“Chance favors only the prepared mind”

Pasteur

New-generation treatments for hypertension: targeting the artery
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Early antihypertensive combination therapy and cardiovascular protection: evolving expectations

by N. R. Poulter, United Kingdom

Given that raised blood pressure (BP) is the biggest single risk factor currently contributing to global death and to the global burden of disease,1 it is clearly critical that we learn to improve our current management of "hypertension". For much of the world—since most people known to have hypertension are treated2—the biggest impact on improving the control of hypertension would be achieved by detecting the problem more effectively. Given the pivotal impact of costs, enhanced detection would be most cost-effectively realized via opportunistic screening in the workplace and/or whatever medical facilities are currently available.

However, for the minority (≈40% globally)2 of those with hypertension who are being treated, great strides in improving BP control can still be made, as only about one third of the 40% of patients have their BPs controlled to what is largely accepted as the current targets of <140 mm Hg systolic and <90 mm Hg diastolic.2

The debate as to which agents should be used as first-line therapy continues, as reflected by a lack of consensus across recent hypertension guidelines.3-5 It is therefore unsurprising that the two-drug combination treatments recommended by these guidelines are also different. This is particularly important because the majority of patients with treated hypertension require two or more agents to achieve BP control.6 Nevertheless, most contemporary hypertension guidelines recommend combining any two of the following three drug classes: calcium channel blockers ("C" drugs), diuretics ("D" drugs), and renin-angiotensin system (RAS) blockers (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers ["A" drugs]).3 In practice, the combinations of A + C and A + D are the most commonly used combinations in the developed world.6

Whichever drug combination is favored, some recent guidelines have recommended that for a significant proportion of patients with hypertension (albeit identifying different subgroups of patients as being eligible), BP-lowering therapy should be initiated with the use of two agents.4,7

Although this recommendation was made several years ago in an earlier iteration of European hypertension guidelines,8 there are essentially no definitive randomized trial data as yet to support the use of this approach compared with the more traditional stepped-care approach. Indeed, whilst the ACCELERATE (Aliskiren and the Calcium ChanneL blocker amlodipine combination as an initial treatment strATEgy for hypertension control) trial9 did show some significant short-term, BP-lowering...
advantages associated with initiating therapy with two drugs versus up titrating monotherapy and later adding a second drug, these benefits (observed at 16 weeks) were largely attenuated after 24 weeks’ follow-up when both groups were taking the same combination therapy.

Nevertheless, there are several lines of argument that do support the preferential use of two antihypertensive agents as initial therapy. First, there is the logical, if perhaps simplistic, argument that if most patients (particularly those with very high pretreatment BP levels, eg, a systolic BP >160 mm Hg) require two or more agents to achieve BP control, why not start treatment with two agents? Subjective support for this approach arises from the idea that there may well be psychological benefits for patients whose BP is rapidly controlled with initial antihypertensive therapy through the generation of confidence in the management process.

Second, evidence from large randomized trials, such as VALUE (Valsartan Antihypertensive Long-term Use Evaluation) and ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial), showed that more rapid BP lowering was associated with greater reduction in major cardiovascular events.12,13 Critically, when these trial findings are linked with those of an extensive review of data from 42 trials including almost 11 000 patients that showed that adding a second agent had about five times the BP-lowering effect of doubling the dose of any single agent,12 it reinforces the potential advantage of initiating therapy with two drugs.

Third, observational data of various types also provide support for this therapeutic approach. Such data include a retrospective review of over 100 000 patients, from 180 clinical sites in the USA, who had antihypertensive medication initiated between 2004 and 2009.14 The BP control rates after 1 year, adjusted for potential confounders, were significantly greater among those whose therapy was initiated with two drugs compared with those started on monotherapy. Incidentally, these results applied whether the two drugs were supplied as a single-pill combination (hitherto frequently and inaccurately described as “fixed-dose combinations”) or as two separate pills (“free combinations”), although the BP-control benefits were greater among those who received single-pill combinations rather than free combinations.

Other supportive findings have been reported in other observational studies in which initial therapy with two antihypertensive agents was associated with significantly increased cardiovascular protection compared with initial antihypertensive monotherapy.14,15

The superiority in terms of BP lowering of two agents compared with one is not surprising, but the large differential and beneficial effect observed by Wald15 associated with adding a second agent compared with doubling the dose of the first agent is less obvious. This result may arise from the fact that two suitably matched agents will act on two or more adverse mechanisms thought to raise BP. Excellent clinical data from a trial by Mahmoud and colleagues support the idea that there are benefits associated with addressing more than one potentially adverse mechanism when treating hypertension.16

This trial compared four drugs from different antihypertensive classes, each at full dose, with a single-pill combination that contained a quarter dose of each of the same four drugs in terms of their effect on BP lowering. In short, the single-pill combination produced significantly greater BP lowering than any of the individual drugs at full dose. These enhanced BP-lowering benefits may also be attributed, in part at least, to the possible overriding by additional components in a single-pill combination of the compensatory physiological mechanisms induced to protect BP levels when an antihypertensive drug is administered.

Similarly, two drugs given together in a single-pill combination may—particularly at lower doses, and if selected appropriately—generate fewer side effects than either of the individual components given at full dose, since with the exception of RAS blockers side effects appear to be dose-responsive. Furthermore, synergistic benefits related to side effect reduction may occur when two antihypertensive drug classes are combined, the obvious example being the combination of RAS blockers and dihydropyridine calcium channel blockers. The combination of drugs from these classes leads to reduced peripheral edema compared with calcium channel blockers alone.17,18 One direct effect of reducing side effects of antihypertensive medication is improved adherence to therapy, which in turn results in improved BP control and enhanced cardiovascular protection.

In summary—on the basis of several types of data, but admittedly in the absence of compelling randomized trial data—recent recommendations to initiate antihypertensive medication with two rather than the traditional one agent seem logical, appropriate, and more likely to be effective in preventing cardiovascular events by virtue of achieving lower BP and more rapid BP control. An important qualification to this generalization must be that the two drugs used in combination should be correctly selected, with a combination of a RAS inhibitor and a calcium channel blocker or diuretic being currently and
appropriately favored in clinical practice. Cost implications notwithstanding, best evidence suggests that the delivery of two antihypertensive drugs is better in terms of BP lowering, adherence, and cost-effectiveness as a single-pill combination of two drugs rather than as two separate pills. Finally, whenever considering antihypertensive combination therapy, the additional concomitant use of statins should always be considered in light of compelling trial evidence of cardiovascular benefits. This merits emphasis because the incremental benefits of adding a statin in terms of preventing adverse cardiovascular events are likely to far outweigh the benefits of adding a third or fourth antihypertensive agent.

References


Keywords: hypertension; combination therapy; blood pressure lowering; adherence; cost-effectiveness; single-pill combination
Les associations antihypertensives précoces et la protection cardio-vasculaire : nouvelles attentes

par N. R. Poulter, Grande-Bretagne

L'élévation de la pression artérielle (PA) est actuellement le principal facteur de risque contribuant à la mortalité et au fardeau de la maladie dans le monde entier. Il devient donc manifestement impératif d'apprendre à améliorer notre prise en charge actuelle de « l'hypertension ». Puisque la plupart des hypertendus connus sont traités, détecter le problème plus efficacement permettrait d'améliorer nettement le contrôle de l'hypertension dans une grande partie du monde. Compte tenu de l'impact majeur des coûts, une détection renforcée serait d'un meilleur rapport coût-efficacité si elle était réalisée par un dépistage opportuniste sur le lieu de travail et/ou dans n'importe quelle structure de santé actuellement disponible.

Cependant, pour la minorité (environ 40 %) des hypertendus traités, de grandes avancées sont encore possibles pour améliorer le contrôle de la PA : en effet, seulement environ un tiers des 40 % de patients sont contrôlés selon les normes actuelles largement acceptées de PA systolique < 140 mmHg et PA diastolique < 90 mmHg.

Comme l’indique le manque de consensus des récentes recommandations sur l’hypertension, la classe du produit à utiliser en traitement de première intention est toujours débattue. Il n’est donc pas surprenant que les associations doubles recommandées dans ces directives soient aussi différentes, ce qui est particulièrement important car la majorité des hypertendus traités ont besoin de deux médicaments ou plus pour contrôler leur PA. Cependant, les recommandations les plus récentes sur l’hypertension préconisent d’associer deux des trois classes suivantes de médicaments : antagonistes calciques (médicaments « C »), diurétiques (médicaments « D ») et inhibiteurs du système rénine angiotensine (SRA) (inhibiteurs de l’enzyme de conversion de l’angiotensine ou antagonistes des récepteurs de l’angiotensine [médicaments « A »]). En pratique, les associations A + C et A + D sont les associations les plus courantes dans les pays développés.

Quelle que soit l’association privilégiée, d’après des recommandations récentes et pour une proportion significative de patients hypertendus (même si différents sous-groupes de patients peuvent en faire partie), le traitement de la PA doit être débuté avec deux médicaments.

Bien que cette directive ait été faite il y a plusieurs années dans une précédente version des recommandations européennes sur l’hypertension, aucune donnée définitive d’études randomisées n’est encore fondamentalement en faveur de cette
approche comparée à celle plus traditionnelle par étapes. En effet, si l’étude ACCELERATE (Ailskiren and the Calcium Channel blocker ER amlopidine combination as an initial treatment strATEgy for hypertension control)2 a montré un effet significatif à court terme, les bénéfices associés de l’abaissement de la PA observés à 16 semaines au début d’une thérapie versus l’augmentation des doses d’une monothérapie et l’addition plus tardive d’un second médicament ont été grandement atténués après 24 semaines de suivi, quand les deux groupes prenaient la même association.

Néanmoins, plusieurs arguments sont en faveur de deux antihypertenseurs comme traitement initial. Premièrement, il existe l’argument logique, peut-être simpliste, consistant à dire que si la plupart des patients (en particulier ceux dont la PA avant le traitement est très élevée, soit PA systolique > 160 mmHg) ont besoin de deux molécules ou plus pour contrôler leur PA, pourquoi ne pas commencer le traitement avec deux produits ? Cette démarche qui peut sembler subjective se fonde sur l’idée qu’il peut exister un bénéfice psychologique pour les patients dont la PA est rapidement contrôlée par le traitement initial grâce à l’installation d’un climat de confiance dans le processus de prise en charge.

Deuxièmement, des données issues de grandes études randomisées, comme les études VALUE (Valsartan Antihypertensive Long-term Use Evaluation) et ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial), ont montré qu’un abaissement plus rapide de la PA était associé à une diminution plus importante des événements cardiovasculaires majeurs

Cette étude a comparé, en termes d’effet sur l’abaissement de la PA, quatre molécules issues de différentes classes d’antihypertenseurs, chacune à dose maximale, à une association en un seul comprimé qui contenait un quart de la dose de chacune des quatre mêmes molécules. Pour résumer, l’association en un seul comprimé a diminué la PA de façon significativement plus importante que chaque des molécules prise individuellement à la dose maximale. Ces effets bénéfiques renforcés sur l’abaissement de la PA peuvent aussi être attribués, au moins en partie, à la neutralisation possible, par les composés supplémentaires de l’association à un comprimé unique, des mécanismes physiologiques compensatoires induits pour protéger les niveaux de PA lors de l’administration de l’antihypertenseur.

Troisièmement, des données observationnelles de différents types soutiennent aussi cette approche thérapeutique. Ces données analyseront rétrospectivement plus de 100 000 patients, issus de 180 sites cliniques aux USA, qui ont débuté un traitement antihypertenseur entre 2004 et 2009. Les taux de contrôle de PA après 1 an, ajustés sur les facteurs potentiels de confusion, étaient significativement plus importants parmi ceux qui avaient commencé le traitement avec deux médicaments qu’avec ceux qui avaient commencé avec une monothérapie.

Soit dit en passant, ces résultats étaient les mêmes que les deux médicaments soient administrés en un seul comprimé (fréquemment et inexactement appelés « associations à dose fixe ») ou en deux comprimés séparés (« associations libres »), bien que les effets bénéfiques du contrôle de la PA aient été plus importants parmi ceux qui avaient reçu l’association en un comprimé unique plutôt que l’association libre.

D’autres résultats favorables ont été rapportés dans des études observationnelles, dans lesquelles un traitement initial avec deux antihypertenseurs était associé à une protection cardiovasculaire significativement plus importante que celle due à une monothérapie antihypertensive initiale.

La supériorité de deux produits en termes d’abaissement de la PA par rapport à un seul n’est pas surprenante, mais l’important effet différentiel bénéfique observé par Wald et dû à l’association d’un deuxième médicament comparé au doublément de la dose du premier médicament est moins évident.

Ce résultat peut provenir du fait que deux produits convergentement associés agiront sur deux mécanismes délétères ou plus, susceptibles d’élèver la PA. D’excellentes données cliniques d’une étude de Mahmoud et al. confirment l’idée qu’il est bénéfique de traiter plus d’un mécanisme potentiellement défavorable pour traiter l’hypertension.

Cette étude a comparé, en termes d’effet sur l’abaissement de la PA, quatre molécules issues de différentes classes d’antihypertenseurs, chacune à dose maximale, à une association en un seul comprimé qui contenait un quart de la dose de chacune des quatre mêmes molécules. Pour résumer, l’association en un seul comprimé a diminué la PA de façon significativement plus importante que chaque des molécules prise individuellement à la dose maximale. Ces effets bénéfiques renforcés sur l’abaissement de la PA peuvent aussi être attribués, au moins en partie, à la neutralisation possible, par les composés supplémentaires de l’association à un comprimé unique, des mécanismes physiologiques compensatoires induits pour protéger les niveaux de PA lors de l’administration de l’antihypertenseur.

De même, deux médicaments administrés en même temps dans une association d’un comprimé unique peuvent, en particulier aux doses faibles et si elles sont choisies convenablement, provoquer moins d’effets indésirables que l’un ou l’autre des composés individuels donné à dose maximale, puisque, à l’exception des inhibiteurs du SRA, les effets indésirables semblent être fonction de la dose. De plus, il existe des bénéfices synergiques liés à la diminution des effets indésirables lorsque deux classes d’antihypertenseurs sont associées, l’exemple évident étant l’association des inhibiteurs du SRA et des antagonistes calciques dihydropyridiniques. L’association des molécules de ces classes diminue l’œdème périphérique par rapport aux antagonistes calciques seuls. L’effet direct de la diminution des effets indésirables est une meilleure observance du traitement antihypertenseur, qui à son tour conduit à une amélioration du contrôle de la PA et à une protection cardio-vasculaire renforcée.

En somme, selon différentes sources, mais certes encore en l’absence de données d’études randomisées irréfutables, les recommandations récentes pour débuter un traitement antihy-
pertenseur avec deux produits plutôt qu’un seul produit standard semblent logiques, pertinentes et probablement plus efficaces en prévention des événements cardio-vasculaires grâce à l’abaissement de la pression artérielle et à son contrôle plus rapide. Il faut cependant préciser que les deux produits utilisés en association doivent être correctement sélectionnés, avec un inhibiteur du SRA et un antagoniste calcique ou un diurétique, actuellement privilégiés de façon pertinente en pratique clinique. Considération financière mise à part et selon les meilleures données, l’administration de deux antihypertenseurs en 1 seul comprimé est plus efficace en termes d’abaissement de la PA, d’observance et de rapport coût-efficacité, qu’avec ces deux médicaments pris en deux comprimés séparés. Enfin, lorsqu’on examine les associations antihypertensives, il faudrait toujours prendre en compte l’utilisation concomitante des statines, compte tenu des données convaincantes des études sur les bénéfices cardio-vasculaires. Ceci mérite d’être souligné, car les bénéfices supplémentaires de l’addition d’une statine en termes de prévention des événements cardio-vasculaires indésirables vont vraisemblablement surpasser largement le bénéfice procuré par l’ajout d’une troisième ou d’une quatrième molécule antihypertensive.
Early vascular modifications in hypertension: pathophysiological considerations

by G. F. Mitchell, USA

Over the past half century, hypertension research has been dominated by a steady-flow hemodynamic model that posited a primary abnormality in resistance vessel structure and function as the key element in the pathogenesis of hypertension. Accordingly, drugs used to treat hypertension were designed and approved based on their ability to reduce peripheral vascular resistance or cardiac output, resulting in a reduction in mean arterial pressure. Large artery stiffness was found to be abnormal in hypertension, but the abnormalities were thought to be secondary to elevation of mean arterial pressure, resulting in excessive wear and tear and accelerated aging. Recent studies have demonstrated that abnormalities in aortic stiffness precede and contribute to the pathogenesis of hypertension, particularly wide pulse pressure hypertension, which is highly prevalent and difficult to control. Increased aortic stiffness and excessive pressure and flow pulsatility also play a major role in target organ damage. A greater awareness of the contribution of aortic stiffness to the pathogenesis of hypertension will facilitate efficient use of existing drugs and rational design of new agents that target primary abnormalities in aortic structure and function.

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Although hypertension is a prototypical complex disease with multiple potential contributors to pathogenesis, vascular structure and function obviously play a major role. Hemodynamic research and drug discovery in hypertension has traditionally focused on microvascular structure and function and on the contributions of peripheral vascular resistance and cardiac output to development of hypertension through elevation of mean arterial pressure. Accordingly, all drugs currently used to treat hypertension were developed and approved based on their ability to reduce mean arterial pressure.

Despite the traditional focus on small vessels as a primary driver of pathogenesis of hypertension, pioneering work some four decades ago by Safar and colleagues in France demonstrated that large artery stiffness is abnormal in patients with hypertension.1 However, at that time, aortic stiffness was largely considered a consequence rather than a cause of hypertension, and was thought to represent “accelerated aging” of the aorta because of exaggerated hemodynamic stress in the presence of increased mean arterial pressure. Recent evidence suggests that aortic stiffness may precede and actively contribute to the pathogenesis of hypertension and may contribute substantially to our inability to control systolic blood pressure,
particularly after midlife, when wide pulse pressure hyperten-
sion is overwhelmingly predominant. Additionally, target or-
gan damage and risk for adverse outcomes may be related
more strongly to pressure pulsatility than to mean arterial pres-
sure. The dissociation between available drugs that target
mean arterial pressure and pathophysiology that includes a
substantial contribution from pulse pressure contributes to
treatment failures and adverse events and suggests that a new
approach to drug design and treatment algorithms is needed.

Epidemiology of hypertension in the modern era
The distribution of hypertension subtypes has undergone com-
plex shifts over the past several decades. For example, in the
Multiple Risk Factor Intervention Trial (MRFIT) screening co-
hort recruited from 1973 through to 1975, the overall preva-
lence of hypertension was 35% and comprised 11% isolated
diastolic, 16% mixed systolic and diastolic, and only 8% iso-
lated systolic hypertension (ISH). In contrast, recent surveys
have demonstrated a predominance of wide pulse pressure
hypertension. ISH is by far the predominant subtype of hy-
pertension among individuals on treatment with uncontrolled
blood pressure. As age increases, hypertension becomes
markedly more prevalent, the proportion of cases with ISH in-
creases, and, unfortunately, the proportion of treated patients
whose blood pressure is controlled to target falls. Failure to
control blood pressure largely represents failure to control
pulse pressure.

