care we give our citizens and improve the rates of getting BP to goal. The skillful use of FDCs will advance this aim.

References
When and in which patients would you initiate antihypertensive treatment with a fixed combination?

The main goal in the treatment of hypertension is reduction of cardiovascular (CV) events and mortality risk. This is only achievable with tight blood pressure (BP) control. Many large studies have shown that BP reduction decreases CV events and mortality risk in hypertensive patients. Twenty-two randomized controlled trials incorporating 210,566 participants were recently analyzed, and the authors concluded that BP reduction per se has significant prognostic value regardless of baseline BP.

Current guidelines on diagnosis and treatment of hypertension recommend target BP 130-139/80-89 mm Hg in all patients, except those with kidney disease (<130/80 mm Hg). The lower limits (systolic BP 110-115 mm Hg and diastolic BP 70-75 mm Hg) should also be kept in mind. Achievement of such a low target BP with a single drug, even at the highest dose, is only possible in one-third of patients with uncomplicated hypertension. In patients with elevated BP and target organ lesions, metabolic syndrome, diabetes, or associated clinical conditions, the efficacy of monotherapy becomes doubtful. It is thus recommended that in patients with high/very high risk, therapy commence with two medications at low doses.

Combination therapy has many advantages: (i) increased antihypertensive effect due to the different drug mechanisms of action, hence increased numbers of patients with stable BP reduction; (ii) less frequent side effects due to lower drug doses and mutual neutralization of side effects; and (iii) the most effective organ protection and reduction of risk and CV events.

Furthermore, it is evident that in the choice of treatment strategy, "the lower the better" should be replaced by "the sooner the better." The need for achievement of BP goal in the shortest time to reduce the risk of CV events and mortality was demonstrated in the VALUE trial (Valsartan Antihypertensive Long-term Use Evaluation). Systolic BP lowering to <140 mm Hg during the first 6 months, regardless of treatment (valsartan or amlodipine), resulted in a significant decrease in the risk of death from CV causes, risk of fatal stroke, number of hospitalizations due to heart failure, and all-cause mortality, compared with patients who retained higher systolic BP.

Combination therapy reduces BP more quickly than monotherapy. The main drawbacks of monotherapy are the need for frequent changes of medication and the delay caused by the need to choose a rational effective treatment.

For combination therapy, both free and fixed-dose combinations (FDC) can be used. However, preference should be given to FDCs, containing two drugs in one pill. The only case for withdrawing an FDC should be impossibility of use, because such a combination: (i) will always be rational; (ii) represents the most effective strategy for achieving and maintaining target BP; (iii) provides the best organ protection and reduction of CV risk; and (iv) reduces the number of tablets, substantially improving patient compliance.

Several studies have demonstrated the advantages of FDCs over free combinations. The largest meta-analysis was published in 2010. This included data for 32,331 hypertensives who received either free combinations or FDCs comprising similar drug classes. FDCs were associated with significantly higher compliance levels, as well as a trend toward greater BP reduction.

The only significant argument against FDCs is limited dosage varieties. The newest FDCs avoid this, as they come with different dose ratios. For example, perindopril/amlodipine is presented in four dosages, containing 5 mg/5 mg, 5 mg/10 mg, 10 mg/5 mg, and 10 mg/10 mg. Perindopril/indapamide is available in three dosages—2.5 mg/0.625 mg, 5 mg/1.25 mg, and 10 mg/2.5 mg.

The era of monotherapy domination has finished and is being replaced by the era of FDCs intended for use in a wide range of hypertensive patients, especially those at high or very high risk, regardless of baseline BP.

References
Evidence suggests that a combination of at least two drugs is often required to control blood pressure (BP), especially in patients with diabetes or renal insufficiency. In the recent ASCOT trial (Anglo-Scandinavian Cardiac Outcomes Trial), 90% of patients required a combination.

There is increasing appreciation of the benefits of initiating antihypertensive treatment with a combination of two drugs instead of the traditional single drug, sequential, stepwise titration strategy. Although this may unnecessarily expose the patient to a second drug, there are several advantages: first, ACCELERATE (Aliskiren and the Calcium Channel Blocker Amlodipine Combination as an Initial Treatment Strategy for Hypertension) showed that initiating treatment with a fixed-dose combination (FDC) of two agents is significantly more effective and quicker in controlling BP than the same two agents in a sequential drug titration strategy. This reassures patients and helps them retain their motivation to comply with long-term treatment. FDC, in a single tablet, once daily, simplifies treatment and improves compliance, and early normalization of BP is beneficial in reducing long-term vascular complications. Second, drugs in combination can act synergistically to reduce BP at lower doses, with lesser side effects. In many instances, they counteract the side effects of one another, further increasing compliance.

For these reasons, recent guidelines recommend initiation of antihypertensive treatment with drug combinations when BP is >20 mm Hg systolic or 10 mm Hg diastolic above the hypertension threshold, or for milder hypertension associated with multiple risk factors or subclinical organ damage. Except in mild hypertensives, I introduce therapy with a single, once daily, FDC. Preferred combinations are: (i) angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) plus thiazide diuretic; (ii) calcium channel blocker (CCB) plus ACE inhibitor or ARB; and (iii) β-blocker plus CCB. Recently, the ACCOMPLISH trial (Avoiding Cardiovascular events in COMBination therapy in Patients Living with Systolic Hypertension) showed that an ACE inhibitor plus CCB FDC is more beneficial than ACE inhibitor plus diuretic. However, the low dose of hydrochlorothiazide used may not have provided as effective 24-hour BP control as the ACE inhibitor plus amlodipine.

In my clinical practice, most patients present with stage 2 hypertension and concomitant disease: I start with an FDC or substitute monotherapy for an FDC using any of the aforementioned combinations depending on cardiac/other conditions. Since many of my patients have coronary artery disease, I often use a long-acting β-blocker along with a CCB. Although the combination of β-blocker plus thiazide diuretic was effective in earlier trials, I avoid it as my first choice in patients at high risk of diabetes.

If adequate BP control is not achieved, the next step would be to add an ARB with a diuretic. In general, I find FDCs containing an ARB more acceptable to my patients than an ACE inhibitor, due to the prevalence of cough among Indians. If a patient has reduced ejection fraction or previous myocardial infarction, I will always add an ACE inhibitor (ARB, if not tolerated). I do not combine an ACE inhibitor with an ARB, as it increases side effects without any additional benefit.

Triple-drug FDCs containing ARB, CCB (amlodipine), and diuretic are available in India. In patients with resistant hypertension, I prescribe this triple-drug FDC in the morning and add an FDC containing bisoprolol with amlodipine at night. The vast majority of my patients are on two tablets daily, each an FDC. This controls about 80% of my patients. With FDCs (of two or three drugs each), no individual, however severe their hypertension, need take more than three tablets a day. This allows target BP control along with long-term compliance.

References
Hypertension is prevalent as a major cardiovascular risk factor. Treating hypertension to target blood pressure (BP) would avert the risk in most individuals. In clinical practice, achieving guideline-dictated target BP is not always an easy task. Monotherapy is seldom successful in reaching target BP, and the majority of patients will need more than one medication to reach it. This has been shown in many large clinical trials such as the HOT trial (Hypertension Optimal Treatment), UKPDS (United Kingdom Prospective Diabetes Study), and ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial).

Fixed-dose combination therapy offers a good option for achieving adequate BP control. Because of the simple dose regimens, fixed-dose combinations allow for better compliance, an important consideration in the management of hypertension, where poor compliance is a major obstacle. Additionally, fixed-dose combinations may produce fewer side effects due to the lower doses of each component and the potential for one agent to nullify the side effects of the other. The most important value of the fixed-dose combination, however, remains its high efficacy compared with simply increasing the dose of one medication to reach the target BP. One meta-analysis involving 42 trials (10,968 participants) showed that the extra BP reduction produced by combining drugs from two different classes is approximately 5 times greater than that from doubling the dose of one drug. This also helps achieve rapid BP control, which helps avoid patient frustration resulting from a lack of ability to reach the desired BP, and it may also have prognostic implications.

The 2007 European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines suggest starting treatment with combination therapy in grade 2 or 3 hypertension, or in cases where the estimated overall cardiovascular risk is high or very high. This was reconfirmed in the 2009 reappraisal of these guidelines. The 2010 Canadian Hypertension Education Program recommendations suggest that combination therapy should be the first option if BP is more than 20/10 mm Hg above target.

Not all drug combinations are equal; the perindopril-amlodipine combination in ASCOT was more effective in lowering BP and providing cardiovascular protection than the combination of a β-blocker and thiazide diuretic—the latter combination was particularly diabetogenic. After 5.5 years of follow-up, there was an 11% difference in all-cause mortality in favor of perindopril-amlodipine (P=0.0247), due to a significant reduction in cardiovascular mortality. The same combination also showed significant advantages regarding other secondary end points such as fatal and nonfatal stroke, fatal and nonfatal myocardial infarction, total coronary events, and total cardiovascular events and procedures. Despite the significant systolic and diastolic BP difference of −2.7 and −1.9 mm Hg in favor of perindopril-amlodipine combination, subsequent multivariate analysis showed that differences in coronary and stroke events was not completely explained by the significant differences in BP, suggesting that the cardiovascular protective effects of perindopril-amlodipine may be, at least in part, related to inherent pharmacological properties of this combination.

ASCOT and many other trials showing the effectiveness and reduced outcomes associated with use of an angiotensin-converting enzyme (ACE) inhibitor/calcium channel antagonist combination have led the ESH/ESC to recommend this combination as one of those for priority use.

References
The percentage of patients achieving target BP was significantly greater in the "low-dose combination" group (49%; P=0.02) and "stepped care" (47%; P=0.005) groups. Moreover, the number of adverse events possibly related to therapy was lowest in the FDC group.

In the Canadian STITCH trial (Simplified Treatment Intervention To Control Hypertension), a simple treatment algorithm involving initial use of a low FDC of diuretic/angiotensin-converting enzyme (ACE) inhibitor or diuretic/angiotensin receptor blocker (ARB) was better than a complex strategy based on current guidelines. Family physicians enrolled patients with uncontrolled hypertension and employed either the STITCH algorithm or usual Canadian guidelines, and then assessed the proportion of patients treated to target BP after 6 months. The proportion was significantly higher in the STITCH group than in the guideline-based group (64.76% vs 52.7%; P=0.026), and multivariate analysis showed that assignment to the fixed combination arm increased the chance of reaching BP target by 20% (P=0.028).

Thus, first-line management of hypertension based on an FDC allows BP normalization in a shorter time and greater proportion of patients, with no increased risk of intolerance. Therefore, initial therapy with a fixed combination should be used in all patients with stage 2 hypertension or BP uncontrolled with monotherapy.

How about patients with stage 1 hypertension? Usually, they start with monotherapy, yet some data also suggest advantages with initiation of an FDC in this group. A recent meta-analysis examined nine randomized double-blind, fixed-dose, placebo-controlled trials (n=4278) comparing monotherapy with fixed combination. Among patients with uncomplicated stage 1 hypertension, after 8 weeks of treatment, 92% achieved their goal BP when started on combination, compared with 72% initially receiving monotherapy. Rates of discontinuation were similar in both groups. Thus, FDCs also allow immediate achievement of BP control in patients with stage 1 hypertension.

I fully agree with the recent statement of the American Society of Hypertension, and advise starting with an FDC routinely in patients requiring BP reduction of at least 20/10 mm Hg. Subjects with stage 1 hypertension can also be started on a low-dose FDC, which is effective and better tolerated.

References
Cardiovascular diseases are the most common cause of mortality worldwide. Hypertension is a major risk factor, causing 54% of strokes and 47% of ischemic heart disease. Its incidence is increasing due to an aging population, sedentary lifestyles, and bad dietary habits. Unfortunately, control is inadequate, despite all developments and available drugs. Achievement of target blood pressure (BP) in most patients is only possible with the use of multiple drugs. In the ASCOT-BPLA trial (Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm), 78% of patients received two or more drugs, and almost one-third of patients in the ACCOMPLISH trial (Avoiding Cardiovascular Events in Primary Care Hypertension) received ≥3 antihypertensives. Monotherapy is inadequate in patients with significant BP elevation. Moreover, it unnecessarily delays BP control in high-risk hypertensives. VALUE (Valsartan Antihypertensive Long-term Use Evaluation) showed the vital consequences of such delay. In the first 6 months of treatment,amlodipine plus valsartan achieved additional BP reduction compared with valsartan treatment alone, and this was accompanied by a decrease in cardiovascular events. Thus, dual drug combination is recommended as initial therapy in patients with significant BP elevation (systolic BP ≥160 mm Hg, diastolic BP ≥100 mm Hg) or high/very high cardiovascular risk. Combined use of drugs with additive pharmacological features provides more BP reduction. Moreover, the lack of side effects from low doses is another advantage over full-dose monotherapy. Fewer side effects, fewer pills, and the possibility of reaching target values quicker enhances patient compliance. Comorbidities accompanying hypertension, in particular in the elderly, make treatment more complicated. Here, the physician may decrease the drug burden by using single-pill combinations. Hypertension guidelines also recommend single-pill administration for multiple-drug therapy. Fixed combinations prevent improper drug combination. Molecules with synergistic action are selected, thus increasing efficacy and decreasing side effects. Fixed combinations should be selected based on the individual patient. The β-blocker/diuretic combination should be approached with caution due to its metabolic effects. In ASCOT, amlodipine/perindopril combination significantly decreased cardiovascular events compared with atenolol/thiazide. In ACCOMPLISH, which included high-risk patients, benazepril/amlodipine combination was compared with the ACE inhibitor/diuretic combination, and was found to significantly decrease cardiovascular events. However, before reaching a negative conclusion regarding diuretics, one should remember the beneficial outcomes in ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial), which used a more potent and long-acting diuretic. The recently-published ACCELERATE trial (Aliskiren and the Calcium Channel Blocker Amlodipine Combination as an Initial Treatment Strategy for Hypertension) emphasized the benefits of starting treatment in combination. Treatment initiation with combination of two drugs (two separate pills) rather than with only amloidipine or aliskiren resulted in a 25% faster lowering of BP in the first 6 months. Although all patients received combination treatment, those having started therapy in combination recorded lower BP values. However, further studies are needed to confirm the prognostic benefits of renin inhibitors.

In conclusion, two drugs combined in low doses should be the preferred first-line treatment in patients with grade 2 or 3 hypertension (systolic BP ≥160 mm Hg, diastolic BP ≥100 mm Hg) or with high/very high risk for cardiovascular events. If target BP values are not reached in patients with slightly elevated BP and low risk, combination therapy should be considered. Starting treatment with a single fixed-combination pill improves compliance. In patients with orthostatic manifestation requiring careful dose adjustment, it would be better to start with the lowest possible dose or switch to single pill combination after identifying the individual doses of two separate drugs. Choice of combination should be based on the individual patient. It should be kept in mind that exercise and lifestyle modification with a salt-restricted diet is the only “combination” that remains unchanged in antihypertensive treatment.
my decision to initiate antihypertensive treatment with a fixed combination depends on several considerations. In general, what I expect from a successful fixed combination is effective blood pressure (BP) lowering with relatively few side effects, and importantly, proven clinical efficacy in terms of cardiovascular event reduction.

The majority of hypertensive patients will need a combination of drugs to achieve their target BP. As pointed out in the 2007 European guidelines for the management of arterial hypertension, add-ons of a second drug are frequent even in hypertension trials of monotherapies. The crucial question for me, therefore, is how to predict who is going to need combination therapy anyway, so that I can start it early and avoid multiple uptitrations.

It has been advised that two drugs should usually be used from the outset when BP is >20/10 mm Hg above goal. According to the 2009 update of the European guidelines, the goal has been redefined to <140/90 mm Hg for most patients. Hence, I do not hesitate to initiate treatment with a fixed combination when BP exceeds 160/100 mm Hg. The exception is an elderly patient (aged 80 years or above), unless systolic BP is more than 170 mm Hg, since there is no good scientific evidence that one should pursue values below 150 mm Hg.

Nevertheless, in many patients, I initiate treatment with a fixed combination even when their BP is lower than the aforementioned cutoff values. The working group of the latest update of the European guidelines has indicated that optimal BP is within the range of 130-139/80-85 mm Hg, and possibly closer to 130/80 mm Hg. This statement may be more important for high-risk individuals. For such patients, I prefer to achieve BP closer to (but not necessarily lower than) 130/80 mm Hg, which makes a case for initiation with a fixed combination when BP is >150/90 mm Hg. Additional (nonhypertension) indications for an antihypertensive agent would be another reason for early combination use; e.g., an angiotensin-converting enzyme (ACE) inhibitor for heart failure or calcium channel blocker (CCB) for angina.

Clinically, a very important aspect frequently overlooked is whether pretreatment BP and on-treatment BP are evaluated only in the clinic or are monitored at home (or with 24-hour monitoring) as well. Home readings are typically lower (<130-135/85 mm Hg considered normal) and better predict cardiovascular risk. Home BP, however, falls approximately 20% less than clinic BP with antihypertensive treatment. Thus, the stronger the data I have to indicate that I am dealing with true hypertension and higher home BP, the more likely I treat my patient with fixed combination therapy from the outset.

The initial choice may also depend on available doses of the fixed combinations. The aforementioned considerations apply to a combination of two agents in standard doses. However, I would prefer small doses of two antihypertensive agents to a standard dose of monotherapy in most cases, should such combination of small doses be available.

In addition to superior efficacy, better tolerability of combinations will contribute to risk reduction via improved adherence. Although combinations seem to have fewer side effects, this may not be true in all cases. Indeed, β-blocker plus diuretic may facilitate development of new-onset diabetes or erectile dysfunction, so it is not my favorite combination unless clearly indicated due to comorbidities. By contrast, the effectiveness of ACE inhibitor plus CCB in combination is not compromised by more frequent side effects such as cough or ankle edema. In fact, the latter is less frequent when CCB is coadministered with an ACE inhibitor.

In summary, fixed combination therapy, especially with an ACE inhibitor and CCB, has become increasingly common initial antihypertensive treatment in my daily practice.

References
Controversial question

When and in which patients would you initiate antihypertensive treatment with a fixed combination?

Control of blood pressure (BP) to the desirable target values (within the range of 130-139/80-89 mm Hg) represents the main mechanism by which antihypertensive treatment reduces cardiovascular (CV) risk. For a long time, monotherapy with dose titration and consecutive add-on therapy has been the main strategy in the treatment of hypertensive patients. However, it is recognized that less than only 40% of treated hypertensive patients worldwide really achieve good BP control. This may be related to low tolerability profiles, complicated regimens, or unaffordable costs, leading to inertia on the part of the physician, and in particular, patient noncompliance, which has been recognized as a major cause of therapeutic failure. Consequently, a more aggressive attitude to improving adherence to therapy is crucially needed to improve BP control in clinical practice.

Around 75% of patients with hypertension will require combination therapy of two or more drugs to achieve desirable BP targets. Initiation of antihypertensive treatment based on the combination of two antihypertensive drugs with complementary mechanisms of action and pharmacokinetic compatibility is now advised by the guidelines, particularly for high-risk patients, based on the available evidence of its advantages over monotherapy. These advantages are greater efficacy, easier achievement of BP targets, rapidity of BP control, increase in the percentage of good responders in any population of hypertensive patients, better tolerability, improvement of patient adherence, and enhanced CV protection.

Once-daily, two-drug fixed combinations share many of the merits of rational free combinations when initiating therapy, particularly with respect to gains in efficacy, efficiency, and tolerability. However, by simplifying treatment, fixed combinations offer additional advantages such as reduction in the number of pills and administrations, improvement of compliance, reduction in health costs, a decrease in the need for repeated medication adjustments and the number of office visits, and facilitation of doctor prescription.

Thus, in my practice, when would I initiate antihypertensive treatment with a fixed combination? First, based on scientific evidence and/or guidelines. Guidelines support the use of two-drug combinations in a single tablet as the first treatment step when high CV risk makes early BP control desirable. So, this could be applied to all hypertensive patients with high initial BP or who are at high/very high CV risk due to the presence of organ damage, diabetes, renal disease, or a history of CV disease, and if there is a 20/10 mm Hg elevation in BP above goal (ie, BP is >160/100 mm Hg for those with uncomplicated hypertension or >150/90 mm Hg for those with diabetes and other comorbid conditions). Second, based on practical needs and “common sense.” Although there is limited evidence to support starting treatment with fixed combinations in patients with mild-to-moderate added risk, evidence illustrates that BP control is achieved more rapidly with fixed combinations than with free combinations of separate drugs.

Meanwhile, the increasing availability of more favorable, effective, and well-tolerated fixed combinations may allow us to consider their use as initial therapy in certain other scenarios, such as: (i) patients for whom multidrug therapy is likely to be needed soon, while there still is a positive risk/benefit ratio estimation for starting with a fixed combination; and (ii) patients with difficulty in understanding multiple prescriptions and in attending frequent consultations, and/or for whom the increased number of medications and frequency of dosing may represent a determinant factor regarding cost constraints, mistakes, and nonadherence.

This approach may contribute to improved compliance and BP control rates, although further evidence is needed to support it.

References
When and in which patients would you initiate antihypertensive treatment with a fixed combination?

The answer to this question stems from the indications for combination of antihypertensive drugs. In 2003, in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VII), experts proposed that all hypertensive patients without compelling indications start on combination therapy if their blood pressure (BP) level was ≥160/100 mm Hg. 1

In 2003, European guidelines offered a choice to physicians: in all patients, they could either start with monotherapy or with low-dose combination therapy, according to their understanding of the clinical condition of the patient. 2

In 2007, the European guidelines were clarified with respect to the indications for prescription of combination therapy from the beginning: high or very high risk level, high BP level (≥160/100 mm Hg), or low target BP level (<130/80 mm Hg, for example). So, combination treatment should be considered as first choice, particularly when a patient is at high cardiovascular risk: ie, individuals in whom BP is markedly above the hypertension threshold (eg, more than 20 mm Hg systolic or 10 mm Hg diastolic above threshold), or milder degrees of BP elevation that are associated with multiple risk factors, sub-

clinical organ damage, diabetes, renal disease, or associated cardiovascular disease. 3 However, this recommendation was not supported with evidence from morbidity/mortality trials, because there were no studies in which the advantage of this approach had been prospectively assessed. The recommendation was based on the arguments that: (i) combination therapy can reduce BP to a greater extent than monotherapy and can achieve the BP goal more promptly; (ii) when a high-risk condition exists, an event may occur within a relatively short time period, thus protective intervention without excessive delay is needed; (iii) the protective effect of BP reduction manifests shortly after initiation of the treatment; and (iv) initial combination treatment is associated with a lower degree of treatment discontinuation.

In the 2009 reappraisal of the European guidelines, the expert position was more assertive, and the text contains the following words concerning fixed combinations: “use of fixed dose combinations of two drugs can directly follow initial monotherapy when addition of a second drug is required to control BP, or be the first treatment step when a high cardiovascular risk makes early BP control desirable.” 4

Briefly, the comparison of free and fixed combination is presented in the Table. The main advantage of fixed-dose combinations of two drugs in a single tablet compared with free combination is simplification of the treatment regimen, which impacts positively on the effectiveness of BP control. Thus, all patients who have indications for starting with combination therapy may receive a fixed combination as the first step.

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Table. Comparison of free and fixed combination drug regimens.

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<td>Flexibility</td>
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*Flexibility is now facilitated by the availability of different fixed-dose combinations of the same two drugs.

References
According to the European Society of Cardiology/European Society of Hypertension (ESC/ESH) 2007 guidelines, dual antihypertensive therapy should be initiated on top of lifestyle interventions in all high and very high cardiovascular risk patients, in those with marked blood pressure (BP) elevation, and each time we opt for lower BP with respect to the traditional threshold. Fixed combination therapy (FCT) is preferred to giving each drug individually, both because of the increase in patient adherence and the improved cost-effectiveness ratio. In the majority of trials to date, combination therapy has been administered with two drugs given separately. However, in the BP-lowering arm of ADVANCE (Action in Diabetes and Vascular disease: Preterax and Diamicron MR Controlled Evaluation), diabetic patients received perindopril and indapamide as dual FCT, with an 18% relative risk reduction in cardiovascular death compared with placebo. The above dual FCT had enough clinical support for its implementation in the above guideline-indicated patients; however, individualization of treatment is equally important, which should be taken into account in clinical practice.

Advanced age is by definition a high cardiovascular risk condition, and there is no trial evidence to support lowering BP below 140 mm Hg in patients of advanced age. Additionally, since the majority of older patients are characterized by concomitant cardiovascular comorbidity, aggressive initial reduction of BP with dual FCT might be harmful. In advanced aged patients, it may be prudent to initiate monotherapy and to eventually add a second drug separately if BP levels continue to be elevated. In a final step, FCT (probably an angiotensin-converting enzyme [ACE] inhibitor plus diuretic based on the results of HYVET [Hyrtension in the Very Elderly Trial]) could substitute for the previously-administered free regimen.

In my view, FCT is advisable for middle-aged patients with minimum stage 2 hypertension and no history of cardiovascular events. The majority of these patients possess additional risk factors such as obesity, diabetes mellitus, or metabolic syndrome, or are characterized by established target organ damage. All these latter conditions upgrade the initial suggestion to a compelling need for early BP reduction.

In patients with a history of cardiovascular disease, FCT should be used when initiating antihypertensive treatment, with the aim of lowering the BP level below the traditional BP threshold. To date, no study has provided solid evidence for BP thresholds below 130/80 mm Hg for the secondary prevention of cardiovascular diseases. In the case of patients post-myocardial infarction, we should recognize that they are already being treated with a β-blocker and an angiotensin-converting enzyme (ACE) inhibitor. Whether the latter drug category should be incorporated into FCT with a diuretic or calcium channel blocker should be based on the individual (depending on the BP levels achieved).

According to a recent meta-analysis, patients with chronic kidney disease should be treated to a more conservative BP threshold. Given that these patients are characterized by volume overload, a thiazide-like diuretic should be administered assuming that the estimated filtration rate is higher than 35-40 mL/kg/1.73m². Along the same lines, a renin-angiotensin system inhibitor is strongly recommended, and thus in chronic kidney disease patients with moderately preserved kidney function, FCT represents a plausible way to initiate antihypertensive therapy.

Triple FCT should be reserved for those whose BP lies outside of the traditional BP goal after dual FCT. So far, there is not enough evidence to support initiation of antihypertensive treatment with three drugs. Finally, by definition, triple FCT nullifies the concept of chronotherapy (implementation of the latter is not fully supported by current evidence, however). Nonetheless, some patients control their BP better when taking part of their medication at bedtime.

References
Hypertension is the leading risk factor for premature death, and according to a 2009 report from the World Health Organization, it is responsible for 7.5 million deaths worldwide. However, despite therapeutic advances, more than two-thirds of hypertensive adults in the United States, Canada, and Europe fail to reach blood pressure (BP) target (<140/90 mm Hg).1

The current guidelines recommend initiating two hypertensive drugs in hypertensive patients when BP is ≥20/10 mm Hg above goal.2,3 The fixed-dose combination (FDC) approach is also recommended by many guidelines, either as a first-line treatment, or early in the treatment of patients with risk factors that necessitate rapid BP reduction.2,4,5

There are many reasons to initiate antihypertensive treatment with two synergistic drugs, or better, with an FDC. In high- or very high-risk individuals, treatment with a combination of two or more antihypertensive drugs is almost always necessary. In many clinical trials such as UKPDS (United Kingdom Prospective Diabetes Study), RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan), ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial), and ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm), an average of more than two antihypertensive drugs was needed to achieve the target BP.

In the Mahmoud study, a single-pill mixture of four drugs at a one-quarter dose each provided a significantly superior BP-lowering effect than that of any of the individual drugs used at a full dose.

Starting antihypertensive treatment with two drugs will achieve more rapid and effective BP reduction; this has been shown in the ACCOMPLISH trial (Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension). A delay in achieving BP control, even for a few months, may lead to an event.

The initial use of two antihypertensive drugs may also have the theoretical advantage of avoiding the compensatory physiological mechanisms induced by initiation of a single drug class. This compensatory physiological mechanism may reduce the BP-lowering efficacy of a single agent.

In comparison with separate pills, FDC therapy achieves better compliance. This was shown in a recent meta-analysis of relevant clinical trials.6 Improved compliance is associated with increased BP control.

Finally, FDCs also reduce the cost of treatment. The second drug in a combination pill is usually free. For example, in a renin-angiotensin-system blocker and diuretic combination pill, the diuretic is “free.” Indirect costs may also be reduced by the use of FDCs because of improved compliance.

References
Hypertension guidelines emphasize that mortality reduction continues to be the ultimate goal of antihypertensive therapy. However, despite substantial achievements in preventive medicine, hypertension remains the leading cause of death. Among the recent hypertension trials, further survival benefits have been demonstrated with perindopril regimens in ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm), ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation), and HYVET (Hypertension in the Very Elderly Trial). These findings, across a broad range of patients, had a large impact on the recent reappraisal of the European Society of Hypertension (ESH) guidelines (2009) and British hypertension guidelines (2011), which both support earlier use of proven antihypertensive combinations, and particularly of an angiotensin-converting enzyme (ACE) inhibitor combined with a calcium channel blocker (CCB) or a diuretic (and particularly a thiazide-like diuretic like indapamide). Lessons from ASCOT, ADVANCE, and HYVET also contributed to advancements in hypertension and provided clinical confirmation of the relationship between reduction in key blood pressure (BP) parameters (brachial BP, BP variability, 24-hour/night BP, and central BP), target-organ damage, and improved survival. Systematic evidence of mortality reduction achieved with perindopril and indapamide, reinforced by the recent meta-analysis of mortality reduction in hypertension trials, reward 40 years of Servier’s research in hypertension. Recently, directly derived from the ASCOT trial, Servier has developed a new combination of perindopril and amlodipine to benefit a large number of hypertensive patients.

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“Chance favors only the prepared mind.”

Pasteur
Indeed, evidence-based medicine from the last decade has significantly enriched our knowledge and showcased examples for upgrading the management of arterial hypertension. Nevertheless, the World Health Organization (WHO) still ranks elevated blood pressure (BP) as the leading cause of premature death worldwide and European hypertension guidelines emphasize that reducing mortality remains the ultimate goal of antihypertensive treatment. To achieve this goal, reduction of elevated BP is an indispensable step. In 1991, STOP-Hypertension (Swedish Trial in Old Patients with Hypertension) showed unsurprisingly higher rates of cardiovascular (CV) events and mortality among patients receiving “pure placebo” (whose mean BP remained 193/95 mm Hg until the end of the study) versus those achieving a mean BP of 166/85 mm Hg with atenolol/hydrochlorothiazide (HCTZ). Since that time, BP goals and ethical requirements for the study design have been tightened. Nowadays, the actual question is which of the various BP-lowering treatments is the most beneficial in achieving further mortality reduction among hypertensive patients receiving contemporary preventive therapy? Indeed, in later trials, a systematic link between the magnitude of BP reduction and mortality could not always be observed.