At the opposite end of the age spectrum, Zachariah et al found
that development of obesity was associated with a marked
increase in pulse pressure in children. McEniery et al found
that ISH (8%) was twice as prevalent as diastolic hyperten-
sion (4%) in young adults (17 to 27 years of age). Grebla et al
found that the prevalence of ISH in young adults has increased
and that obesity was associated with higher odds of ISH in
young adults. Wide pulse pressure in children may reflect
a limited ability of the aorta to remodel in response to the
increase in hemodynamic demand associated with obesity.
The combination of aortic remodeling—in response to a substan-
tial increase in cardiac output that accompanies obesity—and
ongoing remodeling stress—associated with somatic growth—
may transiently overwhelm the ability of the aorta to remod-
el, resulting in a mismatch between aortic diameter and flow
and wide pulse pressure. Alternatively, obesity may have di-
rect adverse effects on properties of the aortic wall.

Elastic lamellae in the aorta develop at an early age and must
then remodel throughout the remainder of life. Remodeling
of this fixed pool of elastin to a larger diameter necessarily in-
creases stress on the elastic fibers, resulting in increased strain.
Higher strain leads to engagement of additional collagen fibers
that are normally loosely woven into the structure of the aor-
tic wall. Since collagen is several orders of magnitude stiffer
than elastin, aortic wall stiffness necessarily increases as col-
lagen is engaged. The long-term consequences of a popu-
lation wide increase in pulse pressure in children and young
adults is unknown and gives cause for concern, particularly
in light of our limited ability to control systolic blood pressure
in older adults.

A brief overview of arterial stiffness measures
The term “arterial stiffness” is imprecise, and putative meas-
ures of “stiffness” are often misinterpreted. The present gold
standard measure of aortic wall stiffness is carotid-femoral
pulse wave velocity (CFPWV), which is assessed by perform-
ing tonometry of the carotid and femoral arteries in order to
measure the transit time between the two sites. CFPWV is
then simply transit distance divided by transit time. CFPWV is
readily measured in a clinical setting with modest equipment
and expertise and is easily interpreted: higher CFPWV is as-
associated with higher risk for target organ damage and ad-
verse clinical events, including incident hypertension. An ex-
tensive body of evidence and two recent meta-analyses have
demonstrated strong, consistent, graded relations between
CFPWV and risk for adverse outcomes, particularly in younger
adults. Importantly, several studies have provided evidence
that CFPWV may be amenable to treatment.

An alternative measure of aortic “stiffness” is achieved by
examining relations between pulsatile pressure and flow in
the proximal aorta. Analysis of pressure and flow allows for
calculation of aortic characteristic impedance (Zc), which is a
measure of the pulsatile pressure produced by a given pul-
satile flow in the proximal aorta in early systole, prior to ar-
ival of reflected waves from the periphery. Aortic inflow dur-
ing systole interacts with Zc to produce a forward traveling
pressure wave (Pf) that accounts for most of the variance in
pulse pressure across the full adult lifespan. Measurement
central aortic pressure and flow provides a comprehensive
assessment of vascular load. However, the test is more diffi-
cult than measuring CFPWV alone and requires limited echo-
cardiography and hence a specialized setting and equipment.
Zc and Pf were recently shown to predict events in models
that consider standard risk factors, including CFPWV, in the
Framingham Offspring cohort. There is evidence that Zc and
Pf are amenable to treatment.

Various measures of wave reflection have been proposed. Aug-
mentation index (AI) is a widely cited, pressure-only measure
of relative wave reflection that is often presented as a meas-
ure of aortic stiffness.

### Selected Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AI</td>
<td>augmentation index</td>
</tr>
<tr>
<td>CFPWV</td>
<td>carotid-femoral pulse wave velocity</td>
</tr>
<tr>
<td>ISH</td>
<td>isolated systolic hypertension</td>
</tr>
<tr>
<td>MRFIT</td>
<td>Multiple Risk Factor Intervention Trial</td>
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<tr>
<td>RC</td>
<td>reflection coefficient</td>
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However, relations between AI and aortic stiffness are complex and, as a result, AI should not be considered a measure of aortic stiffness.23-25 Because wave reflection can either augment pressure or decelerate flow, one must measure pressure and flow in order to assess wave reflection accurately (Figure 1). For example, a failing heart will produce minimal pressure augmentation, whereas a concentrically hypertrophied heart will produce marked pressure augmentation for the same reflected wave. When pressure and flow are both known, it is possible to use wave separation analysis to assess the amplitudes of Pf and the reflected or backward wave (Pb).26 However, when interpreting Pb, it is important to acknowledge that the strongest determinant of Pb is Pf. Therefore, changes in Pf must be interpreted in the context of the associated Pb that gave rise to the reflected component. This is readily achieved by computing the reflection coefficient (RC = Pb/Pf). RC and Pf are reduced markedly by vasodilator drugs or nitrates.27 However, as noted below, the clinical implications of a pharmacologic reduction in wave reflection remain to be determined.

Much has been written regarding the relative merits of central as compared to peripheral systolic and pulse pressure as the best measure to predict risk and monitor therapy. While some studies have shown a slightly stronger relation between central pressures and measures of target organ damage, the incremental value of central pressure remains unclear.38 However, conventionally assessed brachial pulse pressure together with CFPWV provides a complementary and powerful combination for assessing abnormalities in aortic structure and function.

Hemodynamic correlates of rising pulse pressure with advancing age

The substantial burden of disease associated with ISH provides an imperative to better understand factors that are associated with wide pulse pressure hypertension. A number of investigators have insisted that higher pulse pressure is predominantly attributable to premature return of Pb and higher AI.29 In the Framingham Heart Study cohort, AI increased markedly between 20 and 50 years of age.18 However, pulse pressure actually fell during this interval (Figure 2, page 376), as has been shown in other cohorts.30 After midlife, a marked increase in pulse pressure was paralleled by a similar increase in Pb, whereas AI fell. In the Framingham study, approximately 90% of the variance in central and peripheral pulse pressure was attributable to variability in Pf, with most of the remaining 10% of variance associated with the RC. Timing of wave reflection played a minor role. These basic observations suggest that premature wave reflection plays a minor role in age-related widening of pulse pressure.

The falls in pulse pressure, Pb, and Zc between 20 and 50 years of age contrasts with an accompanying increase in CFPWV during the same period (Figure 2).18,30 Dissociation between CFPWV and Zc has been attributed to alterations in aortic diameter.31 CFPWV and Zc are both directly related to wall stiffness and inversely related to diameter. However, Zc is much (5x) more sensitive to diameter. If stiffening of the aorta is associated with an increase in lumen diameter, Zc can fall even as CFPWV increases. In contrast, a combination of stiffening and a reduction in diameter will result in a disproportionate increase in Zc. A resulting mismatch between aortic diameter

Figure 1. Wave separation analysis.
When pressure and flow are both measured, forward (Pf) and reflected or backward (Pb) waves can be separated and assessed. The two cases shown in this figure have similar Pf and Pb amplitude and similar arrival time of the reflected wave. Yet the case on the left has no augmentation, whereas the case on the right has a substantial late systolic augmented pressure (AP), resulting in high augmentation index (AI = AP/PP [pulse pressure] = 22%). Markedly greater augmentation on the right is attributable to differences in the shape of Pf and Pb, rather than timing and amplitude of Pb. The case on the right has prolonged ejection, with a Pb peak in late systole (straight arrow) as well as a steeper Pb upstroke (curved arrow). Overlap of the prolonged Pf with the steeper upstroke of Pb produces marked pressure augmentation. A pressure-only analysis would predict markedly greater wave reflection in the case on the right, which is incorrect.
Early vascular modifications in hypertension: pathophysiological considerations – Mitchell

Wave reflection in the arterial system is often portrayed as harmful. Indeed, excessive wave reflection may augment systolic pressure and increase load on the left ventricle during late systole. However, wave reflection at the interface between aorta and muscular arteries limits penetration of pulsatility into the downstream microcirculation of various vascular beds. High local resistance in precapillary arterioles of some vascular beds produces additional wave reflection that further limits the penetration of potentially harmful pulsatile energy into the microcirculation. The brain and kidneys, however, have limited distal protection from excessive pulsatility because they are obligate high-flow, low-impedance organs. A greater proportion of pulsatile power penetrates into the microcirculation in low-impedance vascular beds. When the aorta stiffens, impedance mismatch at the interface with stiff muscular arteries is diminished and proximal wave reflection at this interface is diminished. As a result of increased transmission of pulsatile power into the periphery, the microcirculation may be dam-

**Figure 2. Pulsatile hemodynamics across the human lifespan in Framingham Heart Study participants.**

In these cross-sectional observations, pulse pressure (PP) falls modestly between young adulthood and midlife and rises rapidly thereafter (panel A). In contrast, augmentation index (AI) increases rapidly prior to middle age but levels off thereafter, suggesting that pressure augmentation is not the main explanation for rising pulse pressure with advancing age after midlife (panel B). The age relations of pulse pressure are closely paralleled by characteristic impedance computed in the time domain (ZcTD) (panel C) and forward wave amplitude (Pf). In contrast to PP, Pf, and ZcTD, carotid-femoral pulse wave velocity (CFPWV) increases monotonically with age; thus, the age-related increase in CFPWV appears to precede the increase in PP in cross-sectional analyses. Data are from reference 18.
Early vascular remodeling in hypertension

Recent evidence has refocused the debate regarding the role of the aorta as passive victim or active contributor in the pathogenesis of hypertension. Prospective findings in the middle-aged and older Framingham Offspring cohort demonstrated that higher CFPWV at baseline was associated with increased risk for blood pressure progression and incident hypertension during 7 years of follow-up. In contrast, once baseline CFPWV was considered in a multivariable model, no blood pressure measure was associated with progression of aortic stiffness. These analyses indicate that in the age range studied, aortic stiffness antedates and contributes to the pathogenesis of hypertension. Importantly, various other measures of vascular structure and function, including forward wave amplitude, augmentation index, brachial artery flow mediated dilation, and resting forearm blood flow, were also associated with increased risk for hypertension when considered together in a single multivariable model, confirming that even among vascular traits, hypertension is a multifactorial disease, with contributions from large and small arteries and endothelial function.

Observations in an obesity model of hypertension in the mouse recapitulate many of the findings of the foregoing Framingham analysis and strengthen the concept that aortic stiffness actively contributes to the development of hypertension. When normal mice were fed a diet high in sucrose and fat, they developed obesity, insulin resistance, and increased aortic pulse wave velocity within 1 month of initiation of the diet, culminating in clinically evident hypertension and farction. Pharmacologic manipulation of peripheral resistance by vasodilator drugs, particularly in patients with ISH who may have little or no abnormality in mean arterial pressure, may unnecessarily expose the microcirculation to additional pulsatile stress and damage. Vasodilator therapy should be avoided in such patients, particularly if mean arterial pressure and diastolic pressure are already normal or low.

![Figure 3. The vicious cycle of aortic stiffening, microvascular dysfunction, and target organ damage.](image)

Various vascular risk factors have been identified that may stiffen the aorta. Increased aortic stiffness imposes pulsatile stress on the microcirculation. The microcirculation remodels, ostensibly to protect the capillaries from pulsatile damage. However, microvascular remodeling and rarefaction impairs reactivity and increases peripheral resistance. Impaired reactivity increases susceptibility to microvascular ischemia in target organs. Increased peripheral resistance drives up mean arterial pressure, resulting in additional stiffening of the aorta. If left unopposed, the vicious cycle culminates in clinically evident hypertension and major clinical events.

**Abbreviations:** CHF, chronic heart failure; LVH, left ventricular hypertrophy; MI, myocardial infarction.

Additional work in animal models and humans has underscored the potential contribution of inflammation to aortic stiffening and development of hypertension. CFPWV is associated with levels of various proinflammatory markers, including C-reactive protein and interleukin 6.

In a mouse model of vascular inflammation and hypertension induced by chronic infusion of low doses of angiotensin II, development of aortic stiffening and hypertension can be prevented by knocking out the adaptive immune system. Adoptive transfer of T cells restores sensitivity to angiotensin II–induced vascular inflammation, aortic stiffening, and hypertension, suggesting that T cell–mediated damage plays a critical role in the pathogenesis of aortic stiffening and hypertension in this model. Importantly, in the largest genome-wide association study of CFPWW, the region of strongest association was in a gene desert on chromosome 14.
volved in selection and maintenance of T-cell identity. However, the BCL11B gene product, COUP-TF (chicken ovalbumin upstream promoter transcription factor) interacting protein 2, is a transcription factor with many functions that might impact aortic structure and function.

Summary

In light of the foregoing, one can hypothesize the potential for a vicious cycle involving aortic stiffness, microvascular dysfunction, hypertension, and target organ damage (Figure 3, page 377). In the early stages of disease, risk factors may increase aortic stiffness directly by various mechanisms. Aortic stiffening increases pressure pulsatility and reduces protective wave reflection at the interface between the normally compliant aorta and stiff muscular arteries, resulting in greater transmission of potentially harmful pulsatility into the microcirculation, particularly in high-flow organs like the brain and kidneys. Microvascular remodeling in response to pulsatile stress impairs reactivity and increases susceptibility to microvascular ischemic damage.

Remodeling and loss of microvessels also increases peripheral vascular resistance, which will increase mean arterial pressure if cardiac output is maintained. The resulting increase in mean arterial pressure further stiffens the aorta and accelerates the vicious cycle. If the cycle is allowed to progress, patients will ultimately develop hypertension and various other forms of target organ damage mediated directly by aortic stiffness or indirectly through the effects of pulsatile stress on microvascular structure and function. Alternatively, if we identify aortic stiffening at an early stage and target existing or novel treatments at the root cause of the pathophysiological cycle portrayed in Figure 3, we can potentially arrest the cycle at an early stage and prevent development of hypertension and target organ damage.

Disclosures: Dr. Mitchell is the owner of Cardiovascular Engineering, Inc., a company that develops and manufactures devices to measure vascular stiffness, and serves as a consultant to and receives honoraria from Novartis, Merck, and Servier and is funded by research grants HL094898, DK082447, HL107385, and HL104184 from the National Institutes of Health.
Keywords: aortic stiffness; carotid-femoral pulse wave velocity; pulse pressure; characteristic impedance; microvascular target organ damage

MODIFICATIONS VASCULAIRES PRIMAIRES DANS L'HYPERTENSION : CONSIDÉRATIONS PATHOPHYSIOLGIQUES

Ces 50 dernières années, la recherche sur l'hypertension a été dominée par un modèle hémodynamique à flux constant, postulant qu'une anomalie primaire de la structure et de la fonction d'un vaisseau résistant est l'élément clé de la pathogénèse de l'hypertension. Les médicaments utilisés pour traiter l'hypertension ont donc été conçus et autorisés sur leur capacité à diminuer la résistance vasculaire périphérique ou le débit cardiaque, diminuant ainsi la pression artérielle moyenne. Dans l'hypertension, la rigidité anormale des grosses artères a été vue comme une conséquence de l'élévation de la pression artérielle moyenne, entraînant une surcharge excessive et un vieillissement accéléré. D'après des études récentes, des anomalies de la rigidité aortique précédent et contribuent à la pathogénèse de l'hypertension, surtout de l'hypertension à pression pulsée augmentée, hautement prévalente et difficile à contrôler. Une rigidité aortique augmentée, une pression excessive et une pulsabilité jouent également un rôle majeur dans la lésion de l'organe cible. Une conscience accrue de la participation de la rigidité aortique à la pathogénèse de l'hypertension facilitera la bonne utilisation des médicaments existants et la conception rationnelle de nouveaux produits ciblant les anomalies primaires de la structure et de la fonction aortiques.
The arterial system is beautifully designed for its role of receiving blood in spurts from the heart’s left ventricle, and passing this on in a (near) steady stream through the tiny vessels of organs and tissues in the body. Optimal heart function seen in adolescence is progressively lost with age as a consequence of arterial (especially thoracic aortic) stiffening. Such stiffening with age is attributable to the fatiguing effects of pulsatile stretch on elastic elements in the aorta. The aortic elastin fibers fracture and the wall stretches, with stresses being progressively transferred to collagen fibers. Progressive stiffening depends on extent of stretch, and so occurs earliest and is most marked in the ascending aorta; with age the aorta changes from the body’s most distensible to its least distensible systemic artery! Ill effects of aortic stiffening are caused by stiffening itself, which causes a greater rise in pressure for a given flow pulse into the aorta, and magnified by wave reflection, which leads to waves returning early, boosting systolic pressure in the aorta and left ventricle, and causing relative reduction in coronary perfusion pressure. In consequence of aging and increase in aortic systolic and pulse pressure, the left ventricle hypertrophies, predisposing to cardiac failure. The increase in systolic and fall in diastolic pressures predispose to myocardial ischemia. Increase in pulse pressure in small and large arteries predisposes to early progression of atherosclerosis. Increase in pulsations in central arteries cause the same fatiguing problem as seen in the aorta, but principally at physically weak arterial bifurcations in the brain, where small aneurysms arise, with risk of rupture and bleeding. Hemodynamic changes also predispose to higher endothelial shear, shedding of endothelial cells, and cerebral artery occlusion, leading to cerebral infarction. The aorta is thus progressively altered by fatiguing effects of cyclic stress into an organ utterly unsuited to its task and responsible for cardiac failure and arterial ruptures and occlusions that are the scourge of the elderly.

Consequences of arterial stiffening and increase in central blood pressure in hypertension

by M. F. O’Rourke, Australia

Aortic stiffening is the major cause of cardiac disease and of cerebral and renal vascular disease in our aging society, and the physiological importance of arterial elasticity has long been known. The aim of this article is to describe the pathophysiological principles that form the blueprint for understanding aortic stiffening and for linking together the topics undertaken by other authors in this issue of Medicographia. Almost one century ago, the importance of aortic stiffening was described by Crighton Bramwell and Nobel Laureate A. V. Hill with respect to left ventricular (LV) work and LV failure.
The amount of energy expended by the heart as measured by its oxygen consumption or CO₂ output has been shown to be proportional to the pressure developed; hence the amount of energy which the heart has to expend per beat, other things being equal, varies inversely with the elasticity of the arterial system.

Bramwell and Hill, 1922⁵

Only in the case of young children do we find that the elasticity of arteries is so perfectly adapted to the requirements of the organism as it is in the case of the lower animals.

Roy, 1880⁶

Modern attention was drawn to the subject of arterial stiffening by early Framingham Investigators, who pointed out the emerging importance of arterial rigidity as well as atherosclerotic disease as a cause of stroke and cardiac failure. The Framingham Investigators were the first to describe pulse waveform analysis as a complement to brachial cuff pressure in a clinical trial.⁷ Pulse wave analyses actually preceded the introduction of the brachial artery cuff method for measuring systolic and diastolic pressure and acceptance of its predictive capacity in life insurance just over one hundred years ago.⁸

The earliest radial artery studies were undertaken by Marey in Paris around 1863⁹ and extended into the clinical arena of aging, hypertension, and renal disease by Mahomed in the 1870s.¹⁰ These studies were next used by Murrell et al in 1879¹¹ to show the effect of nitrates on arterial pulse, and then taken up by Sir James Mackenzie at the turn of the 19th century.¹² All the above were more concerned with aortic stiffness than arteriolar resistance—but in Mackenzie’s name, brachial cuff diastolic pressure was taken up as a measure of peripheral resistance, and the “sine qua non” of arterial hypertension—until the importance of cuff systolic pressure was clarified by Framingham Investigators¹² and then by the Systolic Hypertension in the Elderly Project (SHEP).¹¹

Over the last 50 years, the prime focus of clinicians has been directed toward atherosclerotic disease, and many came to see the arteries in terms of obstructive atherosclerosis, ie, in terms of their conduit function. However, at the turn of the 19th century, Osler in his teachings and undergraduate textbooks, and Mackenzie in his, were stressing the importance of arterial stiffness. Osler, after Councilman at Johns Hopkins, divided arteriosclerosis into nodular arteriosclerosis (now called atherosclerosis), diffuse arteriosclerosis (probably an accompaniment of severe untreated hypertension), and senile arteriosclerosis (which was a consequence of aging). Osler sometimes paradoxically referred to senile arteriosclerosis as “physiological arteriosclerosis”, probably to emphasize that such arterial stiffening was a consequence of aging in apparently normal older subjects without any other sign of disease.¹³

### Physical laws and principles of measurement

Elastic arteries play a major role in the early studies of elasticity, since there were no synthetics, and arteries were readily available from abattoirs together with ligamenta nuchae. The studies of Thomas Young, physician and physicist, on modulus of elasticity (Table I) utilized such tissues, and with others he established the relationships between elastic modulus and pulse wave velocity (PWV) in arteries. The Waterhammer formula describes the relationship between aortic PWV and aortic characteristic impedance (Zc) as numerically almost identical since, when impedance is expressed in terms of velocity, “aortic” PWV multiplied by density equals Zc, since the density of blood is almost one (usually 1.05). Measurements of arterial stiffness include: aortic PWV, Zc, ratio of diameter change to pressure change in relative terms (distributability or stiffness; one the inverse of the other) or absolute terms, as compliance (absolute pressure change to absolute diameter or volume change). Other measures indirectly related to aortic stiffness are brachial pressures—brachial systolic pressure (BSP) and brachial pulse pressure (BPP)—and cen-

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<th>Equation</th>
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<td>((D_s - D_d)/(P_s - P_d)) (D_d)</td>
<td>cm³/dyne</td>
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<tr>
<td>Arterial compliance</td>
<td>((D_s - D_d)/(P_s - P_d))</td>
<td>cm³/dyne</td>
</tr>
<tr>
<td>Volume elastic modulus</td>
<td>([P_s - P_d]/(V_s - V_d)) / (V_d)</td>
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<tr>
<td>Peterson’s elastic modulus</td>
<td>([P_s - P_d]/D_d)/(D_s - D_d)</td>
<td>cm³/dyne</td>
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<tr>
<td>Young’s elastic modulus</td>
<td>([P_s - P_d]/D_d)/(D_s - D_d) h</td>
<td>cm³/s</td>
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<td>Pulse wave velocity</td>
<td>((2 \pi - 2\lambda)/(1 - t_2))</td>
<td>dyne/cm²</td>
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<td>Pressure augmentation</td>
<td>((P_s - P_d))</td>
<td>dyne/cm²</td>
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<tr>
<td>Augmentation index</td>
<td>([P_s - P_d]/(P_s - P_d)) × 100</td>
<td>%</td>
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<tr>
<td>Characteristic impedance</td>
<td>((P_s - P_d)/peak flow (or velocity))</td>
<td>dyne-s/cm² or dyne-s/cm³</td>
</tr>
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<td>Stiffness index (β)</td>
<td>([D_d \ln (P_s/P_d)]/(D_s - D_d))</td>
<td>Nondimensional</td>
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<td>Large artery elasticity index; or capacitive compliance, (C_1)</td>
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<td>Relation between change in oscillating arterial volume and change in oscillating pressure around exponential diastolic pressure decay</td>
<td>cm²/dyne</td>
</tr>
</tbody>
</table>

### Table I. Measures of elastic properties.

**Abbreviations:** \(d\), diastole; \(h\), wall thickness; \(i\), inflection point; \(ln\), natural logarithm; \(P\), pressure; \(s\), systole; \(t\), travel time of pulse; \(V\), volume; \(z\), measuring site.

New-generation Treatments for Hypertension: Targeting the Artery

Central blood pressure in hypertension – O'Rourke

Tral aortic pressures—central systolic pressure (CSP) and central pulse pressure (CPP). Since the arteries have a mixture of elastin and collagen fibers, with elastin predominantly engaged at diastolic pressure and with collagen fibers progressively engaged as pressure rises, elasticity needs be measured by the tangent of the pressure/diameter curves at around mean pressure. Arrangement of elastin and collagen fibers is such that the artery acts as a distensible conduit at physiological pressure, but is prevented from breaking at very high pressure by engagement of collagen fibers.

Other (indirect) measures of arterial elasticity are: augmentation pressure (AP), a measure of the reflected wave and pressure; augmentation index (AIx), a measure of the reflected wave divided by incident plus reflected wave in the ascending aorta; and reflection magnitude, calculated as amplitude of the reflected wave divided by amplitude of the incident wave when a particular incident wave is assumed. The above are practical indices of arterial stiffness, but do depend on approximations—i.e., nonlinear wall elasticity as described, inhomogeneity of the aortic wall, with measured thickness including non–load-bearing as well as load-bearing components of the media. A further assumption is that AIx is a complete measure of wave reflection (it is not, but depends on pattern of flow from the left ventricle as well as wave reflection).

![Figure 1](image.png)

Figure 1. Changes in manifestation and indices of aortic stiffness with age in adult humans (20-80 years).

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Changes Over a Lifetime</th>
</tr>
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<tr>
<td>Brachial Systolic Pressure (BSP)</td>
<td>From ≈120 to 150 mm Hg to ≈150 mm Hg, ≈25%</td>
</tr>
<tr>
<td>Central Aortic Systolic Pressure (ASP)</td>
<td>From ≈100 to 145 mm Hg, ≈45%</td>
</tr>
<tr>
<td>Brachial Pulse Pressure (BPP)</td>
<td>From ≈80%</td>
</tr>
<tr>
<td>Central Aortic Pulse Pressure (APP)</td>
<td>From ≈160%</td>
</tr>
<tr>
<td>“Aortic” Pulse Wave Velocity (PWV)</td>
<td>From ≈250%</td>
</tr>
<tr>
<td>Characteristic Impedance (Zc)</td>
<td>From ≈600%</td>
</tr>
<tr>
<td>Aortic Young’s Modulus (YM)</td>
<td>From ≈600%</td>
</tr>
</tbody>
</table>

Data from reference 13.

Abbreviation: AIx, augmentation index.

There is normally a gradient in distensibility of the aorta down to muscular peripheral arteries, with the aorta expanding by 15%-20% in youth with each beat of the heart, and the femoral or brachial arteries expanding by just 3%-5%. Such is seen in all young mammals we have studied. Humans, however, have a different pattern, so that by the age of around 50, expansion of the proximal aorta is the same as, if not less than, the peripheral arteries. The human life span is so long in comparison to other mammals that degenerative changes with stiffening are ubiquitous in middle-aged humans. Only older birds, with high BP and fast heart rate, show anything similar.

**Selected Abbreviations and Acronyms**

- **AIx**: augmentation index
- **AP**: augmentation pressure
- **ASCOT**: Anglo-Scandinavian Cardiac Outcomes Trial
- **BP**: blood pressure
- **BPP**: brachial pulse pressure
- **BSP**: brachial systolic pressure
- **CAFE**: Conduit Artery Function Evaluation
- **CPP**: central pulse pressure
- **CSP**: central systolic pressure
- **ESC**: European Society of Cardiology
- **ESH**: European Society of Hypertension
- **IDH**: isolated diastolic hypertension
- **ISH**: isolated systolic hypertension
- **J-CORE**: Japan-Combined treatment with Olmesartan and a calcium channel blocker versus olmesartan and diuretics Randomized Efficacy
- **LV**: left ventricular
- **PWV**: pulse wave velocity
- **REASON**: pReTeraX in regression of Arterial Stiffness in a controlled double-blind study
- **S/N**: strain/logarithm of cycle number
- **SDH**: systolic/diastolic hypertension
- **SHEP**: Systolic Hypertension in the Elderly Project
- **SYST-CHINA**: Systolic Hypertension in China
- **SYST-EUR**: Systolic Hypertension in Europe
- **Zc**: characteristic impedance
Physiology

The function of the arterial system is to distribute blood from the left ventricle to the peripheral organs and tissues, according to need. To do this most efficiently it is necessary to accept pulsatile flow from the intermittently contracting left ventricle at the input then pass this on as a near-continuous, nonpulsatile flow to the peripheral tissues.13 Hence there is another function for the arterial system, which is to “cushion” pulsations so that organ flow in the tiny capillaries is continuous or almost so.13,14

This function of the arterial system, undertaken principally by the proximal thoracic aorta, is similar to that of the medieval fire engines, whereby an inverted air-filled dome cushioned intermittent pumping by firemen to produce a continuous stream through the nozzle of a hose, so that water could be directed at the seat of a fire. This analogy was made by Steven Hales15 and described as “Windkessel” in the German translation of his book. The term has stuck to this simple model of the arterial tree and the aorta’s function. This is a useful primary conceptual model, and is approximated by the arterial function in an elderly person with a very stiff aorta. But the concept loses all value when applied to a young person, an elderly person with aortic PWV reduced by hypotension, or when ejection from the heart is shortened by tachycardia. From a clinical perspective, a model for interpreting cardiovascular function must remain appropriate under extreme conditions, such as those encountered in an intensive care ward, and be able to account for changes in BP, heart rate, heart rhythm, and blood vessel dilation (Figure 3).16

The more appropriate model is a single tube, such as that now used for interpretation of cardiac output, peripheral resistance, and BP (Figure 4, page 384). In this model, the heart ejects in to one end; the other end represents peripheral resistance. For mean pressure, cardiac output, and peripheral resistance, this is appropriate; but for pulsatile LV ejection, this model is incomplete. The appropriate model is an elastic tube activated by the left ventricle at one end and with (near) continuous flow against the peripheral resistance at the other. This model allows for the generation of a pressure wave at one end, with the passage of this wave at a finite wave velocity along the tube, wave reflection at the distal end(s), and travel backwards and some re-reflection at the proximal end. This model better represents the function of the arterial tree, optimal matching of the LV and arterial system, and understanding of how arterial function changes with age in humans.

In Figure 4, the present conceptual model for steady flow, mean pressure and peripheral resistance is shown above (Panel A); the distributed model below (Panel B) is appropriate for pulsatile pressure and flow as well as mean pressure and flow. Panel B is a traditional figure showing mean pressure maintained along the aorta and peripheral arteries almost down to the arterioles, with abrupt fall in the high resistance arterioles. There is pulsation around mean pressure, with pulsation suddenly falling at the origin of the arterioles when pulsatile pressure and flow encounter high resistance arterioles and are reflected backwards towards the heart. Reflection is
inevitable at the junction of a high conductance artery and a high resistance arteriole, with flow and pressure downstream being virtually devoid of pulsations. Reflection is strong at the multiple individual peripheral junctions, with some 90% of the pressure wave reflected and just 10% of pulsatile pressure and flow entering the microvessels (arterioles and capillaries) of all but the brain and kidneys at rest. In contrast to peripheral arterioles, wave reflection is minor in the major arteries. Indicative of this is the relative constancy of pressure wave-forms above and below major branches in the proximal and distal aorta, and the trivial drop in mean pressure from the aorta to tiny peripheral arteries.

Pathophysiology

Wave onset in Figure 5, which shows pressure waves recorded sequentially between the aortic arch and iliac arteries in a young human adult (center) and an older adult (right), is timed to the electrocardiogram and seen to be delayed between the proximal aorta and the iliac artery. The wave is delayed more in the younger subject than in the older subject indicating that wave velocity is slower (around 5 m/s) in the younger subject than the older subject, where it is usually in the region of 10-15 m/s. The subsequent waves travelling back to the proximal aorta at the same speed are seen to create the diastolic wave in the younger subject and the late systolic wave (earlier echo) in the older subject.

The LV output flow velocity wave and the pressure wave in the young subject are seen at center in Figure 5 and the older subject at right as expected from wave travel and reflection in the arterial tree supplying the trunk and lower limbs (left). In Figure 5, the initial wave is generated around the same time, some 100 ms after the beginning of ejection, but its amplitude is greater in the older subject as expected from higher $Z_c$ (and PWV). For the same monophasic flow waveform, there are thus two fluctuations in pressure. In the younger subject, the secondary wave—from an appropriately slow return of wave reflection—is seen only in diastole, whereas in the older subject the reflected wave returns earlier, during late systole. The aging change is disadvantageous to the left ventricle, since wave reflection adds to aortic pressure and LV load while reducing pressure maintained during diastole in the aorta, when coronary arteries are perfused after being squeezed shut during systole. The same changes can be explained in the frequency domain from ascending aortic impedance.

Figure 5. Tubular models of the arterial system (left), showing pressure waves recorded sequentially between the aortic arch and iliac arteries in a young human adult (center) and an old subject with aortic stiffening (right).

Increased stiffness of the aortic wall in the old subject causes the initial wave generated by left ventricular ejection to be higher (increased aortic characteristic impedance), then causes the reflected wave to return early (increased aortic pulse wave velocity), boosting late systolic pressure and reducing coronary perfusion pressure.

Increased aortic stiffness increases amplitude of the primary pressure wave—as a consequence of increased aortic $Z_c$ and aortic PWV. Impedance at high frequencies is increased as a consequence of this, as is impedance at lower frequencies. The minimal value of impedance and phase cross over is increased to a higher frequency (from $\approx 3$ to $6 \text{ Hz}$) as a consequence of earlier return of wave reflection. Since most of the energy of the LV ejection wave occurs at the frequency of the first, second, and third harmonics, amplitude of the pressure waves is lower in the younger subject than the older subject, where impedance modulus remains high with a minimal frequency around or above $6 \text{ Hz}$.

**Aging and elastic fatigue and fracture**

<table>
<thead>
<tr>
<th>Aorta</th>
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Typical changes with aging in the aortic media are well known, and are gross, with fracture and fragmentation of load-bearing elastin fibers, and with disorganization of the aortic wall.\(^{13,14}\) The thoracic aorta dilates and stiffens. Changes can be attributed to fatigue, alterations in the crystalline structure of nonliving elastin fibers so that these become brittle and eventually break. A branch of engineering is devoted to these phenomena in various structural nonliving materials, such as steel (bridges and ships), aluminum (aircraft frames and spars), concrete (buildings), timber (buildings), and natural rubber. Different materials have different resistances to fatigue; these resistances are described as S/N curves (Figure 6), the relationship between extent of strain (S) and the logarithm of number of cycles (N) of such strain to the time when fracture is expected.\(^{13}\) These curves are utilized to determine when aircraft spars need be replaced in scheduled maintenance, ships have reached their safe life span, or components of a bridge need to be replaced.

There is no reason to believe that elastin fibers in arteries are immune to this process, which is illustrated in Figure 6,\(^{13}\) which shows the S/N curve for natural rubber. At cycles of 15% stretch, as seen in the proximal thoracic aorta, one would expect to see fracture at $1 \times 10^9$ cycles—at 30 years of age with a heart rate of 60-70 beats per minute—and to progress with further cycles as age advances. Elastin is a long-lasting, structural material laid down in childhood in the body, with a half-life of decades.\(^{13,14}\) The gene that controls elastin synthesis is “silenced” in childhood.\(^{13,14}\) Elastin is not replaced by elastin, but by collagen and mucoid material in the arterial wall. Remodelling of the aorta with age is a degenerative process characterised by chemical and cellular changes. These changes can most rationally be considered as secondary attempts at repair, with the process initiated by physical damage that is a consequence of pulsation and stress in the aorta.

| Small arteries, arterioles |

A similar physical process affects the small arteries and arterioles and helps explain small vessel damage—microinfarcts and microbleeds—that occurs in the brain and kidneys of older persons, particularly when pulsations are increased by aortic stiffening, and so in long-standing hypertension\(^{20}\) and in acute hypertension.\(^{21}\) Susceptibility of brain and kidney microvasculature to pulsatile stresses can be explained by low vascular resistance, which permits passage of greater pulsations of flow and pressure into dilated distal vessels. Such microvascular lesions are rarely seen in other systemic tissues and organs, one exception being similar lesions in the pulmonary vasculature of children born with left to right shunts,\(^{22,23}\) which develop over years and cause irreversible pulmonary hypertension.

The same physical principles of mechanical fatigue and fracture are at play in the microvasculature as in the aorta, but they affect the microvasculature differently. Instead of the elastin fibers being uniformly affected, manifesting as elastin fracture in the aorta, in the microvasculature the process appears to affect the vessels that supply the most vulnerable organs and at weak spots—ie, the brain and kidney, branching points,
and where elastin and connection to muscle is weakened—leading to development of aneurysmal dilatation as described by Charcot and Bouchard. These defects are responsible for rupture with microbleeds and frank cerebral hemorrhage. This microvascular disease takes the form either of disruption of the wall of small arteries as a consequence of high circumferential tension or thrombosis in the lumen caused by higher pulsatile shear with shedding of endothelial cells, with platelet adherence and arterial occlusion causing small infarcts in the area of supply. This is the ultimate endothelial dysfunction. Microvascular disease of this type—quite independent of atherosclerotic disease—is responsible for the initial lesions that, over time, appear to be the cause of Alzheimer’s disease and other cerebral syndromes.

**Consequences of aortic stiffening**

LV load is still commonly related only to peripheral resistance, but this should include terms related to the heart’s pulsatile ejection during systole. The load is best characterised as ascending aortic impedance, and should consider Zc, which increases 2- to 3-fold between the ages of 20 and 80 (Figure 1), and also the effects of wave reflection, which typically increase late systolic pressure for LV and aortic systolic pressure in older subjects with aortic stiffening by 20-40 mm Hg over a lifetime. This occurs even if mean pressure and peripheral resistance are unchanged. Such increase in LV afterload has been described by Katz as the cause of “cardiomyopathy of overload,” which is most common with aging, and in women, and characterised by LV hypertrophy, LV diastolic dysfunction, and LV failure. It can progress in its terminal state to systolic dysfunction, where LV ejection against highly increased aortic impedance is markedly impaired on account of LV weakening.