Better BP reduction achieved with angiotensin receptor blockers (ARBs) in SCOPE (Study on COgnition and Prognosis in the Elderly [mean ΔSBP, 3.2 mm Hg]), TRANSCEND (Telmisartan Randomized Assessment of Memory and Action in the Cognitively Normal Elderly) and PRoFESS (PREvention regimen For Effectively avoiding Second Strokes [mean ΔSBP, 3.8 mm Hg]) did not translate into better reduction in the risk of CV outcomes and mortality versus placebo.

On the other hand, in another study, the reverse was true. In ASCOT-BPLA, CV risk reduction was greater than expected given the achieved difference in mean BP with the two treatments. Indeed, a statistical adjustment analysis showed that the difference in brachial BP (mean ΔSBP, 2.7 mm Hg) could only partially account for the superiority of amiodipine ± perindopril versus atenolol ± bendroflumethiazide in reducing CV events and mortality. Experts are therefore talking about a new era in hypertension management, in which traditional beliefs about the accuracy of “usual” brachial BP to predict the risk of CV events are being challenged, in particular by the use of other “new” key BP parameters, such as central BP and BP variability.

In 2009, the reappraisal of the European guidelines on hypertension management critically assessed results from recent clinical trials. The guidelines prompted physicians to focus treatment strategy on optimizing BP control and survival among patients. Among the major clinical trials that have influenced the guidelines, ASCOT-BPLA, ADVANCE, and HYVET are acknowledged for having demonstrated additional benefits in different clinical situations.

The guidelines supported the earlier use of proven antihypertensive combinations, and particularly combinations of an angiotensin-converting enzyme (ACE) inhibitor with a calcium channel blocker (CCB) or a diuretic, and, according to the recent British 2011 hypertension guidelines, the only recommended combination for step 2 treatment of hypertension (after initial treatment as monotherapy) is that of a renin-angiotensin-aldosterone system (RAAS) inhibitor and a CCB, followed, if need be by addition of a diuretic (step 3), in particular a thiazide-like diuretic such as indapamide, while HCTZ is not advised.

ASCOT-BPLA, ADVANCE and HYVET, despite featuring different hypertensive populations, have at least three major points in common. Firstly, these trials were initiated and designed independently by their respective investigators, in order to answer unresolved clinical questions. Secondly, all three demonstrated significant reduction in all-cause mortality with active treatment. For that reason, ASCOT-BPLA and HYVET were prematurely terminated. Finally, these three trials investigated the efficacy of the ACE inhibitor perindopril, in combination with either amiodipine or indapamide, and were supported totally or partially by Servier.

This article reviews the key lessons from ASCOT, ADVANCE, and HYVET, and examines how they were instrumental in making it possible to achieve further reduction in CV complications and mortality in hypertensive patients.

SELECTED ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>ACE</td>
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<td>angiotensin receptor blocker</td>
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Rationale for ACE inhibition with perindopril (Coversyl) in patients with arterial hypertension

In the early 1980s, perindopril, a third-generation lipophilic tissue-ACE inhibitor, was developed by Servier with the aim of providing all the benefits of ACE inhibition in hypertension with an effective 24-hour efficacy after once-daily dosing. From that time, perindopril (Coversyl) has been extensively studied in more than 1500 preclinical and clinical studies.

◆ Dose-dependent antihypertensive efficacy

A growing body of clinical evidence has specified the relationship between the dose and the 24-hour efficacy of perindopril and showed that trough effects were about 75% to 100% of peak effects.16-18 Large, practice-based trials with participation of more than 76,000 hypertensive patients have demonstrated that BP can be significantly reduced with perindopril on both short-term and long-term use.19-22

The dose-dependent antihypertensive efficacy and safety of perindopril were assessed in a recent observational, multicenter trial in 8300 patients with hypertension.23 The initial dosage of perindopril corresponded to 5 mg of the arginine salt and was titrated up to 10 mg as required for BP control. Mean BP was reduced by 19/10 mm Hg versus baseline (152/89 mm Hg), and, in a separate group of severely hypertensive patients, mean BP was reduced by 36/15 mm Hg. Perindopril dose titration to 10 mg resulted in an additional decrease in mean BP of 10/5 mm Hg in the total population and of 15/6 mm Hg in patients with severe hypertension.

◆ Vascular protection benefits of ACE inhibition with perindopril

Arterial hypertension is a vascular disease, in which hyperactivity of the RAAS is the leading pathophysiological mechanism. ACE, which is present in the endothelium and smooth muscle, is primarily a tissue enzyme (80%-90%). Chronic overexpression of tissue ACE disrupts the angiotensin II:bradykinin balance, leading to a host of negative vascular effects, including vasoconstriction, early vascular aging, and atherosclerosis. Perindopril, due to its strong affinity for ACE—and tissue ACE in particular—together with its long duration of action,16-18 differs substantially from other ACE inhibitors.

Perindopril’s favorable pharmacokinetic profile increases the potency of ACE inhibition, leading to greater reduction in angiotensin II production and greater prevention of vasoconstriction and release of adhesion molecules and growth factors, and decrease in oxidative stress. In addition, perindopril is known to have high selectivity for bradykinin binding sites and effectively decreases degradation of bradykinin. Perindopril induces a marked increase in bradykinin level, resulting in vasodilator, antioxidant, antiinflammatory, profibrolytic, and antiapoptotic effects, as well as opposing the negative actions of angiotensin II.25-27

The clinical evidence for the mode of action of ACE inhibitors in patients with chronic vascular disease was largely enriched by the results of EUROPA (European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease)28 and its substudies. The effect of perindopril on endothelial function in stable coronary artery disease (CAD) was determined by PERTINENT (PERindopril-Thrombosis Inflammation, Endothelial dysfunction and Neurohormonal activation Trial),29 a substudy of EUROPA. These trials showed that perindopril improved the markers of endothelial function by increasing endothelial nitric oxide synthase (eNOS), decreasing the level of von Willebrand factor (vWF), normalizing the angiotensin II:bradykinin balance, and reducing inflammation and rate of endothelial cell apoptosis.
Reduction in apoptosis appears to be one explanation for how perindopril may be able to reverse new atherosclerotic plaque formation when it occurs. A post hoc analysis of the PERSPECTIVE substudy (PERIndopril’s proSPective Effect on Coronary aTherosclerosis by IntraVascular ultrasound Evaluation) of EUROPA found that perindopril was able to regress the size of “young,” noncalcified plaques, as compared with placebo. Finally, perindopril appears to correct the damage of pathologically augmented apoptosis by increasing the production and incorporation of endothelial progenitor cells. Recent clinical data about acute coronary syndrome also suggest that perindopril decreases the rate of endothelial apoptosis, and increases endothelial renewal by stimulating production of endothelial progenitor cells in bone marrow. In contrast, the ARB valsartan does not increase endothelial renewal, nor does it dothelial progenitor cells in bone marrow. In contrast, the ARB increases endothelial renewal by stimulating production of en-

coveram

Figure 1. Reduction in mortality and cardiovascular events in 29 463 patients receiving perindopril (Coversyl)-based therapy.

The consistency of the treatment effect of a perindopril-based treatment regimen in patients with vascular disease or high risk of vascular disease: a combined analysis of individual data of ADVANCE, EUROPA, and PROGRESS trials.


Cardiovascular event prevention with perindopril in patients with established vascular diseases

EUROPA evidenced a significant 20% reduction in risk of CV death, acute myocardial infarction (MI), and resuscitated cardiac arrest in patients with stable CAD treated with perindopril. It also provided further support for the use of ACE inhibitors by showing a prognostic benefit for a target dose corresponding to perindopril arginine 10 mg in patients with stable CAD. Furthermore, the fact that other ACE inhibitors—quinapril in QUIET (QUinapril Ischemic Event Trial) and trandolapril in the PEACE study (Prevention of Events with Angiotensin-Converting Enzyme inhibition)—failed to demonstrate morbidity-mortality benefits in stable CAD suggests that differences in the clinical effects of ACE inhibitors may be related to tissue-ACE affinity (the ability to penetrate into atherosclerotic plaques) and affinity for bradykinin binding sites. Finally, the BPLTTC trial (Blood Pressure Lowering Treatment Trials’ Collaboration) demonstrated that the BP-independent effects of ACE inhibitors indeed contribute to the better reduction in coronary events. Today, use of ACE inhibitors with proven efficacy and at proven dosages is recommended in stable CAD patients.

ASCOT-BPLA: a breakthrough in hypertension

ASCOT was initiated to resolve clinical questions after new BP targets (<140/90 mm Hg) were for the first time established by the US (1997) and UK (1999) hypertension guidelines. In 2001, Peter Sever (UK), the principal ASCOT investigator, wrote: “If recently recommended BP targets are to be reached, the majority of patients will require at least two drugs. So far, no trials have evaluated or compared the efficacy of prespecified drug combinations for hypertensive patients.” ASCOT investigators decided to study the hypothesis that combining newer, but already well-established antihypertensive treatments (amilodipine and perindopril) might provide additional benefits versus an older combination (β-blocker/thiazide diuretic) in patients with hypertension, yet free of CAD. In 2005, ASCOT-BPLA results were considered a breakthrough, as they showed that antihypertensive strategies could differ in CV outcomes, despite producing comparable brachial BP decreases. ASCOT included 19 257 hypertensive patients who had at least three other CV risk factors, but no cardiac disease. The study compared the effect of amloidip-
ine ± perindopril, as required, with atenolol ± bendroflumethiazide, as required, to reach BP targets. ASCOT-BPLA was stopped early due to an 11% difference in all-cause mortality in favor of the amlodipine ± perindopril group (P=0.0247) after a median of 5.5 years. Regarding secondary end points, there was a 24% difference in CV mortality (P=0.001), a 13% difference in all coronary events (P=0.007), and a 23% difference in fatal and nonfatal stroke (P=0.0003). Notably, the rates of CV death in the two treatment arms began to split at the very point where the majority of patients (78%) were already receiving perindopril in addition to amlodipine (Figure 2).42

> **Importance of key BP parameters in assessment and management of arterial hypertension: lessons from ASCOT-BPLA**

ASCOT substudies have provided clinical proof that reduction in BP variability, 24-hour/night BP, and central BP with an amlodipine/perindopril regimen is directly associated with prognostic benefits, additional to those achieved due to better reduction in brachial BP.

> In ASCOT, mean brachial BP reduction versus baseline was 27.5/17.7 mm Hg with amlodipine/perindopril and 25.7/15.6 mm Hg with β-blocker/diuretic with a mean difference of 2.7 mm Hg in systolic blood pressure (SBP). Yet, in 2005, the ASCOT investigators demonstrated that the adjustment for this BP difference only explained about half of the differences in coronary and stroke events.43

> Recently, 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.44 Whether antihypertensive treatment can affect this variability was the subject of a complementary analysis of ASCOT. In this study, amlodipine ± perindopril reduced BP variability and stabilized BP better than atenolol ± bendroflumethiazide.45 This applied both to short-term BP variability (consecutive BP measurements in the doctor’s surgery or 24-hour ambulatory BP monitoring) as well as to long-term BP variability, between visits. As demonstrated by the statistical adjustment analysis, the reduction in BP variability contributed to the better CV event prevention seen with amlodipine ± perindopril treatment in ASCOT. In the wake of these findings, the updated British 2011 guidelines were the first hypertension guidelines to recognize BP variability as an independent CV risk factor for cardiovascular events and to recommend using “the best available evidence-based treatment option to suppress BP variability.”46

> 24-Hour and night BP are known to be superior to mean clinic BP as predictors of CV outcomes or stroke, and this superiority has been recently recognized by the NICE 2011 guidelines.15,46 The ASCOT-ABP substudy (Anglo-Scandinavian Cardiac Outcomes Trial–Ambulatory Blood Pressure), using ambulatory blood pressure monitoring, demonstrated early and effective reduction in nocturnal BP, which was observed across the entire study follow-up, with a mean difference of 2.2 mm Hg in night SBP in favor of the amlodipine/perindopril regimen. The study concluded that different effects on daytime and night ambulatory BP may have contributed to the lower rates of events in patients treated with amlodipine/perindopril.47

> CAFE48 (Conduit Artery Function Evaluation), a substudy of ASCOT, was the largest prospective evaluation of the effects of CV drugs on derived central aortic pressures and hemodynam-

![Figure 2. Reduction in cardiovascular mortality in patients treated with amlodipine/perindopril (Preterax) versus atenolol/thiazide diuretic.](image)

Comparison of the proportion of patients receiving perindopril and amlodipine with the proportion receiving amlodipine without perindopril in the ASCOT-BPLA study (Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm), and the relationship to cardiovascular mortality risk over time. Note the divergence of risk profiles at two years as the proportion of patients receiving perindopril in addition to amlodipine exceeds 50%.

**Abbreviations:** CV, cardiovascular; HR, heart rate; RRR, relative risk reduction.

ics, and showed that central aortic pulse pressure may be a factor affecting clinical outcomes. The CAFE substudy was designed to be initiated 1 year after randomization into ASCOT, when all treatments were uptitrated in order to reach target brachial BP. The study found that despite minimal difference (ΔBP, 0.7 mm Hg; \(P=0.2\)) in brachial SBP between the groups, the differences between the central aortic pressures were substantial and in favor of the amlodipine ± perindopril group (Δcentral aortic SBP, 4.3 mm Hg; \(P<0.0001\); Δcentral aortic pulse pressure, 3.0 mm Hg; \(P<0.0001\)). The investigators concluded that the different effect on central BP between the two treatment arms of ASCOT may offer a potential explanation for the different clinical outcomes observed.

In conclusion: Following and derived from the ASCOT trial findings, Coveram was developed as a fixed combination of amlodipine/perindopril, the only evidence-based combination shown to provide hypertensive patients with the expected lifesaving benefits demonstrated with amlodipine/perindopril in ASCOT patients. Coveram provides rapid and effective brachial BP reduction in a broad range of hypertensive patients and acts synergistically on all the components cited above as having been shown by the ASCOT substudies to be associated with prognostic benefits: brachial BP, central BP, 24-hour/night BP, and BP variability. Thus Coveram, indicated in both hypertension and CAD, stands out among currently available combinations of RAAS inhibitors and CCBs in having proven efficacy in decreasing the risk of death and CV events.49

ADVANCE: a step forward in the management of hypertensive diabetic patients

Like ASCOT, ADVANCE was an investigator-initiated trial. The group of trialists, led by John Chalmers (Australia), sought to identify what BP levels would be associated with the greatest benefit in patients with diabetes mellitus. It was a factorial randomized controlled trial evaluating the effects of BP lowering and intensive blood glucose control on vascular outcomes. The primary hypothesis of ADVANCE was that further reduction in BP values below the 145 mm Hg SBP achieved in the hypertensive diabetic patients of UKPDS (United Kingdom Prospective Diabetes Study), would provide even more benefits in this high-risk population.2

Patients were potentially eligible if they had been diagnosed with type 2 diabetes at the age of 30 years or older; were 55 years of age or older at study entry, and had evidence of elevated risk of CV disease. The study comprised 11 000 patients with a mean entry BP of 145/81 mm Hg, who were subsequently randomized to perindopril/indapamide (2 mg/0.625 mg) or matching placebo. The doses were doubled after 3 months, so that participants were receiving either perindopril/indapamide 4 mg/1.25 mg or matching placebo on top of preventive therapy. BP levels of ADVANCE patients at study entry were at the level of blood pressure achieved among diabetic patients in UKPDS. In ADVANCE, treatment with perindopril/indapamide resulted in further BP reduction of 5.6/2.2 mm Hg. This significantly greater antihypertensive effect of perindopril/indapamide in addition to current therapy in patients with diabetes and hypertension was associated with significant improvement in morbidity and mortality, compared with standard therapy alone: perindopril/indapamide reduced the relative risk of CV disease by 18%, all-cause mortality by 14%, total coronary events by 14% and new microalbuminuria by 21% (Figure 4).2

● Importance of reduction in microcirculatory disorders and target-organ damage in improving survival and CV outcomes among hypertensive patients
● In addition to the further BP reduction and significant survival benefits achieved with perindopril/indapamide, the ADVANCE trial provided the first clinical evidence that reduction in microalbuminuria correlates with morbidity-mortality benefits. Further analysis of clinical trials has shown that, in most

![Figure 3. Further reduction in blood pressure and cardiovascular events with perindopril/indapamide (Preterax) in the ADVANCE trial.](image-url)
antihypertensive treatment trials in patients with type 2 diabetes, reduction in microalbuminuria was associated with evidence of renal protection. ADVANCE was the first and only trial to provide evidence of parallel reduction in microalbuminuria, and CV and all-cause mortality.52 Indeed, in the recent ROADMAP trial (Randomized Olmesartan And Diabetes MicroAlbuminuria Prevention Study), a 20% reduction in microalbuminuria with olmesartan was not associated with outcomes reduction, but rather with a significant increase in mortality rates.53

The effect of perindopril/indapamide on target-organ damage prevention shows that reversal and prevention of microvascular damage is a potentially important clinical goal in hypertension.