A further depressant of LV function is due to ischemia caused by impaired LV coronary perfusion related to a reduction in coronary perfusion pressure, ie, the pressure in the proximal aorta during diastole when the intramyocardial coronary arteries are freed from the throttling effect of the myocardial contraction around them. This impairment is worsened by accompanying LV hypertrophy and diastolic dysfunction that increase ejection duration, shorten the duration available for coronary perfusion, and eventually cause an increase in LV pressure during diastole. All these changes are extremely common in older humans and predispose individuals to myocardial ischemia even in the absence of coronary atherosclerosis. These changes account for increasing disability, dyspnea, and discomfort, especially in women.

**Small blood vessels in the brain and kidney**

These blood vessels, like those in the lungs, have continuously high blood flow through vasodilated arteries at rest as well as during exercise. As previously described, they are subject to greater pulsatile circumferential tensile stresses and to greater longitudinal shear stresses at the endothelial level. The former can account for susceptibility to arterial rupture and micro- or macrohemorrhage, which are part and parcel of “pulse wave encephalopathy” and “pulse wave nephropathy”, as in the presence of acute “malignant” hypertension. In the brain, lesions appear as white matter hyperintensities, lacunar infarcts, and microhemorrhages, even in asymptomatic older persons, and are becoming increasingly common. Lesions are characterized at autopsy by deposition of B-amyloid plaques, tangles, and inflammatory reactions attributable to damage caused by the microhemorrhages, microinfarcts, and cerebral ischemia. Studies on brain circulation and renal circulation continue. Attrition of cerebral and renal cells with age has been known for many years, but had not in the past been linked with increase in pulse waveform intensity (pressure and flow), brought about by aortic stiffening. Even now, it is difficult for many clinicians to consider that cerebral microvascular damage could be due to aortic stiffening, ie, to have a cause so far distant from the brain.

**Principles of prevention**

Emphasis on cause of aortic stiffening and small arterial disruption is directed at physical stresses that are a consequence of the heartbeat, epitomized by Stone’s assertion that “the brain is destroyed by the pulse”. One cannot avoid the fact that changes associated with aging are virtually all degenerative, and in one way or other contribute to death of most humans between 60 and 100 years of age. The word “remodelling” is a euphemism—a graceful term that is easier for patients to hear. This argument is not new, but is a continuation of that offered by William Osler and James Mackenzie 100 years ago. Osler referred to the quality of elastin that had been inherited, and to the “wear and tear” to which this natural rubber had been subjected. Mackenzie referred to physical deterioration and breathlessness in the 4th decade of life as caused by stiffening of the aorta and elastic arteries.

Like Osler and Mackenzie, I agree that arterial stiffening is inevitable and impairs enjoyment of life. These ill effects of aortic stiffening, which can be treated, are not simply due to aortic stiffening, but are magnified by increased PWV and change in the timing of wave reflection. Wave reflection in young adults returns to the heart at the time of aortic valve closure. The wave does not add to LV load, but it does boost aortic pressure throughout diastole, and this aids coronary perfusion. When with aging and aortic stiffening arterial PWV increases, the reflected wave returns early and boosts (augments) the level of pressure against which the heart needs to eject. At the same time, pressure during diastole falls more steeply and coronary perfusion is threatened. The design of the human body evolved to provide optimal ventricular/vascular interaction for 20-30 years, the length of a typical lifetime for our ancestors.

Wave reflection is desirable, and the body is so designed that reflection must occur. However, beyond a certain age, at which in generations past there was no survival benefit and at which...
aortic stiffness develops, wave reflection is no longer beneficial.\textsuperscript{13} Evolution in humans occurred over eons, during which there was no survival benefit in living into, let alone beyond, the fourth decade. This was identified by James Mackenzie.\textsuperscript{7}

From the fourth decade on (and earlier in women), wave reflection is detrimental and becomes a target for therapy. The amplitude of wave reflection can be reduced by arterial dilating drugs, particularly those which have little or no effect on resistance. Such are epitomized by nitrates.\textsuperscript{10,13} Other drugs such as calcium channel blockers can have a similar effect, as can angiotensin-converting enzyme inhibitors and angiotensin receptor blockers.\textsuperscript{13} These drugs can have the effect of “trapping” wave reflection in the peripheral circulation. This effect is apparent on examination of the aortic pressure waveform, and explains the benefits of nitrate in angina pectoris and in acute heart failure in older adults.\textsuperscript{10,13} Aortic stiffening is little affected by nitrates or other vasodilators, so that PWV and timing of wave reflection is not substantially improved in the aorta, but some drugs do appear to reduce stiffness of muscular arteries, and a number of studies attest to this. In present practice, reduction in aortic stiffness is usually improved modestly by reduction in arterial pressure.

**Treatment**

In persons with aortic stiffening, and subject to its ill effects on the heart, brain, and kidney, there is every prospect that improvements in amplitude and timing of wave reflection can be achieved by therapy. We do this now with treatment of isolated systolic hypertension (ISH) in the elderly. Since the major effect is on wave reflection, it may be useful to monitor and identify reflection in the ascending aortic pulse so as to optimize the reduction in systolic pressure and to encourage any increase in aortic pressure during diastole.

ISH in persons over the age of 60 is characterised by a late systolic pressure peak caused by early return of wave reflection. The SHEP study\textsuperscript{11} showed how active antihypertensive therapy reduced cardiovascular events, while SYSt-EUR (Systolic Hypertension in Europe)\textsuperscript{34} and SYSt-CHINA (Systolic Hypertension in China)\textsuperscript{36} showed how active antihypertensive therapy reduced cardiovascular events, while SYSt-EUR (Systolic Hypertension in Europe)\textsuperscript{34} and SYSt-CHINA (Systolic Hypertension in China)\textsuperscript{36} showed how active antihypertensive therapy reduced cardiovascular events.
pertension in China) showed similar benefit in persons over the age 60, irrespective of diastolic pressure. These trials were interpreted by guideline committees throughout the world as applicable to all adults, irrespective of age. Increasing concern has been directed at evidence (or lack thereof) for treating patients with ISH under the age of 60. In young adults, especially tall men, elevation of BSP may not be caused by aortic stiffening, but by exaggerated wave reflection in the arm. This is characterised by normal aortic systolic pressure, but very high brachial and radial pressure from a highly peaked upper limb systolic peak. Ironically this condition is usually seen in fit, tall, young men with low aortic stiffness. While initially considered rare, and described as “spurious systolic hypertension of youth,” it appears to be relatively common and to be a factor in the generation of high systolic pressure in the upper limb in many persons under the age of 60. It has been identified in European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines as a good reason for measuring aortic pressure from the peripheral radial pulse before labelling a person “hypertensive” and prescribing therapy. In such cases, information available from the arterial pulse waveform will support a clinician’s decision not to treat.

In pursuing this issue, the Chicago Heart Association Detection Project in Industry Study has followed a cohort of over 27 000 persons aged 18-49 over 31 years, on the basis of initial BP categorization: normal BP, high-normal BP, ISH, isolated diastolic hypertension (IDH), or systolic/diastolic hypertension (SDH). Cardiovascular mortality at 20 years was low in men with ISH; it was similar to the normal groups, but different to the two groups with IDH and SDH (Figure 7, page 387). This supports a view that results of SHEP cannot be extrapolated to younger populations, and the views of the ESH/ESC that central aortic pressure should be measured in younger subjects with ISH. Surprisingly, the editorialist of the Chicago study set aside authoritative scientific information and came to a different conclusion that supports the “tension of youth,” and to a different conclusion that supports the view that systolic pressure should be treated. This showed greater benefit with the perindopril/indapamide combination for reduction of central, but not brachial, pressure and for reduction in LV mass over 12 months.

Similar results found in the CAFE (Conduit Artery Function Evaluation) substudy of ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) were associated with reduction of a prespecified composite outcome in the amlopipen-perindopril group compared with the atenolol-bendroflumethiazide group. Similar results were seen in the J-CORE (Japan-Combined treatment with Olmesartan and a calcium channel blocker versus olmesartan and diuretics Randomized Efficacy) study. All these studies, which were small, were followed by a series of studies and meta-analyses that have shown there is an advantage of central aortic pressure compared with brachial pressure for the prediction of outcomes.

Although contrary opinions still exist, there is an emerging consensus that central aortic pressure, measured with validated devices, warrants use in future trials of antihypertensive therapies, especially those which deal with aging and aortic stiffening. The ESH has encouraged support of this view, and the most respected group of cardiovascular epidemiologists in the USA have presented the strongest evidence to date.

The first century of hypertension was launched in Chicago by Fischer with his Journal of the American Medical Association article on actuarial data for the life insurance industry. The second century was launched by Greenland, Stamler, and colleagues, also from Chicago, with their questioning of guidelines for treatment of systolic BP in young subjects, and then in their groundbreaking follow-up study of 27 000 persons over 31 years. Life insurance companies are expected to confirm or deny the Chicago views in the very near future.

Conflict of interest: Michael O’Rourke is a founding director of AtCor Medical Pty Limited, manufacturer of systems for analyzing the arterial pulse and Aortic Wrap Pty Limited, developer of devices to improve aortic distensibility, and a consultant to Novartis and Merck.
Keywords: Aortic function, aortic stiffness, pulse wave velocity, wave reflection, augmentation pressure, augmentation index, radial pulse wave, aortic pulse waveform, elasticity, impedance, arteriosclerosis


CONSEQUENCES DE LA RIGIDITÉ ARTÉRIELLE ET DE L’AUGMENTATION DE LA PRESSION ARTÉRIELLE CENTRALE DANS L’HYPERTENSION

Le système artériel est magnifiquement conçu pour recevoir le sang en jets depuis le ventricule gauche et le transmettre par des petits vaisseaux en un flux (presque) régulier jusqu’aux organes et aux tissus du corps humain. La fonction cardiaque, optimale pendant l’adolescence, se dégrade progressivement avec l’âge à cause de la rigidité artérielle (surtout de l’aorte thoracique). Cette rigidité liée à l’âge est attribuée aux effets usants de l’étirement pulsatile sur les composants élastiques aortiques. Les fibres aortiques d’élastine se fissurent, la paroi s’étire, les tensions se transmettant peu à peu aux fibres de collagène. La rigidité progressive dépend de l’étendue de l’étirement et apparaît donc plus tôt et de façon plus marquée dans l’aorte ascendante ; avec l’âge, l’aorte passe de l’artère la plus flexible du corps à la moins souple ! Les effets délétères de la rigidité aortique sont dus à la rigidité elle-même qui provoque une augmentation de pression plus importante pour une impulsion donnée dans l’aorte, amplifiée par la réflexion de l’onde de pouls, les ondes revenant plus tôt, stimulant la pression aortique dans l’aorte et le ventricule gauche, ce qui entraîne une diminution relative de la pression coronaire de perfusion. L’hypertrophie du ventricule gauche, conséquence du vieillissement et de l’augmentation des pressions systolique aortique et pulsée, prédispone à l’insuffisance cardiaque. Une pression systolique augmentée et une pression diastolique diminuée prédispotent à l’ischémie myocardique. Une pression pulsée augmentée dans les petites et les grosses artères prédispente à la progression précoce de l’athérosclérose. La multiplication des pulsations dans les artères centrales provoque le même problème d’usure que dans l’aorte, mais surtout aux points faibles des bifurcations artérielles cérébrales susceptibles d’être le siège de petits anévrismes à risque de rupture et de saignement. Les modifications hémodynamiques prédiposent aussi à un cisaillement endothélial plus important, à la perte des cellules endothéliales, et à l’occlusion des artères cérébrales suivie d’infarctus cérébral. L’aorte, progressivement transformée sous l’effet de l’usure d’une contrainte cyclique, devient totalement incapable d’assurer sa fonction et provoque une insuffisance cardiaque, des ruptures et des occlusions artérielles, fléaux du sujet âgé.
Pulsatile hemodynamics are increasingly recognized as the basic principle of blood pressure, and they are fundamentally involved in the pathophysiology of hypertension and its ill-effects. Stiffness of the aorta and large arteries largely determines how pulsatile pressure and flow, as generated by the heart, are transmitted towards the microcirculation. In the last few decades, we have increasingly focused on more and more specific measures of pulsatile hemodynamics. Brachial pulse pressure, a crude estimate of arterial stiffness, can be readily obtained with a simple cuff, by subtracting diastolic blood pressure from systolic. A value above 60 mm Hg indicates subclinical organ damage, according to the latest European Society of Hypertension (ESH)/European Society of Cardiology (ESC) hypertension guidelines. Central (aortic) systolic and pulse pressure are probably more closely related to organ damage and prognosis, but their measurement is more complex; several issues including calibration of the systems and standardization of the methods need to be resolved before they can be integrated widely into daily routine. Wave reflections from peripheral sites are an integral part of the blood pressure curve. They can be assessed, using a variety of techniques, and have been shown repeatedly to carry prognostic information. Again, consensus on methodological issues and simplification of the measurement are necessary next steps before incorporation into clinical practice. Pulse wave velocity (PWV) as a measure of regional arterial stiffness is a relatively simple, robust procedure. If the aorta is included in the arterial pathway (as with carotid-femoral PWV), many studies have consistently shown its independent prognostic value. Therefore, carotid-femoral PWV has been recommended as a measure of subclinical organ damage in the latest ESH/ESC hypertension guidelines. Based on available data, and a consensus regarding measurement details, a cutoff value of 10 m/s has been proposed.

During the last few decades, considerable scientific effort has been devoted to the investigation of the hemodynamic principles underlying blood pressure itself, its changes with aging, and its influence on development of cardiovascular diseases. Traditionally, the formula “mean blood pressure = cardiac output × peripheral resistance” was used to describe hemodynamics in hypertension, with a focus on diastolic blood pressure (DBP), which is closer to mean blood pressure. This is an overly simplistic approach, however, valid only for steady-flow conditions. In real life, flow and pressure are pulsatile. Measures used to quantify
Pulsatile hemodynamics depend—to a varying degree—on the properties of the pulsatile pump (ie, the heart) and on the properties of the circulation (ie, the aorta and the large elastic arteries).

Pulse pressure, the difference between SBP and DBP, is the most convenient—but crude—measure of pulsatile hemodynamics, and available as brachial pulse pressure with every cuff blood pressure measurement. Pulse pressure increases with stiffening of the aorta and the large arteries, and decreases with severely impaired systolic left ventricular function. In populations, pulse pressure increases with aging, particularly after the age of 55 years. It is more closely related to cardiovascular risk in middle-aged and elderly individuals than other blood pressure components, and can be used to identify patients with heart failure with preserved ejection fraction. Brachial pulse pressure >60 mm Hg is a hallmark of asymptomatic organ damage in the elderly, according to the 2013 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines for the management of arterial hypertension.

Brachial pulse pressure as a measure of arterial stiffness, however, has several limitations: its dependence on cardiac function, which leads to an inverse relationship with outcomes in patients with severely impaired systolic function; its varying increase from the aorta to the brachial artery (“pulse pressure amplification”), which depends among other things on aortic stiffness, cardiac function, heart rate, and arterial geometry; and the fact that brachial pulse pressure is not superior to other blood pressure components in terms of risk prediction in all studies. All of these reasons make more specific measurements of arterial stiffness desirable. These measurements can be broadly divided into measurements of pulse wave velocity (PWV), measurements of central blood pressure...
sures, measurements of wave reflections, and measurements of local arterial stiffness. This latter measurement involves mainly studies of the carotid artery with dedicated ultrasound techniques (echotracking). Its main applications are mechanistic studies in pathophysiology and pharmacology, with very limited implementation in clinical practice and few positive outcome studies. The present review will focus on the other three measurements of arterial stiffness.

**Pulse wave velocity**
The speed of propagation of pulse (pressure or flow or dispersion) waves in an artery is directly related to the stiffness of the vessel (the stiffer the vessel, the higher the velocity) and can be directly assessed, by dividing distance travelled by transit time. As the effects of the aging process (ie, loss of elasticity, increased stiffening) are most pronounced in the human aorta as opposed to the muscular arteries, the aortic pathway should be included in the measurement. In addition, the prognostic value is largely limited to pathways including the aorta, such as carotid-femoral PWV. “Pure” aortic PWV can be measured invasively or with magnetic resonance imaging (MRI). Both are of little value in routine clinical practice due to their invasive nature and limited availability, but are very useful for gaining mechanistic insights and for validation of noninvasive methods.

Carotid-femoral PWV has been used in large epidemiological studies involving thousands of patients. Results have been consistently positive and confirmed by a recent individual patient–based meta-analysis: carotid-femoral PWV is a strong predictor of cardiovascular events in different groups of high- and low-risk patients and in the general population. Clinical utility, calculated as "net reclassification improvement", is best in intermediate-risk patients.

In practice, pulse waves are recorded at the common carotid artery and at the femoral artery, using pressure sensors (mechanotransducers or high-fidelity application tonometers), Doppler flow probes, or echotracking ultrasound. With simultaneous recordings, transit time can be determined directly, usually at the end of diastole ("foot-to-foot"). With sequential recordings, the R wave of the ECG is used as a point of reference (Figure 1). The foot point of the travelling wave can be determined with different algorithms, which may lead to different results. For the purpose of standardization, the method of intersecting tangents is recommended. The determination of travel distance for carotid-femoral PWV has created more scientific discussion and although often labelled "aortic PWV", carotid-femoral PWV differs from true aortic PWV in the following respects: the ascending aorta is not covered (as the pulse wave travels up the carotid artery, it will be travelling down the aortic arch and descending aorta at the same time), but the carotid artery and the iliac-femoral pathway are included (where PWV is different from the aorta). In addition, true aortic PWV involves wave travel in only one direction, but carotid-femoral PWV involves wave travel in two opposite directions (upwards into the carotid artery and downwards along the aortic arch) at different wave speeds, which makes exact determination of travel distance elusive and establishes the need for compromise: whereas direct carotid-femoral distance measurement is simple and reproducible, comparisons with invasive and MRI-based aortic PWV have clarified that it overestimates aortic travel distance and, thus, aortic PWV (by roughly 2 m/s). As a solution, 80% of the direct carotid-femoral distance or subtraction of the suprasternal notch-carotid distance from the suprasternal notch-femoral distance has been recommended recently.

Although the measurement of carotid-femoral PWV is straightforward, standardization is necessary. The most important points are summarized in Box 1. If performed correctly, measurement of carotid-femoral PWV may take 15-20 minutes; it requires a trained operator. This may account for the slower than expected dissemination of the method into routine clinical practice. Accordingly, some simplifications have been introduced. A cuff can be used instead of the tonometer to

**Box 1. Practical aspects for the measurement of carotid-femoral pulse wave velocity.**

- In Europe, carotid-femoral PWV is the gold-standard measurement of arterial stiffness.
- Measurements should be obtained in duplicate, in the supine position, following 10 minutes rest in a quiet, comfortable environment. If the results differ by more than 0.5 m/s, a third measurement should be performed, and the median value should be taken.
- Patients should not speak during the measurement, and they should not consume caffeine, smoke tobacco, or eat a meal in the 3 hours preceding the measurement.
- Heart rate and blood pressure at the time of measurement must be reported.
- Travel distance should be measured either as 80% of the direct carotid-femoral distance or as the difference in distance between suprasternal notch to the carotid site and suprasternal notch to the femoral site.
- Travel distance should be measured with a flexible tape or a straight caliper. The way it was done should be reported.
- For repeated measurements, the same device should be used.
- Repeated measurements should be performed at the same time of day.
- In the presence of arrhythmias (eg, atrial fibrillation), measurements may be unreliable, particularly with sequential waveform recordings and ECG gating.
- Measurement should be avoided with high-grade carotid artery stenosis or carotid sinus syndrome.

**Abbreviations:**
ECG, electrocardiogram; PWV, pulse wave velocity.


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acquire pressure curves at the femoral site. In addition, a partial cuff can be used at the carotid site as well. A different approach utilizes the CKD interval (the time interval between the onset of the QRS on the ECG and the last Korotkoff sound at the brachial artery). Finally, measurements of aortic PWV from single-site waveforms have been suggested. A novel device uses regression—based on age, systolic blood pressure (SBP), and waveform characteristics—to estimate aortic PWV. We recently compared true aortic PWV (from the ascending aorta to the aortic bifurcation as measured invasively during cardiac catheterization) against carotid-femoral PWV and against the novel, waveform-based approach in almost 1000 patients. We found that carotid-femoral PWV (using either the subtracted method or the 80% direct distance method for travel distance estimation) agrees well with the invasive gold standard in the majority of patients. The single waveform–based estimate, however, shows even closer agreement with invasive aortic PWV. Based on their ease of use, the novel single-point estimates of PWV, which are obtained with brachial cuffs, have the potential to change routine clinical practice. Before their use can be recommended, large-scale outcome studies showing predictive value (already available for carotid-femoral PWV) are mandatory (and are currently emerging).

In Asian countries, measurement of brachial-ankle and cardio-ankle PWV is frequently performed, using oscillometric cuffs at the limbs. Its prognostic significance has been proven, but currently we lack larger amounts of data from European populations.

According to the latest ESH/ESC guidelines on the management of hypertension, a carotid-femoral PWV >10 m/s indicates subclinical organ damage in hypertension, puts the patient at high risk of cardiovascular events, and necessitates comprehensive actions to prevent clinical events (normalization of blood pressure, lifestyle changes such as smoking cessation and regular exercise, normalization of lipids, eventually antiplatelet agents, etc). The use of a single cutoff value for all patients is undoubtedly an attractive approach due to its simplicity (and is in line with the single blood pressure threshold of 140/90 mm Hg in all individuals except the very old). However, it does not take into account the direct relationship of PWV with blood pressure (at the time of measurement) nor the age-related increase of PWV. Thanks to a huge reference value project including more than 10 000 individuals, age-specific reference values and age-specific normal values (obtained in individuals free from cardiovascular risk factors) are available.

Central systolic blood pressure
SBP in the ascending aorta and in the brachial artery, the typical site of noninvasive BP measurement, is not the same, but increases from the aorta to the peripheral arteries; whereas mean blood pressure and DBP decrease by 1-2 mm Hg. The increase in SBP is related to changes in arterial stiffness and diameter of the arteries involved, and it is modified by the timing and extent of wave reflection from peripheral sites. As a result, the difference between central and brachial SBP varies among individuals. Central SBP is relevant for two reasons: it seems to be more closely linked to cardiovascular outcomes; and it can be modified differently from brachial SBP by cardiovascular drugs.
Technically, noninvasive estimation of central SBP can be accomplished by: recording peripheral waveforms, typically at the radial (or brachial) artery; calibrating them with brachial blood pressure; and applying mathematical formulae (transfer functions, n-point moving average, waveform characteristics). If waveforms are acquired at the carotid artery, no formula needs to be used, but calibration with brachial pressures is still necessary. The various methods and their invasive validation have been summarized recently. Although the different steps have their limitations, the step responsible for introducing most of the deviation from the invasive gold standard is calibration of the waveforms with brachial SBP and DBP. It has been suggested that oscillometry is more accurate in determining mean (and diastolic) blood pressure than systolic blood pressure at the brachial artery, and therefore using mean/diastolic pressure derived by oscillometry for calibration leads to a more accurate estimate of central SBP. Although studies with hard clinical endpoints (myocardial infarction, stroke, etc) are pending, it has already been shown that the brachial cuff–based estimate of 24-hour central SBP is more closely related to left ventricular mass than 24-hour brachial SBP. However, this is only true if the more accurate method of calibration (mean/diastolic pressure) is used.

So how can we apply central pressures in routine clinical practice in 2015? From another large international reference value project comprising more than 45,000 patients, age- and gender specific values for a normal population (free from traditional cardiovascular risk factors) and for a reference population (free from diabetes, cardiovascular disease, chronic kidney disease, and antihypertensive treatment) are available (Figure 3).

**Figure 3.** Central systolic blood pressure values according to age category for men and women in a normal population (n=18,183; normotensive and free from cardiovascular risk factors) and in a reference population (n=27,253; normotensive or hypertensive, not treated for hypertension or diabetes, and free from cardiovascular disease and chronic kidney disease).

Abbreviations: f, female; m, male; SBP, systolic blood pressure.


So how can we apply central pressures in routine clinical practice in 2015? From another large international reference value project comprising more than 45,000 patients, age- and gender specific values for a normal population (free from traditional cardiovascular risk factors) and for a reference population (free from diabetes, cardiovascular disease, chronic kidney disease, and antihypertensive treatment) are available (Figure 3). A complementary approach was taken by Chen and coworkers: based on two large outcome studies, the proposed central thresholds for optimal blood pressure and for hypertension were 110/80 mm Hg and 130/90 mm Hg.

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**Figure 4.** The effect of aging on blood pressure curves and wave reflections.

The figure shows radial (left) and derived aortic (right) blood pressure curves, obtained with tonometry and a transfer function (SphygmoCor® device), in a young (top), middle-aged (middle), and elderly (bottom) individual. Although peripheral (brachial) blood pressures in these individuals are roughly the same (128/70, 128/87, and 133/80 mm Hg, respectively), the blood pressure curves show dramatic changes over time. These changes are mainly explained by a shift of reflected waves toward systole and their consecutive merging with the incident pressure wave that is generated by the heart. Arrows indicate reflected pressure waves.

Abbreviations: S, systole; D, diastole.
respectively. ESH/ESC guidelines7 suggest that central sBP measurement may be useful in young individuals with isolated systolic hypertension: despite having a high brachial sBP, central sBP for some of them is low due to excessive amplification of the central pressure wave. Drug treatment may be unnecessary for these individuals.45

Wave reflections

The ejecting heart does not only propel the blood column, but also initiates a pressure wave, travelling in the wall of the aorta and the arteries towards the periphery. At locations with impedance mismatch (bifurcations), some of the energy is reflected and travels back towards the ascending aorta (and continues into carotid artery, subclavian artery, etc).46 As the human arterial system is only 1-2 meters long and as wave speed (PWV) is roughly 5-15 m/s, the antegrade and the reflected waves merge during the cardiac cycle. This superimposition of the two waves causes prominent and visible changes to the waveforms of the aorta and peripheral arteries, which change with aging: in younger individuals, propagation of the pressure wave occurs at a lower PWV, and, thus, the reflected wave will return to the ascending aorta mainly in diastole (and will positively affect coronary perfusion). With increasing age, PWV rises, and the reflected wave is shifted more and more towards systole (and increases left ventricular afterload) (Figure 4, page 395). The technique of pulse waveform analysis (PWA), developed by Michael O’Rourke and coworkers,46 utilizes these changes (Figure 5): an early systolic shoulder is identified mathematically on the upstroke of the pulse wave, which is thought to correspond exclusively to the forward wave (P1). The following inflection point is due to the merging of the forward wave with the incoming reflected wave, and the second systolic peak (P2) is due to the maximum effect of the reflected wave on the central pressure contour. Wave reflection thus can be quantified by (P2-P1), called augmented pressure (AP). AP is often related to pulse pressure (PP), and their ratio is the augmentation index (Aix = AP/PP).

As the pulse contour (and, thus, Aix and AP) depends not only on the magnitude, but also on the timing of wave reflection in relation to the duration of left ventricular systole (determined among other things by heart rate and systolic function), wave separation analysis (WSA) has been developed, using simultaneously acquired pressure and flow waves at the same location to separate the pressure wave into its forward (Pf) and backward (Pb) components (Figure 5).47,48 In addition, reflection magnitude (RM), the ratio of Pf/Pb, can be calculated. Whereas pressure waves can be easily recorded, it is inconvenient in clinical practice to record flow waves simultaneously. As a substitute, triangular,49 averaged,50 or model-derived flow waveforms51 have been developed and clinically validated (ie, outcome studies have shown the additive predictive values of WSA-derived measures of wave reflection). A further advanced method is wave intensity analysis (WIA), where a time-domain based analysis of simultaneously acquired pressure and flow waves yields forward and backward compression and decompression waves and wave reflection index.52
All analyses are typically performed at central arteries (aorta and carotid artery). For the latter, waveforms can be used directly; whereas aortic waveforms are derived from peripheral arteries, typically radial or brachial, by the use of transfer functions.46 Waveforms are acquired with tonometers or with recently introduced brachial cuffs. The latter method makes 24-hour recordings feasible46 and may facilitate the performance of large epidemiological and clinical studies as well as the dissemination of wave analysis into everyday clinical practice. Although the concept of wave reflections is scientifically sound, current guidelines do not recommend their use in clinical practice. Reasons for this include the complexity of the various measures (compared to a single value for carotid-femoral PWV), the fact that the indices cannot be used interchangeably, and their failure in some population studies.23 Consensus on the “best” parameter to assess wave reflections and simplification of their assessment (eg, with cuffs instead of tonometers) will be likely to be the next steps on the way towards the incorporation of wave reflection analysis into routine clinical practice.

References
ÉVALUATION ET INTERPRÉTATION DE LA RIGIDITÉ ARTÉRIELLE EN PRATIQUE CLINIQUE

L’hémodynamique pulsatile est de plus en plus reconnue comme le principe de base de la pression artérielle, étant fondamentalement impliquée dans la physiopathologie de l’hypertension et de ses effets délétères. La rigidité de l’aorte et des grosses artères détermine en grande partie comment la pression pulsatile et le débit, générés par le cœur, sont transmis vers la microcirculation. Ces dernières décennies, nous nous sommes de plus en plus intéressés aux mesures spécifiques croisantes de l’hémodynamique pulsatile. La pression pulsée brachiale, estimation brute de la rigidité artérielle, peut être obtenue facilement avec un simple brassard, en soustrayant la pression artérielle brachiale à la pression artérielle basse du pouls à la main. Les pressions systolique centrale (aortique) et pulsée sont probablement plus étroitement liées à la lésion et au pronostic d’un organe mais leur mesure est plus complexe ; il faut résoudre plusieurs problèmes, dont la calibration des systèmes et la standardisation des méthodes, avant de les intégrer largement dans la pratique quotidienne. Les réflexions d’onde de pouls venant de la périphérie font partie intégrante de la courbe de la pression artérielle. Évaluables par différentes techniques, elles ont montré leur puissance pronostique de façon récurrente. Encore une fois, un consensus sur les questions méthodologiques et la simplification des mesures doit précéder la pratique clinique. La vitesse de l’onde de pouls (VOP), mesure de la rigidité artérielle locale, est une mesure relativement simple et fiable. Sa valeur pronostique indépendante a été régulièrement démontrée dans de nombreuses études si l’aorte est comprise dans l’axe artériel (comme l’onde de pouls carotido-fémorale). Les recommandations ESH/ESC les plus récentes citent donc l’onde carotido-fémorale comme mesure de lésion infraclinique d’un organe. Une valeur seuil de 10 m/s a été proposée d’après des données disponibles et un consensus sur les détails des mesures.

Keywords: arterial stiffness; pulse wave velocity; wave reflections; central blood pressure

Évaluation et interprétation de la rigidité artérielle en pratique clinique

L’hémodynamique pulsatile est de plus en plus reconnue comme le principe de base de la pression artérielle, étant fondamentalement impliquée dans la physiopathologie de l’hypertension et de ses effets délétères. La rigidité de l’aorte et des grosses artères détermine en grande partie comment la pression pulsatile et le débit, générés par le cœur, sont transmis vers la microcirculation. Ces dernières décennies, nous nous sommes de plus en plus intéressés aux mesures spécifiques croisantes de l’hémodynamique pulsatile. La pression pulsée brachiale, estimation brute de la rigidité artérielle, peut être obtenue facilement avec un simple brassard, en soustrayant la pression artérielle brachiale à la pression artérielle basse du pouls à la main. Les pressions systolique centrale (aortique) et pulsée sont probablement plus étroitement liées à la lésion et au pronostic d’un organe mais leur mesure est plus complexe ; il faut résoudre plusieurs problèmes, dont la calibration des systèmes et la standardisation des méthodes, avant de les intégrer largement dans la pratique quotidienne. Les réflexions d’onde de pouls venant de la périphérie font partie intégrante de la courbe de la pression artérielle. Évaluables par différentes techniques, elles ont montré leur puissance pronostique de façon récurrente. Encore une fois, un consensus sur les questions méthodologiques et la simplification des mesures doit précéder la pratique clinique. La vitesse de l’onde de pouls (VOP), mesure de la rigidité artérielle locale, est une mesure relativement simple et fiable. Sa valeur pronostique indépendante a été régulièrement démontrée dans de nombreuses études si l’aorte est comprise dans l’axe artériel (comme l’onde de pouls carotido-fémorale). Les recommandations ESH/ESC les plus récentes citent donc l’onde carotido-fémorale comme mesure de lésion infraclinique d’un organe. Une valeur seuil de 10 m/s a été proposée d’après des données disponibles et un consensus sur les détails des mesures.

Keywords: arterial stiffness; pulse wave velocity; wave reflections; central blood pressure
Value of arterial stiffness in predicting cardiovascular events and mortality

by P. Jankowski, Poland

There is a considerable interest in refining cardiovascular risk prediction in order to better target preventive therapy. Arterial stiffness is a well-recognized predictor of cardiovascular morbidity and mortality. Several hypotheses that may explain the association between arterial stiffness and cardiovascular risk are described in the literature. Out of a number of studied parameters, aortic pulse wave velocity is the most validated method used to quantify arterial stiffness noninvasively and is considered today the gold standard index, given its strong prediction of cardiovascular events and mortality. The predictive value of pulse wave velocity has been shown in a broad range of patients, although current evidence suggests a stronger association with the risk of cardiovascular events in younger subjects and in high-risk patients. Current evidence also suggests that the estimation of arterial wall compliance (especially using pulse wave velocity) may improve risk stratification, which is especially important in subjects with intermediate risk.

Medicographia. 2015;37:399-403 (see French abstract on page 403)

Mechanism of arterial stiffness – cardiovascular risk association

Arterial stiffness and its hemodynamic consequences are established predictors of cardiovascular mortality and morbidity. Arterial stiffness is positively associated with systolic hypertension, coronary artery disease, stroke, and heart failure, which are the leading causes of mortality in the developed world. It is important to understand the mechanism of increased cardiovascular risk in subjects with increased arterial stiffness. The literature suggests several concepts to explain this mechanism. The first concept is the relation between arterial wall stiffness and lower diastolic and higher systolic blood pressure in the ascending aorta. Low diastolic blood pressure is related to low perfusion pressure through myocardium and, therefore,
to reduced coronary perfusion. Indeed, it has been suggested that myocardial revascularization procedures may transform the “J” shape of the relation between diastolic pressure and cardiovascular risk into a more linear relation. On the other hand, higher systolic blood pressure increases afterload and the oxygen demand of the myocardium and contributes to left ventricular hypertrophy. The net effect is that an increase in arterial stiffness (higher pulse wave velocity [PWV] and higher central pulse pressure [PP]) leads to an imbalance between myocardial oxygen demand and supply, and hence ischemia. This has been proven invasively by Leung and colleagues, who observed a strong inverse relationship between coronary blood flow and PWV/central PP in patients following a coronary intervention. All these effects may increase cardiovascular risk.

The second concept is that increased stiffness is a symptom of “disease” of the arterial wall. Indeed, structural changes contributing to an increase in arterial stiffness include fragmentation of elastin, increased deposition of collagen, arterial calcification, glycation of both elastin and collagen fibers, and cross-linking of collagen molecules by advanced glycation end products. In line with this concept, atherosclerotic plaques develop more easily in diffusely “diseased” arterial walls, leading to coronary and cerebrovascular events. Indeed, it has been hypothesized that the high predictive value of PWV results from the cumulative influence/damage of cardiovascular risk factors on the arterial wall over long periods. This explanation could also elucidate why aortic stiffness is able to predict cardiovascular risk independently of classic risk factors. Indeed, the intensity of risk factors may change over time leading to diminution of the association between risk factors and cardiovascular risk in cross-sectional, and even observational, studies. Recently, a relation between arterial wall stiffness and carotid intraplaque hemorrhage was found, which was partly independent of PP.

The third concept is that high arterial stiffness increases the pulsatile component of blood pressure, especially central pressure, which in turn leads to the development of atherosclerosis and its complications as well as to damage of microvasculature. The influence of cyclic stretch (due to cyclic changes in blood pressure) on the arterial wall has been documented at every stage in the development of atherosclerosis. Apart from mediating atherosclerosis progression and plaque instability, the pulsatile component of blood pressure is the main mechanism associated with plaque rupture and, consequently, with acute coronary syndromes and other vascular complications. Moreover, PP is the strongest determinant of intraplaque hemorrhages.

The correlation between increased arterial wall stiffness and the presence of risk factors and diseases related to increased cardiovascular risk, eg, diabetes, chronic kidney disease, diffuse atherosclerosis, etc, is the fourth concept. It is not always possible to account for all these factors and diseases when performing multivariate analysis. Other explanations, including damage of microvasculature leading among other things to slow coronary flow as well as to kidney failure (and indirectly to progression of atherosclerosis and its complications), are also possible.

Although structural changes related to increased arterial wall stiffness may be quantified pathologically, the clinical evaluation of arterial mechanical properties is more complex and a complete description of the stress–strain relationship of arteries in vivo is not possible owing to uncertainties arising from nonlinear behavior, viscoelasticity, anisotropy, active tone, residual stresses, and tethering. Many parameters have been proposed to quantitatively represent arterial stiffness and distensibility, such as pressure-strain elastic modulus, stiffness index, PWV, and characteristic impedance. A number of studies have shown that various indices of arterial compliance are related to cardiovascular risk. Although arterial stiffness is a well-recognized predictor of cardiovascular events, the large number of parameters employed to define arterial stiffness and the differing modalities used to assess aortic mechanics have somewhat hampered the current clinical impact of these measures.