Robust evidence suggests that, in hypertensive patients, there are severe alterations in microvascular structure and function, mainly characterized by capillary rarefaction, endothelial dysfunction, and decreased vasodilator reserve. Abnormal microcirculation contributes to impairment of tissue perfusion and thus to end-organ damage.

A recent study showed that capillary density and endothelial response were improved only in controlled hypertensive patients receiving perindopril/indapamide, and not in those receiving agents other than ACE inhibitors or diuretics.54

Further analysis of the ADVANCE trial assessed the effects of the fixed combination of perindopril/indapamide on renal and CV outcomes in patients with type 2 diabetes and concomitant chronic kidney disease (CKD). Among the 10 640 participants for whom CKD status was known, 6125 did not have CKD, 2482 were classified as CKD stage 1 or 2, and 2033 as CKD stage ≥3. Treatment benefits of routine administration of a fixed combination of perindopril/indapamide, in terms of renal and CV outcomes in patients with type 2 diabetes, were consistent across all stages of CKD, with no heterogeneity in the magnitude of effects for any outcome. In contrast, the absolute treatment effects approximately doubled in those with CKD stage ≥3 versus those with no CKD.55

**HYVET: solving the hypertension management dilemma in elderly patients**

Until recently, benefits of BP reduction in elderly hypertensives were largely unclear. In 2003, Christopher Bulpitt (UK) and his team published results of the pilot study for HYVET,56 in which treatment for hypertension (lisinopril and HCTZ), despite being associated with reduction in stroke, was also associated with increase in all-cause mortality versus placebo. Concerning the design of the main HYVET trial, Professor Bulpitt wrote: "In the main HYVET trial, we aimed to resolve persistent areas of clinical uncertainty about the relative benefits and risks of antihypertensive treatment in patients 80 years of age or older."53

HYVET provided the first definite demonstration of the benefits of effective reduction in BP and CV outcomes with indapamide (in combination with perindopril in the majority of patients) in very elderly hypertensive patients. HYVET showed that, even in patients 80 years of age or older, antihypertensive treatment not only prevents CV events, but contributes to prolong life. The study results demonstrated 39% reduction in fatal stroke (P=0.046), 21% reduction in all-cause mortality (P=0.02), 23% reduction in CV mortality (P=0.06), and 64% reduction in the incidence of fatal or nonfatal heart failure (P=0.001).5

This unique study thus shows that it is worthwhile, even in a very old population, to start treatment for hypertension, and that the perindopril/indapamide combination is an evidence-based way to do so.
Finally, HYVET and ADVANCE trials both provided evidence of high antihypertensive efficacy and metabolic neutrality of therapeutic strategies including indapamide. British 2011 hypertension guidelines critically reviewed evidence from the latest trials on diuretic use in hypertension management. Guidelines recommend that thiazide-like diuretics (chlorthalidone or indapamide) are used in preference to a conventional thiazide diuretic, such as bendroflumethiazide or hydrochlorothiazide.15

**Coveram—solid evidence of efficacy in further improving survival in hypertensive patients**

During the last decade, when treatment BP goals <140/90 mm Hg and <130/85 in diabetes and high-risk patients39,40 and preventive medicine were implemented in clinical practice, objectives for, and approaches to, the management of hypertension substantially evolved. RAAS inhibitors are the most recent class to have been developed over the last 20 years for the treatment of hypertension. Paradoxically, despite evidence that BP reduction with RAAS inhibitors is associated with lower risk of stroke and CV events, their efficacy in reducing mortality (the ultimate guideline-recommended goal of antihypertensive therapy) has remained uncertain until now.

A recent meta-analysis by Bertrand et al looked at randomized controlled RAAS-inhibitor trials conducted in the majority of hypertensive patients (>2/3 of study population) during the last decade and evaluated the impact of RAAS inhibitors on further mortality reduction for their main indication, hypertension. It revealed that only Coveram regimens significantly reduce mortality among hypertensive patients.56 This meta-analysis included 19 trials in 165 971 patients, of whom 92% were hypertensive. Trials in heart failure, acute MI or stroke, post-cardiac surgery, and acute atrial fibrillation were excluded due to expected benefits from RAAS inhibition other than BP lowering. The pooled results of ACE-inhibitor trials in 88 860 patients demonstrated a significant 6% reduction in all-cause death (hazard ratio [HR], 0.94; 95% confidence interval [CI], 0.90-0.98; P=0.007). Among ACE-inhibitor trials, only perindopril-based regimens—investigated in ASCOT-BPLA, ADVANCE, and HYVET in 34 242 patients—demonstrated significant reduction in all-cause mortality (HR, 0.87; 95% CI, 0.81-0.94; P=0.0001). No significant reduction in all-cause mortality was demonstrated with ARBs in 12 trials totaling 77 111 patients (HR, 0.99; 95% CI, 0.95-1.04; P=0.75).

The investigators’ conclusion was that because of the high prevalence of hypertension, treatments with proven efficacy such as Coveram-based regimens may result in a considerable number of lives saved (Figure 5).56

### Conclusion

Since its creation, Servier has been persistent in its commitment to therapeutic advancements in cardiology. Today, results of more than 40 years of research and development of evidence-based antihypertensive treatments have contributed to significant improvement in the knowledge of hypertensive disease and its management. Indeed, striking lifesaving benefits of treatment with perindopril (Coveram), either alone or in combination with amlodipine or indapamide, have been extensively demonstrated in trials such as ASCOT-BPLA, ADVANCE, and HYVET.

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**Figure 5. Perindopril (Coveram) regimens demonstrate further significant mortality reduction among hypertensive patients.**

Furthermore, these trials with Coversyl-based regimens have provided the first clinical demonstration that reduction in all key BP parameters (brachial BP, 24-hour/night BP, central BP, and BP variability), as well as in microcirculatory disorders and target-organ damage, can contribute to better reduction in CV complications and mortality among contemporary hyper-
pertensive patients.

Finally, a preliminary report of the meta-analysis of clinical trials in hypertension indicates that strategies that include Coversyl significantly reduce all-cause mortality by 13% among patients with arterial hypertension, thus providing convincing demonstration of the benefit of achieving guideline-rec-
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Hypertension is generally recognized as a complex disease, with a significant genetic component interacting with known and unknown environmental factors. The genetics of Mendelian types of hypertension has been largely resolved, but that of its polygenic counterpart requires further study. Recent skepticism about the usefulness of genetic analysis stems from the relatively small contribution of individual genetic markers to overall blood pressure variance. Here, we discuss several explanations behind this finding. Included are disease heterogeneity, the need for separate analysis by sex and age, ethnic complexity, and the need for analysis of genetic versus environmental contributions. The extent to which genetic determinants modulate the efficacy of a therapeutic agent is, again, better understood for monogenic components. The technology is currently available to dissect the individual and combined pharmacogenomic components of blood pressure and of medication response; however, it must be emphasized that clinical trial testing of these new approaches will be required. At present, the most significant progress has been achieved in accompanying development of novel medications with genetic determinants of their eventual safety and responsiveness in the so-called companion diagnostic paradigm. Along those lines, we propose to pursue network-based identification by comparative network analysis in responders and nonresponders, eventually leading to druggable candidate development.

What are the genetic underpinnings of cardiovascular disease and, especially, hypertension?

Genetic determinants of cardiovascular disease (CVD), and hypertension (HT) in particular, were demonstrated initially by classic studies using correlations between (i) twins, parents and their natural and adopted children, and reconstituted families, and (ii) heritability of blood pressure (BP) within families. These studies illustrated that about 30% to 50% of HT has a genetic determinant, and that the remaining percentage is environmentally influenced. Furthermore, the genetic component is larger in subjects under 50 years of age: the ratio of intrafamilial prevalence of HT to that observed in the same general population, called $\lambda_s$, is 3.7 in young subjects, and is only 2.0 in older subjects from the same families, as determined in our cohort from a relatively isolated population from Saguenay–Lac St-Jean in Quebec, Canada. Initial studies of segregation of genetic polymorphisms with-
in genes of the renin-angiotensin system were introduced in experimental animals, particularly rats, and soon after in humans. The greatest success in elucidating the attributes of genetic HT came from the brilliant studies by Lifton’s group, which investigated monogenic forms of this disease in familial HT syndromes associated with sodium transport mechanisms. Resolution of these Mendelian forms of HT has been aided by pedigree studies, the monogenic involvement, and the absence of mutation in the general population. Major technological developments have facilitated a recent burst of activity in regards to the more complex polygenic form of so-called essential HT. Whereas only a few years ago merely 500 polymorphic markers were known for all chromosomes, there were 50,000 known single nucleotide polymorphisms (SNPs) in the year 2000, and we are currently using over 1 million SNPs and copy number variants (CNV) to pinpoint associations down to a gene, its regulatory elements, or the intergenic regions, which frequently contain relevant structures such as microRNA. We also expect much needed progress in transcriptomic and epigenomic studies to integrate gene-environment interactions into our understanding of biological systems. The term “essential” HT should then be modified to distinguish between monogenic and polygenic disorders, and eventually to further differentiate specific etiological entities based upon their predominant genetic architecture. For example, we have demonstrated that HT in families with obesity and HT in those without obesity is determined by distinct genetic loci.

What are the current directions and achievements in genetics with regard to hypertension?

Major achievements in genome-wide association studies (GWAS) of HT have been reported. Their success has been limited by the requirement of a very large sample size and a need for resolution of a small portion of the BP variance component (less than 0.5 mm Hg BP variance is usually associated with a single SNP, even when highly significantly associated with BP). It should also be noted that a highly significant contribution of SNPs in very few subjects does not exclude unknown causes of monogenic contribution. What are the potential reasons for these characteristics? In our opinion, they include:

- **Heterogeneity of the disease.** We have mentioned that HT with obesity and HT without obesity have distinct genomic architectures. In our studies, we have demonstrated linkage for HT in the proximal part of chromosome 1 in families with high prevalence of obesity; no such linkage for HT was observed in families with low prevalence of obesity in the same population.
- **Sex- and age-dependent genotypes.** In most epidemiological studies, including genomic studies, adjustments are made for sex and age. However, it has been clearly demonstrated in both human and animal studies that such adjustments may obscure contributions that are present in one or the other sex only and/or at a certain age. In our systematic approach, we have demonstrated that an SNP on chromosome 12 (rs575121) was significantly associated with elevated systolic BP in men only, and with a contrasting genotypic effect in women.
- **Geo-ethnicity (intraethnic admixture).** It is generally accepted that the difference in susceptibility to disease between various ethnic groups is mainly due to allelic frequency. Thus, it is important to observe whether or not the allelic frequency of a certain SNP is significantly related to the penetrance of the disease, as is the case in broad ethnic groups, such as Africans, Asians, and whites. The FTO gene is one example of genes shown to have different impacts on risk prevalence in different ethnic groups. For instance, one FTO allele (rs6499640) has been shown to be significantly associated with body mass index, and though it has a high frequency in European countries, it is rare in Asians. This has become even more relevant, as we have demonstrated that this gene is related not only to obesity, but also to HT, as confirmed in two different cohorts, in populations in which HT is frequently associated with obesity.
- **Genes versus environment (allelic penetrance).** In HT, this exploration is still in its early stages, but at least one example should be mentioned about the impact of BP treatment. The fact that most of the studies are performed only in treated subjects is certainly diluting the power of resolution of the studies. In our French Canadian cohort, we performed fine phenotyping that included withdrawal of medication for lipids and HT, which frequently is not feasible in large cohort studies (23rd Scientific Meeting of the International Society of Hypertension, Abstract 215, Vancouver 2010). This allowed us to identify several SNPs within the FTO gene that are highly significantly associated with diastolic BP, but that appeared only after withdrawal of medication. No linkage or association was detected in the same subjects before medication withdrawal.

**To what extent does genetics influence the therapeutic response to antihypertensive treatment?**
Several reports have shown that most treatments used in chronic diseases have an average individual response rate of 50%,10 ranging from 25% for antineoplastic agents to 80% for analgesics. In between, we find a 30% response rate for Alzheimer’s, 48% for osteoporosis, 57% for diabetic agents, 60% for asthma, and 62% for depression. An additive response of combined classes of medication constitutes, from a pharmacogenomic point of view, evidence for distinct genomic targets. Diuretics, such as indapamide, angiotensin-converting enzyme (ACE) inhibitors, and/or calcium channel blockers (CCBs), each acting on their sets of gene targets, elicit an additive response rate when they are combined in the same individual. Pioneering work by Giuseppe Bianchi elicit an additive response rate when they are combined in the same individual. Pioneering work by Giuseppe Bianchi demonstrated the clinical impact of adducin gene polymorphism as a partial determinant of diuretic responsiveness, and underscored the importance of the particular context of ethnicity and gene–gene interaction.11 It is important to realize that therapeutic agents, when they are ineffective, may even have an opposite negative impact in some subjects. One such example is the response to corticosteroids in subjects with specific sequence variants in the corticotropin-releasing hormone receptor 1 gene, CCRHR1, which may result in a positive or negative impact on pulmonary function.12 Clear evidence concerning treatment of HT is incomplete, and there is a need for major clinical trials in which polymorphisms in relevant target genes and metabolizing genes in the subjects are ascertained, in order to initiate development of more personalized therapies for individual subjects or specific groups of subjects.

To what extent can the BP-lowering efficacy of antihypertensive therapy be ascribed to genetic determinants?