**Arterial stiffness and cardiovascular risk**

Because some studies suggest that the predictive value of aortic stiffness may be slightly better than local (eg, carotid artery) stiffness and because of the ease of measurement, aortic (carotid-femoral) PWV has been proposed as the best surrogate to evaluate arterial stiffness, especially in everyday clinical practice. Indeed, the predictive value of PWV has been demonstrated in a number of studies. Many devices measure arterial stiffness, but methodological limitations need to be borne in mind. Some devices measure PWV of an arterial segment in mixed elastic and muscular arteries, thereby weakening their predictive value. Only the compliance of elastic arteries, and not muscular arteries, has been shown to be predictive of cardiovascular morbidity and mortality. Others use methods other than PWV and are frequently and substantially confounded by other factors. Carotid-femoral (aortic) PWV is the most validated method to noninvasively quantify arterial stiffness and is today considered the gold standard index, given its strong prediction of cardiovascular events and mortality.

The first evidence for the predictive value of carotid-femoral PWV was published in 1999. Subsequently a number of prospective studies were published. Almost all of them performed multivariate analysis. Other explanations, including damage of microvasculature leading among other things to slow coronary flow as well as to kidney failure (and indirectly to progression of atherosclerosis and its complications), are also possible.

**SELECTED ABBREVIATIONS AND ACRONYMS**

- CAVI: cardio-ankle vascular index
- PP: pulse pressure
- PWV: pulse wave velocity
The relationship between aortic PWV and cardiovascular risk is present in a variety of subjects, including those with the highest cardiovascular risk: patients with chronic kidney disease, or those with coronary artery disease. Choi et al showed that the risk of cardiovascular events increased by 118% in patients with end-stage renal disease. However, they failed to show such an association when all included in the meta-analysis studies were analyzed. On the other hand, age was related to the predictive value of PWV in a broad range of patients in a more recent meta-analysis by Ben-Shlomo et al. In younger participants, PWV was more strongly related to the risk of coronary artery disease, stroke, and cardiovascular and all-cause mortality (Table II). It should, however, be underlined that the absolute risk increase with increasing PWV may be greater in older patients due to their much greater cardiovascular risk.

The median value of aortic PWV in healthy subjects varies from 6.1 m/s in persons aged <30 years to 10.6 m/s in subjects >70 years of age. Although the relationship between aortic compliance and the risk of cardiovascular events is continuous, a threshold of 10 m/s has been suggested for use in clinical practice as a sign of significant alteration of aortic function.

Brachial-ankle PWV has also been studied extensively. Vlachopoulos et al summarized the results of 18 studies involving 8169 participants and showed that when brachial-ankle PWV increased by 1 m/s, the risk of total mortality, cardiovascular mortality, and total cardiovascular events increased by 6%, 13%, and 12%, respectively. As with aortic PWV, age was inversely related to the predictive value of brachial-ankle PWV in patients with end-stage renal disease.

The Mobil-O-Graph system uses a less direct way of estimating PWV. Recently, an association between PWV as determined using the Mobil-O-Graph system and total mortality in patients with chronic kidney disease was shown, although, probably due to small number of study participants, the association became nonsignificant after adjustment for age.

The authors of the most recent meta-analysis were also able to show that the use of aortic PWV measurements may improve risk stratification, especially in subjects with intermediate cardiovascular risk. However, the importance of choosing the method of aortic PWV measurement should be emphasized. In fact, cardiovascular risk stratification may change in up to 40% of patients depending on the choice of device. Many experts insist that the issue of device standardization needs to be resolved before the technique can be used widely in everyday clinical practice.
Taking into account the predictive value of PWV, it should be mentioned that European Society of Hypertension/European Society of Cardiology experts have not recommended PWV measurement as a required test in patients with hypertension mainly due to the limited availability of PWV measurement outside research centers. It should also be noted that the methodology of PWV measurement has not yet been clearly standardized. The most commonly used techniques are operator-dependent, which limit the generalizability of findings derived from research studies. Additionally, some experts insist that the improvement in cardiovascular prediction obtained by determining PWV does not always justify the costs related to PWV measurement. Indeed, the American College of Cardiology and the American Heart Association do not recommend the use of arterial stiffness measures in clinical practice.

As previously mentioned above, many parameters have been proposed to quantitatively represent arterial stiffness. Of these, PWV is the one that has been most frequently applied to clinical medicine. However, some experts insist that PWV is dependent on blood pressure at the time of measurement, and is therefore not appropriate as a parameter for the clinical evaluation of arterial stiffness. Against this particular backdrop of uncertainty, stiffness index is especially interesting.

Stiffness index is an index reflecting arterial stiffness without the influence of blood pressure. Recently, this parameter was used to develop a new arterial stiffness index, called the cardio-ankle vascular index (CAVI). Although this index is obtained from the PWV between the heart and the ankle, it is essentially similar to the stiffness index; blood pressure changes therefore influence CAVI to a much lesser extent than PWV. CAVI is being extensively used in clinical medicine as a measure for the evaluation of cardiovascular diseases and risk factors related to arteriosclerosis. Today, there are only a few published studies dealing with the relationship between cardiovascular risk and CAVI. It has also been shown that serial measurements of CAVI provide important prognostic information.

Other methods, eg, the timing of Korotkoff sounds (QKD method), have also been proven to be related to the risk of cardiovascular events; however, the evidence base is much smaller compared to that for the methods described above.

Although it is known that reduction in arterial wall compliance has a negative impact on prognosis, an important issue is whether an improvement in arterial compliance translates into a reduction in cardiovascular events. There is only limited evidence on this issue. Lifestyle interventions can reduce arterial stiffness and/or wave reflections. Physical activity is especially effective in reducing arterial wall stiffness. Also, a low-salt diet improves arterial distensibility by reducing BP as well as by direct effects that are independent of BP changes. Direct beneficial effects of fish oils have been reported by several researchers. Weight loss has also been suggested to improve arterial wall compliance. Some researchers have proposed that one of the potential “antiaging” benefits of prolonged caloric restriction is a reduction in the rate at which arterial stiffness increases with age. Most of the mentioned lifestyle interventions are related to improved survival, but it is not known to what extent lifestyle changes decrease cardiovascular risk through reduction in arterial stiffness.

Another important, related question is whether drug-induced improvement in arterial compliance translates into improved prognosis. Although a lot of authors have claimed to have shown drug-induced improvement in arterial compliance, the truth is that in most of these cases, drug-induced blood pressure changes in these studies were not taken into account. Therefore, it is not possible to differentiate between blood pressure–dependent and blood pressure–independent effects. Nevertheless, Guerin et al have shown that a lack of decrease in PWV in response to blood pressure reduction was a strong independent predictor of mortality in patients with end-stage renal disease.

Conclusions
Arterial stiffness is a well-recognized predictor of cardiovascular morbidity and mortality. Aortic PWV is the most validated method used to quantify arterial stiffness noninvasively and is today considered the gold standard index, given its strong prediction of cardiovascular events and mortality. The predictive value of PWV has been shown in a broad range of patients, although current evidence suggests a stronger association in younger subjects and high-risk patients. Estimation of arterial wall compliance, especially using PWV, may improve risk stratification, which is especially important in subjects with intermediate risk.

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aortic stiffness attenuation on survival of patients in end-stage renal failure.

Keywords: blood pressure; hypertension; atherosclerosis; coronary artery disease; cardiovascular risk; arterial stiffness; arterial compliance; risk factor; pulse pressure

INTÉRÊT DE LA RIGIDITÉ ARTÉRIELLE DANS LA PRÉDICTIO

Affiner la prédiction du risque cardio-vasculaire est d’un grand intérêt afin de mieux cibler le traitement préventif. La rigidité artérielle est un prédicteur reconnu de morbidité et de mortalité cardiovasculaires. La littérature décrit plusieurs hypothèses pouvant expliquer l’association entre rigidité artérielle et risque cardio-vasculaire. La vitesse de l’onde de pouls aortique, parmi un grand nombre de paramètres, est la meilleure méthode pour mesurer la rigidité artérielle de façon non invasive. Elle est considérée aujourd’hui comme la méthode de référence, grâce à son fort pouvoir de prédiction des événements et de la mortalité cardio-vasculaires. La valeur prédictive de la vitesse de l’onde de pouls a été démontrée chez un grand nombre de patients, les données actuelles suggérant une association plus forte avec le risque d’événements cardio-vasculaires chez les sujets plus jeunes et les patients à haut risque. D’après ces nouvelles données, l’estimation de la compliance de la paroi artérielle (en particulier en utilisant la vitesse de l’onde de pouls) peut améliorer la stratification du risque, particulièrement importante chez les sujets à risque intermédiaire.
Aortic stiffness is an indicator of target-organ damage in hypertensive patients and a prominent biomarker of cardiovascular risk. Differences in the effects of several pharmacological agents on arterial stiffness form a partial basis for explaining the results or large prospective survival studies that demonstrated superior cardiovascular risk reduction with RAAS blockers and calcium channel blockers compared with diuretics and β-blockers. Arterial stiffness is emerging as a valuable surrogate end point and treatment target.

**Antihypertensive strategies to reverse arterial wall modifications**

by C. Vlachopoulos and D. Terentes-Printzios, Greece

Among other promising biomarkers of cardiovascular disease that are related to arterial wall structure and function, aortic stiffness has proven to be an important asset for the assessment of cardiovascular risk. While hypertension may lead by itself to arterial stiffening, it is aortic stiffness that primarily leads to the development of hypertension. Of the different approaches for estimating arterial stiffness, aortic stiffness assessed by carotid-femoral pulse wave velocity has emerged as the gold standard method because of the wealth of evidence demonstrating its association with cardiovascular hard end points in different populations and disease states, including hypertensive populations, over and beyond traditional risk factors. Recent studies with pharmacological and nonpharmacological antihypertensive interventions suggest that aortic stiffening is a dynamic and modifiable target that could be useful for identifying hypertensive patients at high risk for cardiovascular events, monitoring treatment efficacy, and serving as a treatment target in hypertension. Of the antihypertensive agents available, renin-angiotensin-aldosterone system blockers are the most effective in reducing arterial stiffness in a blood pressure–independent manner. Calcium channel blockers exert beneficial effects on arterial stiffness. Data on β-blockers are equivocal; β-blockers with vasodilating properties show a superior overall profile. Diuretics may reduce arterial stiffness, mainly through blood pressure reduction. The impact of attenuating arterial stiffness on prognosis has been shown in end-stage renal disease, but more studies are warranted in other disease states and populations.

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**Aortic stiffness in hypertension: why we should care**

Many arterial biomarkers, such as ankle-brachial index, carotid intima-media thickness, and endothelial function, have been proposed for clinical use in hypertensive populations. Of these, the biomarker that has shown essential pathophysiological, clinical, and prognostic links with hypertension is arterial stiffness. While a wealth of data relates to aortic stiffness, promising results have also been produced by assessment of arterial stiffness in other arteries, such as the carotid and femoral. Aortic pulse wave velocity (PWV), considered the “gold-standard” measure of arterial stiffness, can be measured easily and noninvasively by a variety of methods. The mechanisms of aortic stiffening are complex and depend on the underlying disease. Age and blood pressure are the major determinants of aortic stiffness. The relationship between aortic stiffness and hyperten-
sion is bidirectional. Hypertension can cause stiffening through both functional and structural mechanisms. Stiffening of elastic tubes (arteries in our case) is increased as distending pressure increases due to hydraulic laws. From a structural standpoint, while thinning, splitting, fraying, and fragmentation of elastic fibers are consequences primarily of aging, sustained hypertension is a cause of the rearrangement of arterial wall elements and changes in their relative composition. Evidence from the Framingham Heart Study suggests that higher blood pressure levels can accelerate aortic stiffening, giving rise to a vicious cycle of accelerated hypertension and further stiffening of large arteries.10 Moreover, annual increases in PWV are higher in hypertensive subjects, suggesting early development of stiffness.11 However, the other side of the bidirectional relationship between aortic stiffness and hypertension is more intriguing and important. Indeed, substantial data show that aortic stiffening in normotensive individuals was a predictor of increased systolic blood pressure and development of hypertension.12

PWV has been shown in large studies to be a marker of increased cardiovascular risk and to improve risk prediction in addition to, and beyond, traditional risk factors.3-5 One of the first studies on the prognostic role of PWV was conducted in hypertensive patients, and it demonstrated the independent role of PWV in predicting both all-cause and cardiovascular mortality.13 In the Framingham Heart Study, higher PWV was found to be associated with a 48% increase in the risk of incident cardiovascular events.4 In a meta-analysis of 17 published studies,6 aortic PWV data from 15 877 subjects followed up for a mean of 7.7 years were compiled. Subjects from the general population and patients with hypertension, diabetes, end-stage renal disease, and coronary artery disease were included. Aortic stiffness was found to be a strong predictor of future cardiovascular events and all-cause mortality; an increase in aortic PWV of 1 m/s was associated with an increase in the risk of total cardiovascular events, cardiovascular mortality, and all-cause mortality of 14%, 15%, and 15%, respectively, after adjustment for age, gender, and cardiovascular risk factors. The results of this meta-analysis were confirmed by another recent meta-analysis5 with individual data from 17 635 subjects, where the addition of PWV improved risk prediction by 13% (Figure 1).14 Of note, reference values and cut-off points, along with a standardized method of PWV assessment, were recently published to facilitate the clinical integration of aortic stiffness in everyday practice.1,15,16 Taken together, this piece of evidence led the European Society of Cardiology/European Society of Hypertension to recommend aortic PWV for the evaluation of the hypertensive patient (level of evidence Ila).17

From a therapeutic standpoint, aortic stiffness is a worthwhile treatment target. Several studies have investigated the effects of different pharmaceutical agents on aortic stiffness.18-20 These studies can be grouped according to the length of intervention, as acute, short/medium-term (<3 months), or long-term (>3 months). Earlier effects are usually due to smooth muscle cell relaxation, while longer-term effects involve distinct components of the arterial wall and changes in the geometry of the vessel. Of special interest are comparative studies between different classes of agents that are scarce and, in most cases, underpowered to provide conclusive re-

### Table: Summary data meta-analysis

<table>
<thead>
<tr>
<th>RR</th>
<th>95% CI</th>
<th>RR (95% CI)</th>
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<tbody>
<tr>
<td>Total CV events</td>
<td>1.41</td>
<td>1.25-1.54</td>
</tr>
<tr>
<td>CV mortality</td>
<td>1.47</td>
<td>1.29-1.67</td>
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<tr>
<td>All-cause mortality</td>
<td>1.36</td>
<td>1.23-1.50</td>
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<table>
<thead>
<tr>
<th>RR</th>
<th>95% CI</th>
<th>RR (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Total CV events</td>
<td>1.45</td>
<td>1.30-1.61</td>
</tr>
<tr>
<td>CV mortality</td>
<td>1.41</td>
<td>1.27-1.56</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.22</td>
<td>1.16-1.27</td>
</tr>
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**Figure 1.** Relative risk (RR) and 95% confidence interval (CI) for a 1-standard-deviation increase in aortic pulse wave velocity and clinical events.

**Abbreviation:** CV, cardiovascular.

results. In general, renin-angiotensin-aldosterone system (RAAS) blockers and calcium channel blockers have produced better results than diuretics and β-blockers.\(^\text{18}\)

Despite strong pathophysiological links, the question of whether amelioration of aortic stiffening leads to an improvement in prognosis has not yet been proven beyond doubt. To date, there has only been one study,\(^\text{21}\) in end-stage renal disease patients, showing that improvement in outcome was mediated through an improvement in aortic stiffness (Figure 2).\(^\text{21}\) More studies are needed to confirm these promising results, and ongoing studies such as SPARTE (Stratégie de Prévention Cardiovasculaire Basée sur la Rigidité Arterielle) will further elaborate the role of PWV as a therapeutic target.\(^\text{22}\)

Summarized below is current evidence on the effect of different antihypertensive agents on arterial stiffness, with emphasis on pathophysiological mechanisms. Areas for future research have also been highlighted.

**Pathophysiological mechanisms of arterial stiffness in hypertension and in antihypertensive treatment**

When trying to put the effects of drugs into clinical perspective, several issues should be considered.

◆ **Interpretation of effects**

First, duration of drug administration is of the essence.\(^\text{18-20}\) Acute effects of drug intervention should not be extrapolated to imply long-term efficacy, and it should not be forgotten that long-term administration may be required to induce changes. Equally important is the dose of the administered drug; favorable effects are usually observed with higher rather than lower doses.\(^\text{23}\)

◆ **Pressure dependency/independency**

The changes that a drug induces in the stiffness of the aorta (an elastic artery) may be indirect, ie, due to reduction in blood pressure (pressure-dependent), since elastic tubes reduce their stiffness when the distending pressure inside them is reduced. Blood pressure reduction in this case occurs in part through a decrease in wave reflections in response to the dilation of small resistant arteries. On the other hand, effects may be direct (pressure-independent), occurring via alteration of arterial wall elastic components, ie, medial smooth muscle cells (mainly acute changes) or elastin and collagen (chronic changes). Pressure-dependent effects are usually acute, while pressure-independent effects occur with long-term treatment. Contrary to elastic-type arteries, muscular arteries (such as the brachial artery) contribute a small percentage of total arterial stiffness. Furthermore, their stiffness is less prone to increase with age, unlike larger elastic-type arteries. However,

![Figure 2. Changes in mean blood pressure (solid circle) and aortic pulse wave velocity (open circle) from inclusion until the end of follow-up in survivors and non-survivors with end-stage renal disease.](image)

**Effects at the cellular level**

Depending on the specific pharmaceutical agent, the underlying mechanism at the cellular level varies, and often the result is a combination of different mechanisms.\(^\text{18,20}\) Low-grade inflammation has been associated with both chronic arterial stiffening (via inflammatory markers/mediators) and acute arterial stiffening (via cause-and-effect associations).\(^\text{24}\) Interestingly, RAAS blockers may additionally exert anti-inflammatory effects. Moreover, endothelial function has an important regulatory role in PWV, thus improvement of endothelial function by drugs such as RAAS blockers may explain their effects. Genetic predisposition may also play its part, since findings that a reduction in PWV in response to angiotensin-converting enzyme (ACE) inhibition depends on AT\(_1\) (angiotensin II re-
ceptor type 1) gene polymorphisms support the involvement of genetic background. Collagen turnover has also been implicated, as angiotensin II stimulates the production of various types of collagen fibers. Inhibition of aldosterone, a potent activator of fibrosis, may also be involved.

Effects of different antihypertensive agents on arterial stiffness

Despite the fact that all antihypertensive agents have a direct and substantial effect on lowering blood pressure, their effects on arterial stiffness are more complex (Table I, Figure 3).

- **Renin-angiotensin-aldosterone system (RAAS) blockade**
- **ACE inhibitors**

ACE inhibitors are the oldest and best-studied class of RAAS inhibitors. Acute beneficial effects of ACE inhibitors have been well established. As regards mid- and long-term effects, a significant body of studies suggests that the reduction of aortic stiffness may be, in part, independent of blood pressure lowering in hypertensive patients. Moreover, recent studies have shown that blood pressure–independent changes in aortic stiffness are feasible with most antihypertensive drugs, but predominantly with RAAS inhibitors, and that these changes are amplified with a higher dose and long-term treatment. Plausible explanations for these results are the delayed response to the long-term normalization of blood pressure and cardiovascular risk factors and the slow turnover rate of the extracellular matrix with arterial remodeling. Results extend to all types of arteries and are generally not related to a specific agent. Perindopril reduced stiffness of the carotid artery in hypertensive patients with type 2 diabetes with long-term administration, a finding that was dose-dependent and blood pressure–independent, indicating favorable effects with high-dose perindopril via inward remodeling. These results were corroborated by two meta-analyses that showed that long-term administration of treatment, including ACE inhibitors, has a beneficial blood pressure–independent effect on aortic stiffness (Figure 4, page 408).