Pharmacogenomics as a science was pioneered by Motulsky and colleagues13 in their investigation of the need to avoid specific anesthetic agents, and is based on detection of susceptibility to certain adverse drug reactions. More recently, David MacLennan’s group has demonstrated such susceptibility in malignant hyperthermia populations. They describe mutations in the ryanodin receptor type 1 gene, RYR1, a sarcoplasmic reticulum calcium release channel, and the CACNA1S gene that codes for the α1 subunit of the voltage-gated calcium channel receptor, known as dihydropyridine receptor.14 Subjects with mutations within these genes are obliged to avoid volatile anesthetics, which could cause a lethal hypermetabolic crisis that is associated with this autosomal dominant disorder. The polymorphism within these genes was recently reported to be related to sensitivity of hypertensive subjects to CCBs. Specific and sometimes unexpected therapeutic responses are described in monogenic forms of severe HT, including glucocorticoid-mediated attenuation of HT in Laidlaw’s syndrome of glucocorticoid-remediable hyperaldosteronism targeting CYP11B1 and CYP11B2. Triamterene, usually a weak antihypertensive, is lifesaving in patients with Liddle’s syndrome, targeting the genetic abnormality of the β-subunit of the epithelial sodium channel, SCNN1B and SCNN1G. In general, regarding the polygenic and complex form of essential HT, several levels of genetic determinants will have to be considered when aiming at genetically designed BP-lowering therapy.

- Phenotypically prescribed drugs have variable efficacy: the rate of absent or incomplete response varies from 10% to 30% for ACE inhibitors, 15% to 25% for β-blockers, reaching 30% to 70% for statins, and 40% to 70% for β1-agonists.
- The BP change observed during treatment in trials of most currently used antihypertensive agents, including converting enzyme inhibitors, is usually between 5 to 10 mm Hg, but has been demonstrated to vary from an extreme of 25 mm Hg BP reduction to even an increase in BP in up to 15% of subjects. This is a reality not frequently reported in the literature. The specific genomic architecture of nonresponders, and even opposite responders, is unknown at present.
- Certain polymorphisms have been determined for some therapeutic targets, including a polymorphism in the β1-adrenergic receptor motif, which alters cardiac function and β-blocker response in human heart failure: subjects homozygous for arginine 389 have been shown to benefit from a 38% reduction in mortality when treated with bucindolol, which contrasts with the effect in the 30% of subjects with a glycine 389 polymorphism, who had no clinical response compared with placebo-treated subjects.15,16 The above mentioned sensitivity to CCBs in subjects with polymorphisms within the CACNA1 gene is another example.
- Naturally, polymorphisms in drug-metabolizing enzymes is an important factor that is well known, described, and included in the Medical Compendium designed for physicians; yet, these polymorphisms are not widely taken into consideration at present due to the lack of availability of pharmacokinetic diagnostics in the majority of clinical settings.

Most recently, associations of hypertension drug target genes with BP and hypertension have been evaluated and validated in 86,000 individuals.14 The strongest signals were in the ADRB1 and AGT genes. Additional signals were described in the genes ACE and CACNA1A.16 Hundreds of SNPs will have to be included as a base unit of genetic scores rather than as isolated genes. This new approach, called variable set enrichment analysis, should be applied for its practical utility; however, it needs to be validated in prospective, genetically stratified therapeutic clinical trials in the future.17

What are the applications of patient-centered genetics and genomics in current clinical practice?

In 1898, Sir Archibald Garrod coined the term “chemical individuality” to describe inherited predispositions to metabolizing sulfonyl drugs. It took 100 years, until 1998, for Herceptin, a drug effective in 25% of the subgroup of breast cancer patients, to be approved by the Food and Drug Ad-
ministration (FDA) for use in tandem with genetic diagnostic testing on this eve of personalized health care. Personalized medicine, sometimes called “precision medicine,” is defined by the international Personalized Medicine Coalition for its clinical applications, aiming to shift the emphasis in medicine from reaction to prevention. Other goals include selection of optimal therapy, reduction of the use of the trial-and-error model in prescribing, and safer use of drugs through avoiding adverse reactions. Yet, major developments in patient-centered medicine at present are based on “companion diagnostics.” This term has been coined to characterize the development of a diagnostic tool alongside that of medication, such that medication will be given only to subjects that satisfy the predefined criteria, ie, those predicted to respond to the drug and for whom the drug is predicted to be safe. The first model, the Herceptin model, was actually based on a failed clinical trial. Further research, however, demonstrated that the drug was effective in a subset of subjects with breast cancer, and its genetic detection is now widely recognized as a prerequisite for prescription of this costly medication, which has significant side effects, but is effective in a significant subset defined by the presence of human epidermal growth factor receptor 2 (HER2) on breast cancer cells, providing a clear benefit to those patients. This area has been recently summarized by Hamburg and Collins, respectively, the Commissioner of the FDA and Director of the National Institutes of Health (USA). Currently, there are 3 FDA-approved drugs used with companion diagnostics in clinical practice: i) Herceptin (traztuzumab), which targets HER2 to treat metastatic breast cancer, and the approved companion diagnostics—an immunohistochemistry test and a gene amplification test; ii) Erbitux (cetuximab), which targets epidermal growth factor receptor (EGFR) to treat metastatic colorectal cancer, and its companion diagnostic—an immunohistochemistry test; iii) Glivec (imatinib), which targets the cell surface tyrosine kinase receptors in gastrointestinal tumors, and its companion diagnostic—an immunohistochemistry test.

As mentioned above, most clinical applications of genomics are in the area of monogenic diseases, and include detection and prevention, such as in monogenic HT. Only future prospective evaluation of the efficacy of genetic prediction in clinical trials, randomized using tools of genomic stratification, will pave the way to application of individually targeted medicine in hypertension.

**What are the future perspectives for genetics and genomics in hypertension with regard to the development of new drug therapies?**

A thorough analysis of the theme of genomics in drug discovery and development has been published as a monograph by Semizarof et al., demonstrating the importance of genomics in new target identification. This new classification of disease should take into account expression profiles and gene copy number in addition to genomic sequence. As such, in June 2011, the FDA approved determination of the copy number of the HER2 gene as a diagnostic tool for better Herceptin use in targeted individuals. To our knowledge, this is the first time that a drug therapy is to be applied subsequent to prediagnosis based on copy number variance. Furthermore, animal models of disease should be submitted to genetic profiling in concordance with human genetic architecture. The next step is target validation, the targeted subtraction or addition of genes in vitro and in vivo, followed by validation of gene function using microarray and pathway analysis. Lead compound identification and optimization and in vitro biomarker discovery includes the identification of polymorphisms, copy number, gene expression, methylation, other epigenetic markers, and microarray profiling as associated with drug sensitivity.

Another area where genomics can be of help is the dissection of druggable targets, summarized as the druggable genome. An update by Russ and Lampel proposes the evaluation of the most frequent targets, including rhodopsin-like G protein-coupled receptors (GPCR), protein kinases, ion channels, proteases, and enzymes, as they have classically been used by the pharmaceutical industry before the use of novel genomic technologies. It is clear that the “one gene, one target” paradigm, which in the past was considered the goal for the industry, is progressively being abandoned, as molecular targets and their therapeutic utility are determined by the balance of their actions and not by their absolute specificity. The pleiotropic impact of drugs is of highest interest, as we are learning more and more about the balance of metabolic networks, which will be the future blueprint for drug discovery. As proposed by Barabási and his colleagues: “Advances in genome analysis, network biology, and computational chemistry have the potential to revolutionize drug discovery by combining system-level identification of drug targets with the atomistic modeling of small molecules capable of modulating their activity.” The future direction in therapeutic areas such as HT and diabetes will be based on past successes, yet be guided by the evidence that residual risk is still present and can be targeted genetically. Therefore, we propose the first phase should be organization of network-based identification, followed by unmet needs identification, validation, and optimization. As a next step, outcome-dependent comparative network analysis should be performed in responders and nonresponders, based on their respective genomic signatures. We believe that this will accelerate the progress toward identification of new targets in nonresponders as well as new targets in responders. Virtual screening of druggable candidates should be performed in parallel to this step, leading to further validation, optimization, and the addition of novel technologies, such as deep sequencing.
Hypertension artérielle et génétique comme approche individualisée du patient : où en sommes-nous ?

L’hypertension est généralement reconnue comme étant une maladie complexe, dotée d’une composante génétique significative interagissant avec des facteurs environnementaux connus et inconnus. Les modèles génétiques de l’hypertension de type mendélien ont été largement élucidés, mais ceux de son homologue polygénique ont besoin d’être étudiés plus amplement. Le scepticisme récent au sujet de l’utilité de l’analyse génétique provient de la contribution relativement faible des marqueurs génétiques individuels à la variation globale de la pression artérielle. Nous analysons ici plusieurs explications sous-tendant ce résultat, dont l’hétérogénéité de la maladie, la nécessité d’une analyse séparée par sexe et âge, la complexité ethnique et la nécessité d’une analyse des contributions respectives de la génétique et des facteurs environnementaux. La façon dont les déterminants génétiques modulent l’efficacité d’un traitement demeure, encore de nos jours, mieux comprise pour les composantes monogéniques. La technologie actuelle permet de séparer les composantes pharmacogénomiques individuelles et combinées de la pression artérielle et de la réponse au médicament ; cependant, il faut souligner qu’il faudra soumettre ces nouvelles approches à l’épreuve d’études cliniques. À l’heure actuelle, les progrès les plus significatifs ont été réalisés dans le développement de nouveaux médicaments tenant compte des déterminants génétiques des réponses thérapeutiques et tolérances éventuelles dans le modèle dit diagnostique double. Enfin, nous proposons de poursuivre l’identification par réseau par une analyse comparative de réseau chez les responsables et les non-répondeurs, conduisant finalement au développement d’un candidat-médicament.
Resistant hypertension, defined as the failure to reach blood pressure targets despite treatment with ≥3 antihypertensive drugs (one being a diuretic), is a major challenge. Blood pressure in the general population is frequently uncontrolled. Therefore, new interventional techniques are necessary to improve blood pressure control. A novel catheter-based procedure, which leads to the ablation of the sympathetic nerves in the adventitia of the renal arteries, has been developed. The first-in-man studies and one controlled trial (Symplicity [not an acronym] HTN-2 [hypertension]) showed that reducing sympathetic afferent and efferent activity achieved marked reductions in blood pressure, by up to 35 mm Hg, as well as much better control rates than conservative drug treatment. Furthermore, there is evidence that such a procedure can improve metabolic parameters, which is a common comorbidity of resistant hypertension. Further studies will be needed to address the value of this procedure in reducing hypertension and its associated morbidity and mortality.

Medicographia. 2012;34:100-104 (see French abstract on page 104)
sure control. If following treatment with \(\geq 3\) hypertensive drug classes (one being a diuretic), blood pressure values do not meet the targets set by hypertension management guidelines, patients fulfill the criteria for resistant hypertension. Using this definition, it is estimated that about 10% of diagnosed hypertensive individuals are resistant to drug treatment. Resistant hypertension frequently occurs in the presence of 6 or 7 or more antihypertensive agents. Thus, there is a clear need for novel nonpharmaceutical approaches such as devices or interventional treatments.

**Pathophysiology**

The pathophysiology of essential hypertension often involves the activation of the sympathetic nervous system. Moreover, sympathetic activation may be one mechanism that counteracts the blood pressure–reducing effects of several antihypertensive agents. The renal sympathetic nerves, which arise from the sympathetic ganglia of the thoracolumbar segments (Th10-L1), are a crucial component of sympathetic regulation. They lie, netlike, in the adventitia of the renal arteries, thereby eliciting the most complete renal denervation possible.

Historical data on surgical renal denervation in the early 1930s and 1950s have shown that supradiaphragmatic splanchnicotomy was used as an *ultima ratio* for malignant hypertension. Significant reductions in blood pressure by up to 70 mm Hg were observed. However, there were severe postoperative complications such as orthostatic hypotension, syncope, incontinence, erectile dysfunction, and neurological disturbances. Several animal experiments have also shown that renal denervation reduces the activity of the sympathetic nervous system, which is followed by a reduction in blood pressure and end organ damage.

**Interventional renal denervation**

In order to overcome the shortcomings of surgical renal denervation, an interventional technique requiring femoral artery catheterization was developed. By placing the tip of the catheter (Figure 2, page 102) into the distal renal artery and applying high radiofrequency energy to the vascular wall, heating occurs at the adventitia of the lumen of the renal artery. Thanks to the cooling action generated by the relatively high blood flow in the renal artery, the effects of the applied radiofrequency primarily occur in the adventitia, thereby denervating the sympathetic nerve fibers. After the initial radiofrequency application, the catheter is pulled back by about 5 mm, and then rotated circumferentially before energy is applied again. This procedure is repeated 4 to 6 times in each renal artery. The goal of the procedure is to hit the whole circumference of the renal arteries, thereby eliciting the most complete renal denervation possible (Figure 3, page 102). Since the renal sympathetic fibers are accompanied by C fibers, patients often require intravenous morphine and sedative agents during the ablation.
Proof-of-concept study
The first-in-man study evaluated the safety and efficacy of the blood pressure reduction obtained following a reduction in sympathetic activation. Patients with a blood pressure >160 mm Hg, uncontrolled at study entry despite the use of ≥3 antihypertensive agents, were recruited after confirmation of their adherence to treatment and exclusion of secondary hypertension. Imaging of the renal arteries was used to exclude patients with significant arterial stenotic disease and renal abnormalities including more than one artery. Renal denervation in 45 patients significantly reduced blood pressure beginning at 1 month, and the reduction persisted until the final visit at 12 months. The data of an extended cohort with a 24-month follow-up are available. There was a significant reduction (by about 35 mm Hg) in systolic blood pressure, which remained stable over a 24-month period.

Recently, a randomized parallel-group design study (Symplicity HTN-2 [hypertension]) was performed and published. The Symplicity HTN-2 trial assessed 106 patients with treatment-resistant hypertension and office systolic blood pressure >160 mm Hg (>150 mm Hg for patients with diabetes mellitus) despite the use of ≥3 antihypertensive drugs. The patients were randomly assigned to a treatment group (52 patients) or to a parallel controlled group (54 patients), which were both followed up for 6 months. Renal denervation resulted in a significant reduction in office blood pres-
sure by 32 mm Hg (systolic) and 12 mm Hg (diastolic) after 6 months. In the control group, the blood pressure remained completely unchanged (Figure 4). The procedure was performed safely without any significant adverse events. According to the available data, renal vasospasm responsive to nitroglycerin occurred temporarily in some patients. The complications were similar to those consecutive to routine cardiac catheterizations, with the development of some pseudoaneurysms. There was no apparent change in renal function. Therefore, in patients with therapy-resistant hypertension, this interventional procedure is effective and apparently safe. Blood pressure control was achieved by this novel interventional procedure and some of which will require further investigation. Therefore, long-term follow-up in these patients will determine whether the decline in blood pressure is sustained. During exercise, the adaptation of cardiac output, blood pressure, and heart rate during stress conditions crucially depends on an intact sympathetic nervous system. Therefore, data will have to be generated to determine whether treated patients exhibit impaired adaptation to exercise, and in particular whether a phenomenon related to chronotropic incompetence may be limiting their exercise capacity. Furthermore, following a reduction in sympathetic activation, other clinically important effects, like a reduction in its metabolic effects, may be important.

First evidence shows that there may be some positive effects such as an improvement in metabolic syndrome or type 2 diabetes mellitus. In addition, the reversal or prevention of the adverse consequences of hypertensive end organ damage, such as impaired renal function, development of microalbuminuria, arterial stiffness, and left ventricular hypertrophy, have to be addressed by long-term follow-up. Finally, it will be most exciting to see whether or not this procedure could achieve a reduction in cardiovascular outcomes, like morbidity and mortality, that will exceed the effects of blood pressure adjustment achieved by pharmacological interventions.

The novel technique of sympathetic renal denervation provides fascinating perspectives for the treatment of patients with resistant hypertension who are at high risk due to significant comorbidities like diabetes mellitus. More investigations will be needed to clarify the underlying pathophysiology and safety issues and provide insight into indications for a broader use. These new indications may include: patients with mild hypertension and metabolic syndrome, patients with type 2 diabetes mellitus and even, when safety issues are resolved, the treatment of patients with heart failure.

Open questions
Some questions remain, some of which will be answered during the long-term follow-up of the patients undergoing this novel procedure, and some of which will require further investigation. Reinervation occurs in mammals, particularly in rodents, and this may be a concern in treated patients. Therefore, long-term follow-up in these patients will determine whether the decline in blood pressure is sustained. During exercise, the adaptation of cardiac output, blood pressure, and heart rate during stress conditions crucially depends on an intact sympathetic nervous system. Therefore, data will have to be generated to determine whether treated patients exhibit impaired adaptation to exercise, and in particular whether a phenomenon related to chronotropic incompetence may be limiting their exercise capacity. Furthermore, following a reduction in sympathetic activation, other clinically important effects, like a reduction in its metabolic effects, may be important.

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Keywords: catheterization; denervation; renal artery; resistant hypertension; sympathetic activation

**NOUVELLES STRATÉGIES INTERVENTIONNELLES DANS LE TRAITEMENT DE L’HYPERTENSION RÉSISTANTE**

L’hypertension résistante, définie comme l’échec de l’obtention des valeurs cibles de pression artérielle malgré un traitement comportant 3 antihypertenseurs ou plus (dont un diurétique), représente un défi majeur. La pression artérielle est souvent mal contrôlée dans la population générale, de nouvelles techniques interventionnelles devenant donc nécessaires pour améliorer son contrôle. Une nouvelle procédure basée sur l’ablation des nerfs sympathiques dans l’adventice des artères rénales au moyen d’un cathéter a été développée. Des études initiales chez l’homme et une étude contrôlée (Simplicity [pas un acronyme] HTN-2 [hypertension]) ont montré que la diminution de l’activité du sympathique afferent et efférent a permis des réductions marquées de la pression artérielle, jusqu’à 35 mmHg, ainsi qu’un bien meilleur taux de contrôle qu’avec le traitement conservateur. De plus, il semble qu’une telle technique peut améliorer les paramètres du syndrome métabolique, qui est une comorbidité courante de l’hypertension résistante. Il faudra d’autres études pour prendre en compte la valeur de cette technique dans la réduction de l’hypertension et de sa morbi-mortalité associée.
A TOUCH OF FRANCE

Make a test: compare a photo of a rose and one of Redouté’s botanical illustrations. A rose by any other name? Look again! Today’s ubiquitous recourse to photography in science will never match the meticulous hand-painted illustrations of previous generations and their wealth of detail. This is the point the Touch of France articles would like to... illustrate, with the example of anatomy and ornithology. A feast for the eyes—and Medico-graphia at its lavish best!

Body painting: five centuries of French anatomical illustrations
C. Régnier, France


John James Audubon: finding life in birds
R. Rhodes, USA

The first representations of the body were allied with a strange pictorial amalgam of plants, architectural elements, and allegories. Anatomy illustrations aspired to the status of works of art... With the invention of lithography, artists offered their services to surgeons and anatomists whose requirements in terms of accuracy were no longer negotiable. The ceremonial depiction of human cadavers accompanied by allegories was now unthinkable. There was one anatomy for physicians and another for artists.

More than any other branch of medicine, anatomy should be pictorial, illustrative, visual. Anatomy takes a critical, esthetic, as well as a practical look at the human body, through the eyes of a scientist, physician, student, surgeon, scholar, and artist. Without visual representation anatomy would scarce exist, and artwork has been used to illustrate descriptive text in anatomy books since the 16th century. Anatomist and artist had to work together, to give and take, the anatomist wedded to graphic faithfulness to what the scalpel reveals, the artist wielding crayon, burin, or brush to represent the body, the cadaver, death itself. Great was the temptation for anatomists to illustrate their dissections themselves, to make do without, or to seek to emulate, an artist’s ways of seeing. French anatomists stood at the crossroads of the great Northern European schools of anatomy, close to the German master engravers, influenced by the artists of the Italian Renaissance. They were therefore well placed to make an original contribution to the history of anatomy and its artistic representation, and it was in France that the first attempts were made to print anatomical plates and drawings in color. Throughout the 19th century, the French school of anatomy reinvented the relation between the body and its ailments: accurately illustrated organs and sick bodies, surgical procedures rooted in a new descriptive and topographic anatomy stripped of all stylistic flourishes. Anatomists in France made great strides through mastery of chromolithography (the making of multicolor prints) and the invention of techniques for preserving bodies. And then came the modern era with its photography, x-rays, electron microscopy, and computing.


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In the Renaissance, liberation of the mind and the emergence of the humanist movement benefited medicine and more particularly anatomy, which assumed the status of a "science." The Flemish anatomist Andries van Wesel (1514-1564), better known as Andreas Vesalius, was one of the first to ally the acuity of the anatomical view and the beauty of artistic representation. Vesalius studied in Paris around 1533-1536 under the French anatomist Jacques Dubois (1478-1555), known also as Sylvius, but they fell out, as Sylvius opposed the use of illustrations in anatomy books and refused to countenance that Galen's anatomy could be challenged. Heedless of censure, Vesalius dissected cadavers from the gibbet of Montfaucon (near the current Buttes Chaumont Park in the 19th arrondissement of Paris) and from the Cemetery of the Innocents (the place Joachim-du-Bellay in the “Les Halles” district in the center of Paris now covers the site of the cemetery). This work enabled Vesalius to correct numerous anatomical errors in the canons of osteology and myology. In 1543 he published in Basel his masterwork *De Humani Corporis Fabrica Libri Septem* ("On the Fabric of the Human Body in Seven Books"; 661 pages), which was illustrated by 300 plates by Jan Stefan Van Kalkar and others working in the studio of Titian. These were the first plates in which scientific representation of the body was allied with a strange pictorial amalgam of plants, architectural elements, and allegories. Anatomy illustrations aspired to the status of works of art through the drawing and engraving techniques used and the way the image was portrayed. Anatomist and artist became at one and the same time associates and rivals.\(^1\)\(^2\)\(^3\)\(^4\)

Charles Estienne, father of French anatomy

In their printworks on the rue Saint-Jean-de-Beauvais in Paris, the Estienne family published the works of Galen and Sylvius. Charles Estienne (ca 1504-1564) studied medicine in Padua and in 1534 graduated in Paris, where he met Vesalius. Together they surreptitiously dissected the cadavers of torture victims and the hanged. By 1536, Estienne had almost completed his projected three-volume work on human anatomy *De Dissectione Partium Corporis Humani Libri Tres*. However, legal proceedings brought against the Estienne family in 1539 by the surgeon and draftsman Étienne de la Rivière delayed publication, and the book only appeared in 1545 in its Latin version and the following year in French. De la Rivière was the initiator of the book and wanted his name to appear on the engravings that Estienne had re-used, together with simple anatomical illustrations engraved separately. Court artists at Fontainebleau did the 62 wood engravings in a somewhat Italianate style.\(^2\)\(^4\)

Gerard de Lairesse, artist to Govert Bidloo

In the 17th and 18th centuries, the emergence of microscopy revolutionized anatomical studies, linking organs to their function and thrusting physiology into the field of anatomy. It was also the era of comparative and of functional anatomy. Artists and anatomists pursued their collaboration, but were beginning to go their separate ways. Artists no longer sought to depict the absolute truth of forms, but rather to establish aesthetic canons. Anatomists, on the other hand, wanted to use their observations to explicate physiology and to understand
pathology. In 1690, Govert Bidloo (1649-1713), a professor of anatomy in Leiden, published Ontleding des Menschelyken Lichaams (Anatomy of the Human Body), which was illustrated by 107 intaglio engravings by Abraham van Blooteling, based on drawings and paintings by Gerard de Lairesse, a student of Rembrandt.

Lairesse observed and painted during Bidloo’s dissections, which were often swiftly done, thus accounting for numerous anatomical approximations in the resulting artwork. Keen to show the cadaver pinned to the dissecting table, and as a master of the technique of shading, Lairesse produced work bearing the aesthetic hallmarks of French 17th-century classicism. Bidloo’s book was not a success, either in Dutch or in the later Latin edition (1685), but its engravings took on a life of their own when the English anatomist William Cowper (1666-1709) purchased and published them in 1697 under his own name and with his own legends.2-5

Gautier d’Agoty and the advent of color

From the 18th century onwards, black and white line drawings gave way to color illustrations, which created a sense of tissue volume and texture. Jacques Fabien Gautier d’Agoty (1717-1785), an artist from Marseille, published the first mechanically printed, color intaglio anatomy books. D’Agoty learned three-color printing (blue, yellow, red) from the printer Le Blon, adding black in the process, to increase sharpness and draw shadows. He published Myologie Complète en Couleur et Grandeur Naturelle, a treatise on muscle anatomy, in 1746, Anatomie Générale des Viscères (General Anatomy of the Viscera) four years later, and Exposition Anatomique du Corps Humain (Anatomical Exhibition of the Human Body) in 1759, all with full-size, color illustrations, some two meters high. This return of color, which had been used in the Middle Ages, enhanced lifelikeness, but three-color printing was costly and d’Agoty’s illustrations were mediocre and wanting in anatomical accuracy, and the books were commercial failures.1,2,6,7

Félix Vicq d’Azyr: the return to anatomical realism

Félix Vicq d’Azyr (1748-1794) was Queen Marie-Antoinette’s physician and a member of the French Academy of Sciences and of the Academy of Medicine. He wrote the section on pathological anatomy in L’Encyclopédie by Denis Diderot and
Jean le Rond d’Alembert, and in 1786 published *Traité d’Anatomie du Cerveau*, which was lauded as one of the most realistic works of neuroanatomy. To illustrate his treatise, Vicq d’Azyr called upon the engraver Alexandre Briceau and his daughter Angélique, who used aquatint, an intaglio printmaking technique. A layer or successive layers of acid-resistant resin are baked onto a copper plate, which is then immersed in nitric acid to create different tones in the unprotected areas between resin particles, depending on acid concentration and exposure time. The plate is inked and prints are made. This complex technique achieves the delicacy of wash-paints, crayons, watercolors, and pastels. The etcher makes three plates, using aquatint (ocher), point engraving (red), and cutting wheel (black)²,⁷,⁸

Anatomists and artists: diverging paths
By the early 19th century, artists and anatomists had parted ways forever: artists gravitated toward the fine arts while anatomists focused on medical matters. Microscopy and the work of Xavier Bichat (1771-1802) on tissues and organs gave birth to applied anatomy. Bichat’s studies initiated a period marked by the preeminence of the French school: Béclard, Portal, Rouvière, Ranvier, Mathias Duval, Breschet, Sappey, Testut, and Latarget. In the early 1830s, the Parisian phar-
macist Jean-Nicolas Gannal proposed a new
technique for preserving cadavers by inject-
ing sulfate of alumina into the carotid artery.
Anatomists were therefore no longer pressed
for time in their dissections and other anatom-
ical preparations.

With the invention of lithography, a new pro-
cess of reproduction, artists offered their serv-
cices to surgeons and anatomists whose re-
quirements in terms of accuracy were no
longer negotiable. The ceremonial depiction of
human cadavers accompanied by allegories was now unthink-
able. There was one anatomy for physicians and another for
artists, as seen in this hybrid work illustrated by aquatints pro-
duced with two copper plates and published in 1812 by Jean-
Galbert Salvage, who was both an anatomist and artist.2-5,9

Lithography at the service of anatomy
Jules Germain Cloquet (1790-1883), the son of a famous en-
graver and illustrator, studied under, and became the friend
of, the surgeon Achille Cléophas Flaubert, the father of Gus-
tave Flaubert, in Rouen. He worked for a while making wax

Jean-Galbert Salvage. Anatomie du Gladiateur
Combattant. Applicable aux Beaux-Arts, ou
Traité des Os, des Muscles, des Mécanismes
des Mouvements, des Proportions et des Carac-
tères du Corps Humain. Paris, France; 1812.
Among 22 self-published printed plates, is this
study of a gladiator after an ancient Greek statue.
Salvage, who was a military doctor under Napoleon,
aranged the cadavers of soldiers in gladiatorial
poses before making his sketches. © BIUM, Bibliothèque Interuniversitaire de Médecine.

The question of how to illustrate anatomical subjects (col-
or or not) has been at the heart of publishing ever since the
invention of the printing press. Over the centuries, techniques
followed one upon another, overlapped, dovetailed, enjoyed
a heyday, stood the test of time, or fell the wayside.

- **Wood engraving (xylography)**, the oldest of techniques
  for reproduction of engravings, appeared around 1400. The
  artist uses gouges to engrave in wood (boxwood, apple,
  pear) drawings and text which can be printed in relief. Col-
  or is applied manually using a stencil or successive wood
  engravings. After falling into disuse for a number of cen-
  turies, wood engraving enjoyed a revival in the early 19th
  century with the development of the written press.

- **Copper plate engraving** emerged in 1430 from the tech-
  niques of gold and silver working in the Rhine Valley
  and then 20 years later in Italy. The copper plate is incised,
  inked, and damp paper is placed on top before the whole is
  passed between two rollers which apply a pressure of one
  metric ton. The engraving appears when the paper is pushed
  into the ink-filled grooves in the copper. The main intaglio
  techniques for incision of copper are the burin ("cold chis-
  el"), aqua fortis (nitric acid), drypoint (using a metal or dia-
  mond "needle"), and aquatint. The 17th century saw the in-
  vention by Ludwig von Siegen of another intaglio printmak-
  ing technique, mezzotint (Italian for half-tone) or "black man-
  ner" which produces a large range of tones. Color mezzotints
  can be produced by use of a separate copper plate for each
  color, or using a cloth to dab different areas of a single plate
  with colored inks.

- **Three-color printing** was developed by Jacob Cristoph
  Le Blon (1667-1741) in Amsterdam around 1710. He used
  separate copper plates for the three primary colors (red,
  blue, yellow) and passed the paper through the printing
  press three times, once for each color.

- **Lithography** was invented by Alois Senefelder, a German
  playwright and actor, 1796 by making use of the mutual
  repulsion of water and oil (greasy ink). Using ink or soft lead
  pencil, the image is drawn directly on limestone (which ab-
  sorbs water), without the need for engraving. Multiple prints
  can therefore be produced, and the limestone can be pol-
  ished and used again. Lithography was introduced in France
  around 1818 by Louis-François Lejeune and Edouard Knecht.
  In chromolithography the image is transferred to the paper
  from several stones, depending on the colors chosen.
anatomical models at the Paris Faculty of Medicine, and later became a surgeon and professor of external pathology, and a member of the Academy of Medicine and of the Academy of Sciences. This was a time when Paris was the center of anatomy and its hospitals supplied physicians of the state health services with a large number of cadavers for dissection. Cloquet and his sister Lise, whose father had taught them to draw, took up lithography, which greatly reduced the cost of printing. In the first lithography studio in Paris, founded by Charles Philibert de Lasteyrie, the artists Feillet, Langlumé, and Frey made black and white lithographs of 300 anatomical plates drawn by Haincelin. Cloquet used these in his five-volume *Anatomie de l’Homme*, published from 1821 to 1831 in Paris, the first anatomy atlas to be illustrated with lithographs. In 1825 Cloquet published his *Manuel d’Anatomie Descriptive du Corps Humain*, an easy-to-use and affordable quarto book illustrated by 340 plates, some hand-colored, and by pictures of tissue samples and microscopic anatomy drawings not included in the 1821 treatise. Still beyond the means of students, these great anatomy treatises were to be found in the libraries of the fast-growing bourgeoisie.