Two essential prospective long-term studies investigated whether arterial stiffness and wave reflections indices had an effect on cardiovascular events (in the CAFE [Conduit Artery Function Evaluation] study, an ancillary study of ASCOT [Anglo-Scandinavian Cardiac Outcomes Trial]) or surrogate end

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**Table I.** Antihypertensive treatments and their effects on arterial stiffness.

<table>
<thead>
<tr>
<th>Antihypertensive treatment</th>
<th>Type of effect on arterial stiffness</th>
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<td></td>
<td>Deleterious</td>
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<td>ACE inhibitors</td>
<td>●</td>
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<tr>
<td>AT1 receptor blockers</td>
<td>●</td>
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<tr>
<td>Direct renin inhibitors</td>
<td>●</td>
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<tr>
<td>Calcium channel antagonists</td>
<td>●</td>
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<tr>
<td>Diuretics</td>
<td>●</td>
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<tr>
<td>Vasodilating β-blockers</td>
<td>●</td>
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<tr>
<td>Nonvasodilating β-blockers</td>
<td>●</td>
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<tr>
<td>Aldosterone antagonists</td>
<td>●</td>
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<tr>
<td>Nitrates</td>
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<tr>
<td>PDE5 inhibitors</td>
<td>●</td>
</tr>
<tr>
<td>α-Blockers</td>
<td>●</td>
</tr>
</tbody>
</table>

Key for effect on arterial stiffness: beneficial, ●; neutral, ●; deleterious, ●.

Abbreviations: ACE, angiotensin-converting enzyme; AT1, angiotensin II receptor type 1; PDE5, phosphodiesterase type 5.


Figure 3. Effect of different classes of antihypertensive agents on arterial stiffness. The width of the arrows represents the size effect on arterial stiffness and the darkness of the arrows, the degree of blood pressure–independent effects on top of effects dependent on blood pressure reduction (darker arrows imply more blood pressure–independent effects).

femoral PWV at 2 months, an effect that was still present 6 months after starting treatment. Other studies with ACE inhibitors have also shown reductions in large artery stiffness independent of blood pressure change, implying a beneficial class effect. A meta-analysis confirmed that ACE inhibitors are associated with beneficial effects on PWV as well as on aortic augmentation index (AIx), an index of wave reflections.
Antihypertensive therapy and arterial wall modifications – Vlachopoulos and Terentes-Printzios

Figure 4. Reductions in pulse wave velocity according to hypertensive drug class in long-term trials. *P<0.05 versus placebo.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; BB, β-blocker; CCB, calcium channel blocker.


Figure 5. Mean brachial pulse pressure (solid symbols) and mean derived central aortic pulse pressure (open symbols) versus time for patients randomized to atenolol/hydrochlorothiazide (circles) or amlodipine/perindopril (triangles) in the CAFE (Conduit Artery Function Evaluation) study.

Abbreviations: AUC, area under curve; PP, pulse pressure.


results underline that aortic stiffness and wave reflections do not always change in parallel or to the same degree, and they may have different clinical value. In the REASON study, the combination of perindopril/indapamide produced larger decreases in systolic blood pressure than atenolol. This was attributed to superior reduction in wave reflections with the perindopril/indapamide combination, as reduction in PWV was similar with the two regimens. This hemodynamic superiority of the combination is believed to translate into survival improvement in hypertensive patients with high cardiovascular risk.

Angiotensin II receptor type 1 (AT₁ receptor) blockers

AT₁ receptor blockers also improve aortic stiffness to an extent that is comparable, and often additive, to that of ACE inhibitors. Data support a reduction in arterial stiffness independent of blood pressure changes with both short- and long-term treatment. However, it must be stressed that despite the fact that combining ACE inhibitors and AT₁ receptor blockers produced appealing aortic stiffness results in hypertension, these results were not associated with clinical benefit in large survival studies like ONTARGET (ONGOing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial), due to the increased risk of adverse reactions with the drugs. On the other hand, a combination of an AT₁ receptor blocker with a calcium channel blocker has shown evident superiority compared with a β-blocker/calcium channel blocker combination.

Direct renin inhibitors

The direct renin inhibitor aliskiren has been shown to decrease aortic stiffness when administered in hypertensive patients.
However, not only does it not seem to provide any additional clinical prognostic benefit beyond that of existing antihypertensive therapies, but it might even be harmful.

**Calcium channel blockers**

Calcium channel blockers differ substantially to ACE inhibitors in their mechanisms of action, and the effect of calcium channel blockers on aortic stiffness compared to ACE inhibitors is somewhat smaller. Dihydropyridines are the best-studied agents, especially amlodipine.

**Diuretics**

Studies on the effect of diuretics on aortic stiffness have provided mixed results, both neutral and positive. Diuretics appear to reduce wave reflections; however, this has not been shown in all studies. In elderly patients with isolated systolic hypertension, hydrochlorothiazide in combination with amiloride was equally effective to ACE inhibitors in reducing arterial stiffness; this effect was mediated through blood pressure reduction. While the combination of diuretics with AT\(_1\) receptor blockers or ACE inhibitors has an additive effect in improving arterial stiffness, the combination of AT\(_1\) receptor blockers or ACE inhibitors with calcium channel blockers seems to provide greater improvement.

Aldosterone levels are associated with arterial stiffness in hypertensive patients. Eplerenone, a highly selective aldosterone antagonist, was as effective as amiodipine in reducing PWV in elderly hypertensive patients. Another aldosterone antagonist, spironolactone, has been shown to reduce aortic PWV in a partially blood pressure–independent manner without changing brachial artery stiffness. The beneficial effect of spironolactone has been confirmed in dilated cardiomyopathy, as well as in chronic kidney disease.

**\(\beta\)-Blockers**

Most studies suggest that \(\beta\)-blockers reduce aortic stiffness in a pressure-dependent way, most likely due to an increase in systolic ejection time and a decrease in dP/dt. It is easier for an aorta to accommodate a stroke volume that is ejected at a lower pace and does not lead to an increase in distending pressure. However, \(\beta\)-blockers increase wave reflection indices by increasing systolic and diastolic period, thus allowing the reflected wave to return to the aorta at a relatively earlier point in the cardiac cycle (in systole instead of diastole). Additionally, they may increase wave reflections by peripheral vasoconstriction, as with atenolol. Nevertheless, data suggest that the case may be different for \(\beta\)-blockers with direct vasodilating properties (carvedilol, dilevalol) or those that are nitric oxide (NO) donors, such as nebivolol. In several studies, nonvasodilating \(\beta\)-blockers, such as atenolol, have been shown to be less successful than vasodilating drugs—such as calcium channel blockers, RAAS antagonists, or other \(\beta\)-blockers such as nebivolol (a selective \(\beta\)\(_1\)-receptor blocker with a NO-potentiated vasodilatory effect)—in reducing wave reflections and central hemodynamics, although aortic stiffness seems to be similarly reduced with all these drug classes.

The REASON trial, which compared a perindopril/indapamide combination with atenolol, showed that normalization of brachial systolic blood pressure is achieved with a significantly greater reduction in carotid systolic blood pressure after a 12-month treatment with the combination. This suggests that brachial measurements tend to underestimate the effect of the combination on aortic systolic pressure. In the same study, the perindopril/indapamide combination was associated with a greater loss in left ventricular mass, compared with atenolol, and this was related to carotid, but not brachial, blood pressure.

**Other antihypertensive agents**

Data on \(\alpha\)-blockers are scarce. However, doxazosin, the most investigated drug in this class, showed a modest favorable effect on arterial stiffness. Nitrates have a beneficial effect, predominantly on muscular arteries. Sildenafil and vardenafil, phosphodiesterase type 5 inhibitors prescribed for erectile dysfunction and primary pulmonary hypertension, produced mainly beneficial results in decreasing aortic stiffness after short- and medium-term administration, respectively.

Effect of antihypertensive treatment on arterial stiffness and prognosis

While aortic stiffness provides useful prognostic information regarding cardiovascular events, evidence for the value of aortic stiffness for the reduction in cardiovascular events in patients on treatment is less well founded. The relevant, key question is whether a reduction in indices, such as PWV, is associated with a concomitant reduction in cardiovascular events, independently of the normalization of classic cardiovascular risk factors. To date, the only evidence for the predictive value of attenuating aortic stiffness for the reduction of cardiovascular events has been provided by Guerin et al in end-stage renal disease patients, in whom insensitivity of PWV to reduced blood pressure was an independent predictor of mortality.

Furthermore, it must be noted that in two recent studies, in which central blood pressures and AIx were used as therapeutic targets in hypertensive and heart failure patients, respectively, there were modest but clinically apparent benefits for the patients. Clearly, there is a need for studies addressing this key question in the general population, populations with risk factors, and populations with other disease states, such as hypertension (currently under investigation in the ongoing SPARTE study).

Conclusions

Aortic stiffness is an indicator of target-organ damage in hypertensive patients and a prominent biomarker of cardiovas-
New-generation treatments for hypertension: targeting the artery

cular risk. While there are ample double-blind, randomized, controlled trials attesting to the beneficial effect of pharmacological antihypertensive interventions on arterial stiffness, they suffer from a relatively small number of subjects, short follow-up periods, and lack of hard end points. Further large prospective studies with PWV-guided therapy are warranted to confirm the clinical applicability of these findings in everyday practice. Nevertheless, differences in the effects of several pharmacological agents on arterial stiffness form a partial basis for explaining the results of large prospective survival studies that demonstrated superior cardiovascular risk reduction with RAAS blockers and calcium channel blockers compared with diuretics and β-blockers. Arterial stiffness is emerging as a valuable surrogate end point and treatment target.

References
39. London GM, Asmar RG, O’Rourke MF, Safar ME; REASON Project Investigators. Mechanism(s) of selective systolic blood pressure reduction after a low-


Keywords: arterial stiffness; pulse wave velocity; wave reflections; central blood pressure; cardiovascular risk; hypertension; angiotensin

**STRATÉGIES ANTIHYPERTENSIVES POUR INVERSER LES MODIFICATIONS DE LA PAROI ARTÉRIELLE**

La rigidité aortique est un atout important pour l'évaluation du risque cardio-vasculaire, parmi d'autres biomarqueurs prometteurs de cette maladie, liés à la fonction et à la structure de la paroi artérielle. L'hypertension peut conduire par elle-même à une rigidité artérielle, mais la rigidité aortique est la principale responsable du développement de celle-ci. Parmi les différentes méthodes d’estimation de la rigidité artérielle, la rigidité aortique évaluée par la vitesse de l’onde de pouls carotido-fémorale apparaît comme la méthode de référence absolue. D’après de nombreuses donnes, elle s’associe à des critères cardio-vasculaires rigoureux dans des populations et des états pathologiques différents, comme les populations d’hypertendus, en plus et au-delà des facteurs de risque traditionnels. Des études récentes, analysant des méthodes antihypertensives pharmacologiques et non pharmacologiques, indiquent que la rigidité aortique est une cible dynamique et modifiable qui pourrait être utile pour l’identification des hypertendus à haut risque d’événements cardio-vasculaires, pour la surveillance de l’efficacité du traitement et pour servir de cible thérapeutique dans l’hypertension. Parmi les antihypertenseurs disponibles sur le marché, les antagonistes du système rénine-angiotensine-aldostérone sont les plus efficaces pour réduire la rigidité artérielle indépendamment de la pression artérielle. Les antagonistes calciques exercent des effets bénéfiques sur la rigidité artérielle. Les données sur les β-bloquants sont équivoques; ceux qui ont des propriétés vasodilatatrices ont un meilleur profil global. Les diurétiques peuvent aussi diminuer la rigidité artérielle, principalement par la diminution de la pression artérielle. L’impact de l’amélioration de la rigidité artérielle sur le pronostic a été démontré chez des patients en insuffisance rénale terminale, la plupart des études cautionnant d’autres populations ou états pathologiques.
Residual cardiovascular (CV) risk is a crucial issue in the management of hypertensive patients, whose CV-event rate is reduced, but not normalized, by effective BP control. In high-risk patients with multiple comorbidities, the CV-event rate at 10 years remains unacceptably high despite extensive use of lipid-lowering, glucose-lowering, and antiplatelet drugs. From this point of view, choosing a drug class able to provide an additional vasculoprotective benefit is a promising strategy.

In hypertension, cardiovascular (CV) risk stratification of patients is very important for choosing a therapeutic strategy. For estimating CV risk, the current European Society of Cardiology (ESC)/European Society of Hypertension (ESH) Guidelines recommend considering not only blood pressure values and target organ damage, but also the presence of other risk factors beyond hypertension. This approach is justified by the fact that associated risk factors critically influence morbidity and mortality in hypertensive patients, determining the so-called residual risk. For example, the cardiovascular event rate, though perhaps reduced by blood pressure control may remain unacceptably high in some patients. Thus, the possibility of using drug classes that exert additional vasculoprotective benefits beyond their main action is appealing. This article aims to review recommended therapeutic options for risk factors associated with arterial hypertension, focusing on the most effective options for vascular protection. In particular, the effects on hard end points as well as on vascular function and structure of old and new lipid-lowering drugs (including statins, fibrates, omega 3 polyunsaturated fatty acids, ezetimibe, and high-density lipoprotein–raising drugs), glucose-lowering drugs (including insulin providers, insulin sensitizers, and glucose absorption inhibitors), and antiplatelet drugs will be discussed.

Table I provides a brief summary of the known effects of such drugs on vasculoprotection in patients with CV risk factors.

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Which drugs should be combined with antihypertensive agents to ensure synergistic vascular protection?

by S. Taddei and R. M. Bruno, Italy
Lipid-lowering drugs

◆ Statins

Several randomized controlled trials (RCTs) have demonstrated the benefit of statin therapy either in primary or in secondary prevention for myocardial infarction and stroke, regardless of the presence of hypertension. For example, in the Heart Protection Study—the largest RCT testing a lipid-lowering drug ever conducted—simvastatin reduced the incidence of CV events in patients with established CV disease. This effect was evident even in the hypertensive subgroup (41% of the overall population), regardless of the antihypertensive drug class used.2 When overt coronary heart disease is present, there is clear evidence that statins should be administered to achieve low-density lipoprotein (LDL) cholesterol levels below 70 mg/dL.3

<table>
<thead>
<tr>
<th>Drug class</th>
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<th>Blood pressure</th>
<th>Endothelial dysfunction</th>
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<td>+ / -</td>
<td>++</td>
<td>+ / -</td>
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<td>Metformin</td>
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<td>Antiplatelet drugs</td>
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Table I. Summary of known effects of lipid-lowering, glucose-lowering, and antiplatelet drugs on vasculoprotection in patients with cardiovascular risk factors.

“+,” “++,” and “+++” indicate a positive effect; “−” indicates a negative effect; “=NA” indicates a neutral effect; NA, data not available.

Abbreviations: DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HDL, high-density lipoprotein; n-3 PUFA, omega-3 polyunsaturated fatty acid.

The ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial) and ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) studies specifically recruited hypertensive patients in primary prevention, and obtained conflicting results. In the ALLHAT study, pravastatin administration (40 mg/day) significantly reduced total and LDL cholesterol levels without influencing CV morbidity and mortality.4 Conversely, in the ASCOT study, atorvastatin administration (10 mg/day) caused a greater reduction in cholesterol levels than that seen in the ALLHAT study (20% reduction vs 11%), accompanied by a significant reduction in CV events (reduced by 36%) and in stroke (reduced by 27%).5 On the basis of the ASCOT results, current ESC/ESH Guidelines recommend the use of statins in patients with a 10-year CV risk greater than 20%, with a target level for LDL cholesterol of 115 mg/dL and for total cholesterol of 190 mg/dL.1 Among additional benefits, statins might have a BP-lowering effect per se,6 though this finding was not confirmed in all studies.7 Other studies highlighted an effect on central, but not peripheral, BP values8; however, a degree of uncertainty exists due to scarce, conflicting data. In the ASCOT-LLA study (ASCOT – Lipid-Lowering Arm), the carotid augmentation index and carotid systolic BP levels were significantly lower after 18 months of atorvastatin treatment than in the placebo group.

Figure 1. The effects of atorvastatin or placebo in the amlodipine/perindopril-based and atenolol/thiazide-based arms on the cumulative incidence of myocardial infarction and fatal coronary artery disease in the ASCOT study.

Abbreviations: ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; CI, confidence interval; HR, hazard ratio.

After reference 10: Sever et al. Eur Heart J. 2006;27:2982-2988. © 2006, European Society of Cardiology. All rights reserved.
group. Conversely, in the CAFE-LLA study (Conduit Artery Function Evaluation – Lipid Lowering Arm), another ASCOT substudy, atorvastatin lowered LDL cholesterol by 32.4 mg/dL in comparison with placebo, but had no impact on augmentation index and central aortic BP. Interestingly, CV prevention induced by statins was greater in hypertensive patients enrolled in the amlopidine/periindopril arm, with a significant 53% reduction in the primary outcome, as compared with those enrolled in the atenolol/thiazide arm, according to a subanalysis of the ASCOT study, suggesting a synergistic effect between certain antihypertensive drug classes and statins (Figure 1, page 413). Experimental and clinical studies have also shown beneficial actions of statins for the vasculature that may extend beyond their lipid-lowering properties, such as improvement of endothelial function, inhibition of vascular smooth muscle cell proliferation, and reduction in vascular inflammation. However, it is interesting to note that in hypertensive patients with normal cholesterol levels, a 2-week treatment with fluvastatin did not modify BP, endothelial function, and oxidative stress.

Conversely, studies investigating the effect of statins on arterial stiffness have given contradictory results, especially those recruiting hypertensive hypercholesterolemic patients. However, this finding could, in some cases, result from methodological limitations (eg, small sample sizes, short duration of the intervention, and nonrandomized clinical design) rather than represent the absence of a true treatment effect. With regards to mechanistic background, the possible “destiffening” effect of statins is not related as much to changes in serum lipid profile as to improvement in endothelial function and reduction in oxidative stress.