**Master of anatomic pathology**

Jean Cruveilhier (1791-1874) was a medical student in the same class as Jules Cloquet, and later became professor of anatomy and head of anatomy studies at the Faculty of Medicine in Paris, where he turned anatomic pathology into a whole new medical discipline. Cruveilhier, like Flaubert’s Dr Larivière, the physician called to attend to the dying Emma Bovary after she swallowed arsenic, “belonged to that great school of surgery begotten of Bichat.” Cruveilhier followed the teachings of the surgeon Guillaume Dupuytren and was president of the Anatomical Society from 1826 to 1866. Apart from a treatise on descriptive anatomy (*Traité d’Anatomie Descriptive*: 1834), his main work was *Anatomie Pathologique du Corps Humain*, which he started in 1828 and completed in 1842. It was illustrated by 233 splendid lithographs produced by Langlumé from hand-colored drawings by Antoine Chazal, the resident artist and professor of drawing at the National Museum of Natural History in Paris. Every day he and Cruveilhier spent hours poring over and checking the plates.

**Jean Cruveilhier.** *Anatomie Pathologique du Corps Humain, ou Descriptions, Avec Figure Lithographiées et Coloriées des Diverses Altérations Mortides Dont le Corps Humain est Susceptible, Paris, France: Baillière; 1829-1842.*

Kidney diseases. Figure 1. “Renal phlebitis,” Figure 2 and 2’. Fatty cysts in the renal cortex. Figure 3. Atrophy of the medullary substance. Volume 2, Part 3, Section 36, plate 2. © BIUM, Bibliothèque Interuniversitaire de Médecine.
From France to America: anatomy color plates
In Paris in 1829 Jean-Baptiste Sarlandière (1787-1838) published Anatomie Méthodique ou Organographie Humaine (Methodical Anatomy or Human Organography). Republished the following year, and then in Latin in 1831, it appeared in two American editions (1835 and 1837) under the title Systematized Anatomy. This 32-page book designed to educate and enlighten the general public contained 15 plates, based on the anatomical preparations of Leboyer, Talrich, and Pichonnière, lithographed and hand-colored in 54.8 × 35 cm format by Langlumé, Delaporte, and Courtin. Sarlandière was a friend of François Magendie, professor of medicine at the Collège de France and one of Claude Bernard’s teachers, and also devoted himself to acupuncture, electrotherapy, electropuncture, and massage techniques.2-4,7,10

Jean Marc Bourgery’s anatomy treatise: a monumental work of the 19th century
Jean Marc Bourgery (1797-1849) studied under Jean-Baptiste Lamarck, worked in Paris as an intern for René Théophile Laennec and Guillaume Dupuytren, and devoted his life to anatomy.2,3,5,11 His Traité Complet de l’Anatomie de l’Homme,2,5,11

Comprenant la Médecine Opératoire (Complete Treatise on Human Anatomy, Including Surgery) is one of the most remarkable works in the history of anatomy, and the greatest of the 19th century. Published in Paris between 1831 and 1854, this 8-volume work contained 2108 pages of folio-sized text (80 × 30 cm) illustrated by 725 plates comprising 3750 lithographed figures. It covered descriptive and physiological anatomy, surgical anatomy and surgery, philosophical anatomy and embryology, and microscopic anatomy. The last volume was edited by Claude Bernard (1813-1878) after Bourgery’s death, as was the second edition. Claude Bernard in person supervised (and sometimes performed) the dissections, and Nicolas Henri Jacob, a student of Jacques-Louis David, did the drawings, with help from Ludovic Hirschfeld.

Ludovic Hirschfeld, the sedulous student
As a demonstrator and laboratory assistant, Ludovic Hirschfeld (1816-1876) helped Bourgery prepare his famous treatise. He worked at the surgical clinic run by Léon Rostan at the Hôtel-Dieu in Paris, and his passion for neuroanatomy led him to publish in 1853 Néurologie ou Description du Système Nerveux, a treatise on neurology illustrated by 92 chromolithographs by Léveillé, a celebrated Parisian lithographer.

A second enlarged and corrected edition appeared in 1866, when Hirschfeld was a professor of anatomy in Warsaw (see his “Dissection of the armpit,” page 113, as well as the illustration at the beginning of this article, page 107).3,10

A farewell to the anatomy of yesteryear
From the end of the 19th century onwards, the anatomical image was transformed by new techniques that captured “reality” like photography and radiology. The last treatises to be illustrated by hand drawings were rolling off the presses, and in the 1860s, some 25 years before the discovery of x-rays, Vincent Paulet and Jules Sarazin published a superb book on topographic anatomy illustrated by 244 watercolors printed as chromolithographs. Paulet did the anatomical preparations and Sarazin, a doctor in the imperial army, painted the watercolors. Paulet later held the chair of anatomy at the Faculty of Medicine in Lyon (1877 to 1884) and then in Montpellier (1888). Sigismond Laskowski (1841-1928), an anatomist of Polish origin exiled in Paris and professor of anatomy in Geneva, published in 1894 Anatomie Normale du Corps Humain: Atlas Iconographique de XVI Planches Dessinées d’Après les Préparations de l’Auteur par S. Balicki. Geneva, Switzerland: Braun et Cie, 1894. © BIM, Bibliothèque Interuniversitaire de Médecine.
male du Corps Humain with 16 color plates, prints of which were used for teaching purposes. Laskowski became a renowned embalmer and considerably improved the preservation of bodies through his inventions of arterial injection of sodium borate and glycerin, the use of phenol, and venous drainage.2,5,9,11

Epilogue
In the contemporary era, radiologic anatomy (computed tomography and magnetic resonance imaging), a new branch of anatomy with direct practical applications, and electron microscopy, since the 1960s, have revolutionized anatomy. Contemporary anatomists focus on the teaching of anatomy, notably its relation to physiology and medicine, quantitative anatomy (development of measurement techniques, introduction of statistical methods), the use of real-time in vivo imaging, and questions of international nomenclature. And in the 21st century, anatomy entered the digital era. Three-dimensional computer graphics are used to represent the human body, as in the Visible Human Project, in which the body of a man was cut into over 1800 one-millimeter slices which were photographed and digitized.12

References

One reason bird illustration was so stilted before Audubon and ornithology so limited was that ornithologists and artists worked with stuffed skins rather than complete birds. They hired market hunters to collect specimens for them and delivered only the arsenic-dusted skins, which they stuffed into lumpish form with frayed rope. Field observation had hardly begun; Audubon would be one of the first in North America to study birds in their natural habitat.

John James Audubon, born illegitimately in Saint Domingue in 1785, grew up in Couëron, on the Loire below Nantes, during the tumult of the French Revolution. His father, Jean, taught him the names and characteristics of local birds; later a family friend, the physician father of the naturalist d’Orbigny, added field collection to his skills and introduced him to Buffon’s Natural History. Jean Audubon sent his only son to America in 1803 to avoid conscription. In the new country, just then beginning to be settled beyond the Appalachian Mountains, young Audubon drew the birds of the western wilderness for his own pleasure while marrying, settling in the new state of Kentucky, and establishing himself as a successful businessman. Bankrupted in the financial panic in 1819, he took up portrait drawing to support himself and his family, then grandly conceived of producing an unparalleled work of life-sized colored engravings, The Birds of America, four volumes of plates sized 60x92 centimeters. After years of arduous field work, when he supported himself teaching fencing, dancing, and drawing to the children of wealthy plantation owners in Louisiana, he carried his first 250 drawings to England. There he supervised their production at a London engraving house, sold subscriptions, made further expeditions to America to add new discoveries, and across ten years supported a work of 435 large engravings in an edition of about 200 that would cost about $2 million to produce today. He returned to America in 1839 a famous man.
“There is no timber that has not strong roots among the clay and worms,” the Irish poet John Millington Synge declared in a 1907 preface. Art is a timber that grows from strong roots, roots of strenuous practice surely, but also, and at greater depth, the roots of early experience. For many artists that early experience may be more of trauma than of bliss: Art is always a search for meaning, and finding meaning in past trauma is the most effective way of resolving it. John James Audubon, the early-nineteenth-century artist of American birds, himself grew from strong French roots along the Loire downriver from Nantes, and particularly in the neighborhood of his father Jean Audubon’s country house in the village of Couëron.

The Audubons owned a two-story limestone villa in Couëron, La Gerbetière, a cool, cream-colored house with a formal garden and an orangery. It was the family’s summer residence during most of John James’ childhood. An easy walk downriver led to the extensive forested marshes below Couëron that Cistercian monks had drained in medieval times, where the boy hunted—and studied—birds.

A Caribbean childhood curtailed

From his birth in 1785 on the eastern Caribbean island of Saint Domingue, where his father owned and operated a sugar plantation, until 1793, the boy had been Jean Rabin, his father’s bastard son by a twenty-seven-year-old French chambermaid, Jeanne Rabin. The infant’s mother had died of an infection within months of his birth. Saint Domingue was France’s most prosperous colony, accounting in sugar and indigo for two thirds of her foreign trade. Jean Audubon had worked his way up from cabin boy to captain in his many years at sea. His shipping profits had paid for his plantation and its several hundred African slaves, though some of the investment had probably come from his wife Anne Moynet, an older widow in France whom Jean Audubon had married.

In 1789, however, Jean Audubon had hastily sold the plantation when slave uprisings on the Caribbean islands of Guadeloupe and Martinique and the first stirrings of revolution in France and on Saint Domingue itself had alerted the shrewd négociant to potential disaster. He invested the proceeds of the sale in another handsome plantation in Pennsylvania just above Gettysburg, a substantial property called Mill Grove—115 hectares of lush farmland and woods with a two-story fieldstone mansion set high on a steep lawn, stone barns and outbuildings and a working water-powered flour mill down the lawn on broad Perkiomen Creek.

The vagaries of the French revolution

Two years later, in 1791, back in Nantes and an officer in the Republican Guard, Jean Audubon arranged to have his only son and the boy’s younger half-sister Rose, the daughter of a second, quadroon mistress, delivered to him from Saint Domingue. The two children departed their birthplace barely in time; the slave rebellion that eventually established the Republic of Haiti engulfed the island that August. Anne Moynet, who was childless, generously welcomed her husband’s two natural children to Nantes and would raise them as her own.

The guillotine was installed as the official method of execution in France just two months after six-year-old Jean Rabin and his four-year-old half-sister arrived at Nantes. Though Jean Audubon had been a colonist and a slave owner, he had taken the Revolution’s measure and wisely joined his lot with the Revolutionists. But the Revolution consumed its own. No one was safe after the King himself was guillotined late in January 1793. Tens of thousands of loyalist peasants rose up against the Revolutionists in the Vendée, the département that bordered Nantes below the Loire.

The Vendéan counterrevolution began in mid-March 1793 when the peasants advanced on Nantes armed with scythes and blunderbusses. The National Guard Blues engaged the ragged peasant army outside the city walls, but the Vendéens fought bravely enough that they were not defeated until June. On 7 March, a contemporary document records, only days before the storm broke, “Jean Audubon, commanding the war sloop Cerberus, vessel of the Republic, aged forty-nine years, native of Les Sables d’Olonne, department of La Vendée, and Anne Moynet his wife, aged fifty-eight years,” just
had time to arrange his two natural children’s adoption at the Nantes town hall, shielding them with the Audubon name and protecting their inheritance. Jean Rabin thus became Jean-Jacques Fougère Audubon, “Fougère”—“fern”—an offering to placate the Revolutionary authorities, who scorned the names of saints.

Counterrevolution was not the worst of it; the worst was the Terror that descended on Nantes in October in the person of a nightmarish Representative, Jean-Baptiste Carrier, sent out from Paris bent on reprisal. Carrier hardly distinguished between Revolutionaries and Loyalists; the Audubons were nearly destroyed. John James Audubon’s future father-in-law heard the story from the artist himself, in America in 1806. “Mr. Audubon,” William Bakewell wrote an English cousin, “gives us some horrid accounts of the cruelties practiced during the time of that monster Robespierre & his agents Carrier & others in Nantes where his father lives. His parents with himself & sister were imprisoned for a considerable time & made their escape in a very dangerous manner.”

The fledgling artist

Great talents have deep roots. Audubon traced his attachment to birds back to the time when he had just learned to walk and to speak. “They soon became my playmates; …I felt that an intimacy with them…bordering on frenzy must accompany my steps through life….None but aerial companions suited my fancy. No roof seemed so secure to me as that formed of the dense foliage under which the feathered tribes were seen to resort.” His father was his first guide and mentor, taking the boy for walks, picking flowers and catching birds for him, sharing his enthusiasm for them and his years of observation from the decks of ships and the shores and forests of France, North America and the Caribbean. It was his father who first encouraged young Audubon to observe them, who “would…speak of the departure and return of birds with the seasons, would describe their haunts, and, more wonderful than all, their change of livery; thus exciting me to study them.”

With a child’s natural avarice he came to wish to possess birds totally. That wish was inevitably frustrated, he wrote, because “the moment a bird was dead, however beautiful it had been when in life, the pleasure arising from the possession of it became blunted.” In Audubon’s era, without cameras or even binoculars, artists had no choice but to draw from dead specimens. One reason bird illustration was so stilted before Audubon and ornithology so limited was that ornithologists and artists worked with stuffed skins rather than complete birds. They hired market hunters to collect specimens for them and deliver only the arsenic-dusted skins, which they stuffed into lumpish form with frayed rope. Field observation had hardly begun; Audubon would be one of the first in North America to study birds in their natural habitat before collecting and drawing them.

In Couëron, however, at La Gerbetière, where the Audubons retreated after they escaped the Terror in Nantes, Jean Audubon found a way to help his cherished son deal with the frustration of death. “I wished to possess all the productions of nature,” the son recalled, “but I wished life with them. This was impossible.” What was to be done? “I turned to my father, and made known to him my disappointment and anxiety. He produced a book of illustrations. A new life ran in my veins. I turned over the leaves with avidity; and although what I saw was not what I longed for, it gave me a desire to copy nature. To Nature I went, and tried to imitate her.”

So a desire literally to revivify the dead lay at the heart of the boy’s struggles to learn to draw birds in lifelike attitudes. The metaphors Audubon used to characterize his early attempts at drawing clearly connect them to his experiences of trauma. “My pencil gave birth to a family of cripples,” he wrote. “So maimed were most of them that they resembled the mangled corpses on a field of battle compared with the integrity of living men.”

A French naturalist in the United States

Audubon’s father secured a false passport for his son in 1803 and sent him to America to escape the conscription of young men into Napoleon’s armies. Jean Audubon had no intention of allowing his progeny to become cannon fodder; as he wrote his business manager in Philadelphia, “This is my only son, my heir, and I am old.” Crossing to America, the eighteen-year-old once again changed his name, this time to John James, the name he would use for the rest of his life (although his English wife, the former Lucy Bakewell, would call him LaForest, perhaps a variation of Fougère).

Safe in the United States, financially comfortable, living like a young country squire at Mill Grove, John James Audubon finally had the leisure he needed to solve the problem of how to represent birds realistically.

He flourished there. Lucy Bakewell’s younger brother Will left us a vivid impression of his future brother-in-law’s naturalist pursuits:

Audubon took me to his house. … On entering his room, I was astonished and delighted to find that it was turned into a museum. The walls were festooned with all kinds of birds’ eggs, carefully blown out and strung on a thread. The chimney-piece was covered with stuffed squrels, raccoons, and opossums; and the shelves around were likewise crowded with specimens, among which were fishes, frogs, snakes, lizards, and other reptiles. Besides these stuffed varieties, many paintings were arrayed on the walls, chiefly of birds. He had great skill in stuffing and preserving animals of all sorts. He had also a trick in training dogs with great perfection, of which art his famous dog Zephyr was a wonderful example. He was an admirable marksman, an expert swimmer, a clever rider, possessed of great activity [and] prodigious strength, and was notable for the elegance of his figure and the beauty of his features, and
John James Audubon: finding life in birds – Rhodes

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Confinement to Couëron was confinement in a paradise of birds. Audubon soon befriended his family’s thirty-five-year-old physician, Charles-Marie d’Orbigny, a French Navy officer and a passionate naturalist who shared with his new protégé a Saint Domingue birth. He lived nearby with his young wife and infant son. “The doctor was a good fisherman, a good hunter, and fond of all objects in nature,” Audubon wrote. “Together we searched the woods, the fields, and the banks of the Loire, procuring every bird we could, and I made drawings of every one of them—very bad, to be sure, but still they were of assistance to me.”

Honing his skills

Bad or good, Audubon’s Couëron bird drawings, done in pastel and pencil, were the best he could do at the time, largely self-taught as he was; he meant to give the collection to Lucy when he returned to the United States and he worked hard on it. On 4 June he drew a greater redheaded linnet. On 6 June he diverted from birds to draw a fat, furry marmot complete with two pellets of scat dropped behind it like the eggs he sometimes included in his bird drawings; hunters find animals’ characteristic feces almost as useful as their prints in tracking them. He titled the drawing Marmotte de Savoye. He was always a quick study. In the first fourteen days of July he drew a grosbeak, a nightingale, a nut robber, a goelette, a sedge sparrow and a creeper, the last two on the same day.

By August 1804 Audubon could record the 209th addition to his burgeoning list of American birds, a wood thrush, that pot-bellied, black-speckled relative of the American robin. He was determined now to marry the young woman, Lucy Bakewell, who lived on the next plantation up the hill, whose family had emigrated from England in 1801. His father’s business manager in Philadelphia had taken a dislike to Audubon and had discouraged the marriage; the young lover decided to return to France to win his father’s permission even at the risk of being conscripted. He sailed in mid-March 1805; his ship, held up for a week for repairs, entered the Loire and anchored at Paimboeuf nineteen days later. Audubon soon persuaded his father to agree to his eventual marriage to Lucy, after the young man had found a means to support himself.

France, Audubon recalled, “was at that time in a great state of convulsion; the republic had, as it were, dwindled into a half-monarchical, half-democratic era. Bonaparte was at the height of success, overflowing the country as the mountain torrent overflows the plains in its course. Levies, or conscriptions, were the order of the day, and...my father felt uneasy lest I should be forced to take part in the political strife of those days.” Jean Audubon instructed his son to stay out of Nantes and close to home.
de Buffon’s best-selling forty-four volume *Natural History*, which significantly included field observations, something most contemporary ornithologies lacked.

In August Audubon and his sister Rose stood up beside Charles and Marie-Anne d’Orbigny as godparents to their newborn second son Gaston-Édouard. Their firstborn, Alcide-Charles, was then a lively toddler, not quite three. Testifying to their father’s gifts as a mentor, both sons were destined to become distinguished naturalists, Alcide famously so for his studies in South America.

Another mentor young Audubon learned from was François René André Dubuisson, an herbalist and mineralist who owned a shop on the Rue Saint Jean in Nantes and may have supplied medicinals to d’Orbigny and pastels to Audubon. Dubuisson would be appointed director of the first museum of natural history in Nantes in 1806 (the museum opened its doors in 1810). In a dispute with the town many years later he claimed to have taught Audubon ornithology.

**Audubon’s brainwave**

Thus instructed, the young would-be artist came to his great breakthrough after he returned to the United States in 1806. Living again at Mill Grove, increasingly frustrated by his inability to make the birds he drew look alive, he experimented both with sketching in the field and with arranging his freshly killed subjects unstuffed. “I betook myself to the drawing of specimens hung to a string by one foot,” he ridiculed one early attempt, “with the desire to shew their every portion as the wings lay loosely spread as well as the tail—in this manner I made some pretty fair signboards for poulterers!” When sketching from life refused to work for him, he tried suspending his freshly-killed bird specimens like puppets. “By means of threads I raised or lowered a head, wing, or a tail and by fastening the threads securely I had something like life before me, yet much was wanting—when I saw the living bird I felt the blood rise in my temples and almost in despair spent a month without drawing, but in deep thought.”

Puppetry led him next to the idea of constructing a manikin, a sort of Universal Bird. During his limited course of formal art training in France he had worked from manikins as well as from Classical sculpture. Thinking about manikins, he “cogitated how far a manikin of a bird would answer for all of them? I labored in wood, cork, and wires, and formed a grotesque figure which I cannot describe in any other terms than by telling you that when sat up it was a very tolerable looking ‘Dodo’! A friend present laughed heartily and raised my blood by assuring me that as far as I might wish to represent a tame gander or bird of that sort my model would do. I gave it a kick, demolished it to atoms, walked off and thought again.”
And then persistence paid its prize: Audubon dreamed the solution to his problem of making birds look alive. “Long before day, one morning, I leaped out of bed fully persuaded that I had obtained my object.” He ordered up a horse, refused to say where he was going and rode off at a hard gallop toward Norristown, eight kilometers away. Since it was still dark, the town was not yet awake, so Audubon rode on down to the Schuylkill River and took a morning bath. Back in Norristown a little later he entered the first shop he found open, bought lengths of wire of several different gauges and galloped back to Mill Grove. His housekeeper thought he was crazy when he rejected breakfast and called for his gun:

Off to the creek and down with the first kingfisher I met! I picked the bird up and carried it home by the bill, I sent for the miller and made him fetch me a piece of soft board—when he returned he found me filing into sharp points pieces of my wire, and proud to show him the substance of my discovery, for a discovery I had now in my brains, I pierced the body of the fishing bird and fixed it on the board—another wire passed above his upper mandible was made to hold the head in a pretty fair attitude, smaller skewers fixed the feet according to my notions, and even common pins came to my assistance in the placing [of] the legs and feet. The last wire proved a delightful elevator to the bird’s tail and at last there stood before me the real manikin of a kingfisher!

Too excited to be hungry, Audubon sat down then and there and drew the bird’s now vivid and three-dimensional outline, using a drawing compass to match the outline to the dimensions of the specimen. “My honest miller stood by me the while and was delighted to see me pleased. Reader, this was what I shall ever call my first attempt at drawing actually from nature, for then even the eye of the kingfisher was as if full of life before me whenever I pressed its lids aside with a finger.” Sharpened wire pins that allowed him to impale his fresh specimens on a board in lifelike attitudes set them up in a context his previous art training had made familiar. It was a simple system that he could rig from easily available materials wherever he might go in search of birds, and by scribing a grid into the board he could use its parallax to work out the foreshortening that transferring lifelike attitudes from three dimensions to two would require. This arrangement put the grid behind the specimen and made the bird seem to float in space in whatever position Audubon chose to impale it.

Now that he had a way to mount fresh specimens in lifelike attitudes, Audubon still had years of work ahead to master the art of drawing and painting them. As he married, moved west over the Appalachian Mountains into the American interior, set up in the general merchandise business first in Louisville, Kentucky, on the Ohio River, and then on the western Kentucky frontier, he worked tirelessly in his spare hours to study the birds of the American wilderness and to practice drawing them. One way he forced himself to improve was to burn or put out of sight each year’s collection of drawings and effectively start anew. That self-denial led to an event that became a world-wide legend when Audubon himself told the story in his Ornithological Biography: upon returning to Kentucky from a visit to Pennsylvania in 1812, the artist discovered that Norway rats had found their way into a trunk containing several hundred drawings and shredded them for nesting material. “Yet after all,” he wrote a friend, “who can say that it was not a material advantage, both to myself and to the world, that the Norway rats destroyed those drawings?” Elsewhere he added that, as a result of the rat damage, “I felt pleased that I might now make much better drawings than before, and, ere a period not exceeding three years had elapsed, I had my portfolio filled again.” A well-known Japanese woodcut dated 1850 or later commemorates the event, depicting an uncharacteristically mustached and sideburned Audubon surprised and triumphant rat frisking away.

**Birds of America**

Audubon considered his two general stores and steam-powered lumber mill in western Kentucky his real business and his bird studies merely a hobby until he went bankrupt along with most other businessmen on the American frontier during a financial panic in 1819. (Ironically, the panic was brought on by the need to finish paying France in gold for the vast Louisiana Purchase that had doubled the size of the United States.) He discovered then that he could earn his living as an artist, selling black chalk portrait sketches of the living and the recently dead, teaching drawing, and painting diorama backgrounds for a new museum. When he conceived of his great work The Birds of America, in 1820, he never looked back: leaving Lucy and their two sons all the money he could raise, he took passage as a pot hunter on a commercial flatboat and collected specimens all the way down the Ohio and Mississippi Rivers to New Orleans.

For the next five years Audubon labored to assemble a definitive collection of drawings of American birds while struggling to support himself and his family. The great work of art and ornithology he had decided to produce would comprise four hundred 60x92-centimeter engraved, hand-colored plates of American birds “at the size of life” to be sold in sets of five and collected into four huge leather-bound volumes of 100 plates each, with five accompanying volumes of pioneering “bird biographies” worked up from his field notes. He found a paradise of birds in the pine forests and cypress swamps of Louisiana, north of New Orleans along the Mississippi, where prosperous cotton planters hired him to teach their sons to fence and their daughters to draw and dance the cotillon. Elegant Lucy, when finally she was able to move south, opened a popular school of piano and deportment on a cotton plantation nearby.

Finally, in May 1826, he was ready. With the equivalent of about ten thousand dollars in gold in his purse as a stake, he sailed from New Orleans on a merchant ship bound for Liverpool with a load of cotton. James Fenimore Cooper’s novel The
Last of the Mohicans was a best-seller in England that year; Audubon, with his shoulder-length hair and rough frontier pantaloons, a real-life Natty Bumppo, was soon a sensation. To earn money for engraving he sold tickets to showings of his brilliantly colored, life-sized drawings of American birds, hundreds of them pinned up in public halls in that drab age before aniline dyes that must have flooded the senses of their viewers, for whom America was still a romantic mystery.

He found his first engraver in Edinburgh, a second and better in London. Across the next ten years he, Robert Havell Jr, and a large staff of young women “colorists” produced his five-plate “Numbers” of The Birds of America, 87 of them in all—435 engraved, hand-colored plates—pay as you go. Subscribers could keep their Numbers in open folios or, when each hundred had arrived, pay to have them bound.

Audubon paced the flow of funds to his engraver so that, as he said proudly, “the continuity of execution” was not “broken for a single day.” He paced the flow of drawings as well, and before that the flow of collections, returning to America regularly for collecting expeditions to the Carolinas and East Florida, the Republic of Texas, northeastern Pennsylvania, Labrador, and the Jersey Shore. He personally solicited most of his subscribers in England and France and personally serviced most of his accounts.

In the end, he estimated that producing his great book cost him $115,640—about $2 million today. Unsupported by gifts, grants or legacies, he raised almost every penny of that immense sum himself from painting, exhibiting and selling subscriptions and skins and supported himself and his family besides.

He returned to America in 1839 a famous man, one of only two Americans before 1860 to be elected members of the Royal Society of London, the preeminent scientific society of its day. The other was Benjamin Franklin.

John James Audubon lived through many lives, first as a French colonial, then as a young Frenchman enduring a time of great turmoil in his country’s history, then as an American frontiersman, finally as an artist of international reputation who fused the knowledge of a field naturalist with the skills of a great painter. He was not the first, nor would he be the last, to turn traumatic childhood experience into adult pre-occupation and profession, even into art.

Postscript: As this article was going to print, Audubon once again made history at an auction at Christie’s in New York, held on the 20th of January 2012, where a first edition of Birds of America was offered for sale by the heirs of the Fourth Duke of Portland and fetched $7.9 million, going to an American collector whose name was not disclosed. This confirmed Audubon’s monumental opus as the most expensive book in the world, even if it didn’t surpass the $11.5 million record set by an auction at Sotheby’s in London in December 2010. Out of the original 200 copies produced between 1827 and 1838, 120 remain accounted for today, with 107 belonging to institutions and 13 to private individuals.

Paint box of John James Audubon.
Private Collection/Photo. © Bollin Picture Library/ Bridgeman Giraudon.

All illustrations of birds: by John James Audubon, engraved by Robert Havell Jr, published in The Birds of America between 1827 and 1838. The fox squirrels comes from The Viviparous Quadrupeds of North America, by John James Audubon and John Bachman, originally published in three volumes between 1845 and 1848.


**AUDUBON : UNE VIE AVEC LES OISEAUX**

John James Audubon, enfant illégitime mais chéri par son père comme fils unique, naquit à Saint Domingue en 1785. Il grandit à Couëron, au sud de Nantes, loin des révoltes d’esclaves qui rendaient la situation délicate dans l’île, mais fut vite exposé aux tumultes de la Révolution française. Son père, Jean, aimait à lui apprendre les noms et les caractéristiques des oiseaux de cette région de Loire. Plus tard, un ami de la famille, médecin et père du naturaliste d’Orbigny, l’initia à l’observation sur le terrain et lui fit découvrir l’Histoire Naturelle de Buffon. Fils unique, son père l’envoya en Amérique en 1803 pour éviter la conscription militaire dans les armées Napoléoniennes. Dans son nouveau pays d’adoption, qui commençait juste à s’étendre au-delà des Appalaches, le jeune Audubon se mit à dessiner les oiseaux des étendues sauvages de l’ouest pour son propre plaisir, tout en prenant femme et en s’installant dans l’état du Kentucky récemment fondé pour débuter une prometteuse carrière d’homme d’affaires. Mais il fit banqueroute lors de la crise financière de 1819 et pour subvenir aux besoins de sa famille se lança dans l’art du portrait. Il se prit à rêver à la création d’une œuvre sans précédent de gravures en couleurs à taille réelle, avec des oiseaux montrés dans leur milieu naturel et dans des poses vivantes, à l’opposé de ce qui se faisait jusqu’alors. L’idée des Oiseaux d’Amérique était née, ouvrage monumental en quatre volumes avec des gravures de 60×92 cm. Après des années de travail assidu sur le terrain, tout en joignant les deux bouts avec des leçons d’escrime, de danse et dessin pour les enfants des riches planteurs de Louisiane, il traversa l’Atlantique pour gagner l’Angleterre avec ses premiers 250 dessins. Il en contrôla étroitement l’exécution sous forme de gravures à Londres et lança une souscription. Il refit plusieurs expéditions en Amérique afin d’ajouter à ses collections d’oiseaux, et en une dizaine d’années aboutit à une œuvre de 435 gravures qu’il fit reproduire en 200 exemplaires pour un coût qui de nos jours s’élèverait à près de 2 millions d’euros. En 1839, devenu célèbre, il retourna pour de bon en Amérique.
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 photograph of main author.
- On the title page, provide: a title (concise and informative); full names of authors (first name, middle name initial, and last name); highest academic degrees (in country-of-origin language); affiliations (names of department[s] and institution[s] at the time the work was done); a short running title (no more than 50 letters and spaces); keywords (5-10); corresponding author’s complete mailing address and telephone No., fax No., and e-mail address; acknowledgments (on title page, or at end of main text).
- Include an Abstract of 200-230 words for all texts except Editorials and replies to the Controversial Question.
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