**Fibrates**

Fibrates are lipid-lowering drugs, acting as peroxisome proliferator-activated receptor (PPAR)-γ agonists and are prescribed mainly for their beneficial effects on triglyceride and high-density lipoprotein (HDL) cholesterol levels, accompanied by total and LDL cholesterol reduction. Their beneficial effect on CV outcome was demonstrated in high-risk patients when administered as an alternative to statins; however, in the ACCORD study (Action to Control Cardiovascular Risk in Diabetes), combination therapy between fenofibrate and statin did not reduce the incidence of CV events in type 2 diabetic patients, despite significant amelioration of the lipid profile. Interestingly, a small RCT enrolling hypertriglyceridemic hypertensive patients compared fenofibrate, candesartan, and combination therapy: whereas an improved flow-mediated dilation (FMD) was found in all three treatment arms, combination therapy was superior in terms of reduction in plasma malondialdehyde, high-sensitivity C-reactive protein, and soluble CD40L levels. Furthermore, a BP-lowering effect of fenofibrate was demonstrated, at least in salt-sensitive hypertensive patients. The authors hypothesized a counteracting effect on the kidney, reducing renal vasoconstriction mediated by the renin-

### Table: Selected Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
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<tbody>
<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>ALLHAT</td>
<td>Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial</td>
</tr>
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<td>ARBITER</td>
<td>ARterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol 6-HDL And LDL Treatment Strategies in atherosclerosis</td>
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<tr>
<td>ASCOT</td>
<td>Anglo-Scandinavian Cardiac Outcomes Trial</td>
</tr>
<tr>
<td>ASCOT-LLA</td>
<td>Anglo-Scandinavian Cardiac Outcomes Trial – Lipid Lowering Arm</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>CAFE-LLA</td>
<td>Conduit Artery Function Evaluation – Lipid Lowering Arm</td>
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<td>CIMT</td>
<td>carotid intima-media thickness</td>
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<td>cardiovascular</td>
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<td>DPP-4</td>
<td>dipeptidyl peptidase-4</td>
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<td>ENHANCE</td>
<td>Ezetimibe and simvastatin in Hypercholesterolemia enhANces atherosClerosis rEgression</td>
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<tr>
<td>EPA</td>
<td>eicosapentaenoic acid</td>
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<td>ESC</td>
<td>European Society of Cardiology</td>
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<tr>
<td>ESH</td>
<td>European Society of Hypertension</td>
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<td>EXAMINE</td>
<td>EXamination of cardiovascular outcome with alagliptin versus standard care in patients with type 2 diabetes mellitus and acute coronary syndrome</td>
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<td>flow-mediated dilation</td>
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<td>GLP-1</td>
<td>glucagon-like peptide-1</td>
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<td>HbA1c</td>
<td>glycated hemoglobin A1c</td>
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<td>HDL</td>
<td>high-density lipoprotein</td>
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<td>Hypertension Optimal Treatment</td>
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<td>HPS2-THRIVE</td>
<td>Heart Protection Study 2 – Treatment of HDL to Reduce the Incidence of Vascular Events</td>
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<td>JELIS</td>
<td>Japan EPA Lipid Intervention Study</td>
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<td>n-3 PUFA</td>
<td>omega-3 polyunsaturated fatty acid</td>
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<td>PPAR</td>
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<td>PROactive</td>
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<td>RCT</td>
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<td>UK Prospective Diabetes Study</td>
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angiotensin and sympathetic nervous system. Currently, since fibrates have not been specifically tested in hypertensive patients for CV-event reduction, the strongest evidence of benefit is for their addition to statin treatment in high-risk patients with type 2 diabetes and dyslipidemia.

◆ **Omega-3 polyunsaturated fatty acids**

Omega-3 polyunsaturated fatty acids (n-3 PUFA), and in particular eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are essential components of the phospholipidic membrane that should be introduced mainly by fish consumption or commercially available supplements. Among RCTs, the JELIS study (Japan EPA Lipid Intervention Study) enrolled 18,000 hypercholesterolemic patients randomized to statin alone or in combination with EPA (600 mg three times a day). This study demonstrated a significant reduction in coronary events after a 4.6-year follow-up only in patients with established CV disease. Though this result might be due to known antiarrhythmic effects of n-3 PUFA, a vasculoprotective effect is also suggested. Experimental studies have demonstrated that n-3 PUFA can reduce the production of vasoconstrictor, proinflammatory, and prothrombotic molecules and can modulate the expression of proinflammatory and proatherogenic genes. Thus, it has been hypothesized that n-3 PUFA might exert a particular vasculoprotective action that goes beyond the triglyceride-lowering effect. Furthermore, a BP-lowering effect was demonstrated in hypertriglyceridemic patients with high-normal BP. In conclusion, supplementation with n-3 PUFA is indicated in hypertriglyceridemic hypertensive patients; additive benefits are suggested by some studies, but do not justify widespread treatment.

◆ **Ezetimibe**

Ezetimibe is an inhibitor of intestinal absorption of cholesterol. The use of ezetimibe is of interest in clinical practice because it allows achievement of LDL targets with statins used at low doses and thus might be used in statin-intolerant patients. Its clinical efficacy has been questioned since publication of the ENHANCE study (Ezetimibe and simvastatin in Hypercholesterolemia EnhANces atherosClerosis Regression), which demonstrated a smaller reduction in intima-media thickness and a higher incidence of CV events, despite a greater LDL reduction, with statin plus ezetimibe than with statin plus niacin in patients with established CV disease or risk-equivalent. That study suggested a lack of vascular protection from ezetimibe, despite the lipid-lowering efficacy, which translates into a lack of effect on hard end points. Importantly, a post hoc analysis on 159 patients randomized to ezetimibe within the ARBITER 6-HALTS study (Arterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol 6-HDL And LDL Treatment Strategies in atherosclerosis) demonstrated a paradoxical increase in carotid intima-media thickness (CIMT) associated with LDL-cholesterol reduction: the greater the exposure to ezetimibe, the greater the CIMT increase. The authors hypothesized off-target mechanisms and/or counterregulatory mechanisms that may interfere with the positive effects from the lowering of LDL. According to the ARBITER 6-HALTS study (ARterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol 6-HDL And LDL Treatment Strategies in atherosclerosis), the primary outcome measure was the change from baseline in FMD of the right brachial artery. After 36 weeks, no change in FMD despite increased HDL levels was demonstrated. Accordingly, an RCT enrolling 234 coronary artery disease patients with LDL cholesterol levels below 70 mg/dL after treatment with atorvastatin 10 mg randomized the patients to doubling of the atorvastatin dose or adding ezetimibe 10 mg to the treatment regimen. In the group randomized to doubling of the atorvastatin dose, LDL reduction was less marked than in the ezetimibe–add-on group, but endothelial function showed greater improvement, as measured by peripheral arterial tonometry.

Conversely, in a different study, ezetimibe 10 mg plus simvastatin 10 mg had an effect similar to simvastatin 80 mg on endothelial function in obese patients with metabolic syndrome.

As the SHARP study (Study of Heart And Renal Protection) enrolling 9438 patients with chronic kidney disease demonstrated a significant reduction in CV events—proportional to LDL reduction—in patients randomized to ezetimibe 10 mg plus simvastatin 20 mg as compared with placebo, it seems reasonable to recommend this association in hypertensive patients with chronic kidney disease. To our knowledge, vascular protection with ezetimibe in the hypertensive population has yet to be studied.

◆ **High-density lipoprotein–raising drugs**

Up to now, drugs designed to raise the level of HDL cholesterol have had disappointing results for reduction in CV events. For example, extended-release niacin, which was effective in reducing CIMT, failed to reduce CV events and increased adverse events in 25,673 high-risk patients enrolled in the HPS2-THRIVE study (Heart Protection Study 2 – Treatment of HDL to Reduce the Incidence of Vascular Events). The dal-cetrapib story tells us a lot about the importance of vascular protection for effective CV reduction in high-risk patients. In the dal-VESSEL RCT (a study showing the safety, tolerability, and effect on endothelial function of dalcetrapib in patients with or at risk of coronary heart disease), 466 patients received either dalcetrapib (a cholesteryl ester transfer protein inhibitor) at 600 mg/day or placebo for 36 weeks on top of standard therapy (including statins). The primary outcome measure was the change from baseline in FMD of the right brachial artery. After 36 weeks, no change in FMD despite increased HDL levels was demonstrated. Accordingly, no benefit on CV events in the dal-OUTCOME study (a study showing the effect of dalcetrapib on CV mortality and morbidity in clinically stable patients with a recent acute coronary syndrome) was observed, suggesting that short-term RCTs using vascular biomarkers as surrogate end points might be useful in CV research as they may speed up selection of the most promising drugs without setting up long-term, expensive RCTs for hard end points.

**Glucose-lowering drugs**

Hypertensive patients with diabetes mellitus are automatically classified as having a very high CV risk by ESC/ESH Guidelines; thus, glucose control is a crucial issue for achieving CV...
protection in hypertensive diabetic patients. In past decades, a number of large RCTs were designed to address this issue. The effects on macrovascular complications—on CV events in particular—and the glycated hemoglobin A1c (HbA1c) threshold to reach in order to obtain benefits in that regard, was then investigated in the ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN-MR Controlled Evaluation) and ACCORD studies. In the ADVANCE study, intensive glycemic control (HbA1c approximately 6.5%) led to a significant reduction in the primary composite end point (micro- and macrovascular complications), whereas CV events were not significantly reduced and severe hypoglycemic episodes were increased in comparison with standard treatment. The ACCORD study was prematurely stopped due to increased mortality in the intensive treatment arm. Later meta-analyses have documented that more intensive glycemic control is likely to reduce nonfatal coronary events and myocardial infarction, as well as nephropathy, but not stroke or all-cause or CV mortality. Thus, international scientific societies recommend, even in hypertensive diabetic individuals, a target HbA1c of 7%. Caution should be used in patients with a positive history of severe hypoglycemia, long diabetes duration, and multiple comorbidities, for whom higher (less stringent) HbA1c targets are acceptable.

Arterial hypertension and type 2 diabetes mellitus often coexist and are both characterized by increased arterial stiffness and endothelial dysfunction. Endothelial dysfunction is a determinant of aortic stiffness in hypertensive diabetic patients, but not in hypertensive patients without diabetes, suggesting a mechanistic role for endothelium-related mechanisms. For this reason, a number of studies investigated possible differences in vasculoprotection exerted by different glucose-lowering therapeutic agents.

* **Insulin providers**

This group includes insulin, sulfonylureas, meglitinides and incretin mimetics, including glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors; these drug classes all act by stimulating endogenous insulin secretion by the pancreatic β-cell. The GLP-1 receptor agonists also favor weight loss, by modulation of the sense of satiety: this beneficial effect is associated with a significant reduction in BP values in comparison with insulin, as demonstrated by a retrospective analysis of a large cohort database (Figure 2). Furthermore, a retrospective analysis performed on the LifeLink database demonstrated that exenatide treatment was associated with a lower risk of CV events and CV-related and all-cause hospitalizations in comparison with other glucose-lowering therapies. However, there are no RCTs available that specifically address this point.

In contrast, sulfonylureas may lead to body weight gain, thus promoting the development of hypertension: this adverse effect might explain the neutral effect on arterial stiffness despite the glucose-lowering effect. A 10-year post-trial follow-up of UKPDS (UK Prospective Diabetes Study) revealed that the patient group treated with either sulfonylurea or insulin...
(sulfonylurea-insulin) had a significantly reduced risk of myocardial infarction and all-cause death; however, metformin outperformed sulfonylurea-insulin as far as CV protection was concerned. In a meta-analysis of clinical trials, combination therapy with metformin and sulfonylureas was associated with reduced survival. Scarce data are available on the CV safety of miglitol; however, nateglinide was neutral on CV outcomes in individuals with impaired glucose tolerance.

The effect of the DPP-4 inhibitor saxagliptin on CV outcomes in patients with type 2 diabetes was investigated by the SAVOR-TIMI 53 trial (Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus – Thrombolysis In Myocardial Infarction 53). Despite improvement in glycemic control, results of that trial, enrolling 16,492 patients followed-up for 2.1 years, were neutral in terms of ischemic events rate, with a significantly increased rate of hospitalization for heart failure in the treatment arm compared with placebo. Also, in the EXAMINE trial (EXamination of Cardiovascular Outcomes with Alogliptin versus Standard Care in patients with type 2 diabetes mellitus and acute coronary syndrome), the rates of major adverse CV events were not increased by alogliptin treatment in diabetic patients who had a recent acute coronary syndrome. From the pathophysiological point of view, DPP-4 inhibitor use is associated with improved endothelial function, antioxidant and anti-inflammatory actions, and renal effects. For example, in type 2 diabetic subjects, vildagliptin caused an increase in vasodilation in response to acetylcholine, a measure of endothelial function. Furthermore, DPP-4 inhibitors might have a direct BP-lowering effect, by modulation of the cross-talk between the sympathetic nervous system and angiotensin II at the renal vascular level. Indeed, a small reduction in BP was observed in nondiabetic hypertensive patients treated with the DPP-4 inhibitor sitagliptin.

- **Insulin sensitizers**

  This group of therapeutic agents includes metformin and glitazones. Glitazones are PPAR-γ agonists with partial α effects, which lower glucose by ameliorating insulin resistance, while metformin is a biguanide that exerts similar effects through adenosine monophosphate (AMP) kinase activation.

  In addition to its hepatic-mediated hypoglycemic actions in human subjects, the CV benefits of metformin were demonstrated early on by the UKPDS study in patients with type 2 diabetes mellitus, particularly in overweight diabetic patients. A meta-analysis of 35 clinical trials suggested a beneficial effect on CV morbidity and mortality that was more evident for younger patients and longer treatment duration. Metformin improved endothelial function in patients with type 2 diabetes mellitus via an action that seems to be unrelated to its hypoglycemic actions, but rather to insulin resistance and oxidative stress amelioration; a direct vascular effect is also possible. Metformin was also shown to reduce arterial stiffness in several studies, including in patients with type 2 diabetes mellitus.

  CV safety of glucose-lowering drugs was a neglected issue for many years, until publication of a 42-trial meta-analysis highlighted an excess rate of myocardial infarction in patients treated with rosiglitazone, a PPAR-γ agonist. Conversely, pioglitazone in the PROactive study (PROspective pioglitAzone Clinical Trial In macroVascular Events) achieved a significant reduction in a secondary composite outcome of all-cause mortality, fatal myocardial infarction, and stroke. Treatment with pioglitazone was shown not only to improve insulin resistance and glycemic control, but also to decrease arterial stiffness and improve endothelial function in obese glucose-tolerant men.

- **Glucose absorption inhibitors**

  This group includes α-glucosidase inhibitors and sodium-glucose cotransporter-2 (SGLT2) inhibitors. The α-glucosidase inhibitor acarbose reduces glucose absorption from the gastrointestinal tract, and the SGLT2 inhibitors act on the proximal renal tubule to reduce glucose absorption.

In the STOP-NIDDM trial (Study to Prevent Non–Insulin-Dependent Diabetes Mellitus), acarbose reduced CV morbidity and mortality in individuals with impaired glucose tolerance. Beyond the known reduction mainly of postprandial glucose...
levels, acarbose provides additional benefits in terms of weight loss, BP reduction, and lowering of triglycerides.\(^5\,6\)

The SGLT2 inhibitors represent a promising treatment option for diabetes and hypertension. Emerging data suggests that the SGLT2 inhibitors provide a significant reduction in BP, possibly due to a combination of diuresis, nephrorn remodeling, reduction in arterial stiffness, and weight loss.\(^5\,6\) Interestingly, in 40 normotensive type 1 diabetes mellitus patients, empagliflozin determined a decline in arterial stiffness. The underlying mechanisms may relate to pleiotropic actions of SGLT2 inhibition, including glucose-lowering, antihypertensive, and weight reduction effects (Figure 3, page 417).\(^7\,8\)

**Antiplatelet drugs**

Based on current evidence, antiplatelet therapy is indicated in hypertensive patients with previous CV events and should be considered in patients with reduced renal function, provided that BP is well controlled.\(^1\) A large meta-analysis analyzed CV and hemorhagic events in 6 primary prevention trials (95,000 individuals) and 16 secondary prevention trials (17,000 individuals), demonstrating that absolute CV benefit is greater than harm for antiplatelet therapy only in the latter group.\(^5\,6\) A subanalysis of the HOT study (Hypertension Optimal Treatment), which was especially designed to evaluate risks and benefits of antiplatelet therapy in hypertensive patients, demonstrated that in patients with a glomerular filtration rate below 45 mL/min/1.73m\(^2\), the risk of bleeding was negligible in comparison with CV benefit.\(^5\,6\) Additional benefits of aspirin might be due to a BP-lowering effect, as suggested by Hermida and coauthors, who highlighted a reduction in systolic BP of about 7 mm Hg and in diastolic BP of 5 mm Hg by 24-hour BP monitoring, when aspirin is administered at bedtime, but not when administered on awakening.\(^5\,6\)

The bedtime timing of aspirin intake seems to enable it to better influence renin-angiotensin activity and levels of cortisol and catecholamine, all of which increase in the early morning hours according to a circadian pattern.\(^5\,6\)

**Conclusions**

Residual CV risk is a crucial issue in the management of hypertensive patients, whose CV-event rate is reduced, but not normalized, by effective BP control. In high-risk patients with multiple comorbidities, the CV-event rate at 10 years remains unacceptably high despite extensive use of lipid-lowering, glucose-lowering, and antiplatelet drugs.\(^5\,6\) From this point of view, choosing a drug class able to provide an additional vascularprotective benefit is a promising strategy. This aspect should be considered as a key factor for the development of new CV drugs. Finally, it is highly important that vascularprotective effects of new and old drugs be tested specifically in the hypertensive population.\(^9\)

**References**


Keywords: antihypertensive; antiplatelet; cardiovascular; glucose-lowering; lipid-lowering; vasculoprotection
QUELS MÉDICAMENTS COMBINER AVEC LES ANTIHYPERTENSEURS POUR OBTENIR UNE SYNERGIE VASCULAIRE PROTÉCTRICE ?

La stratification du risque cardiovasculaire chez les patients hypertendus joue un rôle important dans la décision de la stratégie thérapeutique à prendre. Les recommandations actuelles de la Société Européenne de Cardiologie (ESC) et de la Société Européenne d’Hypertension (ESH) préconisent de prendre en compte non seulement les valeurs de pression artérielle et les lésions des organes cibles, mais aussi la présence d’autres facteurs de risque au-delà de l’hypertension. Cette approche se justifie par le fait que des facteurs de risque associés influent gravement sur la morbidité et la mortalité des hypertendus, déterminant ce qu’on appelle le risque résiduel. Par exemple, le taux d’événement cardio-vasculaire, bien que réduit par le contrôle de la pression artérielle, peut rester élevé chez certains patients de façon inacceptable. C’est pourquoi la possibilité d’utiliser des classes de médicaments aux bénéfices vasculoprotecteurs supplémentaires en dehors de leur action principale, est attrayante. Cet article présente les choix thérapeutiques recommandés pour les facteurs de risque associés à l’hypertension artérielle, en insistant sur les plus efficaces pour la protection vasculaire. Nous allons analyser en particulier les effets des anciens et des nouveaux hypolipémiants (statines, fibrates, acides gras oméga 3 polyinsaturés, ezétimibe et médicaments augmentant les lipoprotéines de haute densité), des hypoglycémiants (fournisseurs d’insuline, insulino-sensibilisateurs et inhibiteurs de l’absorption du glucose) et des antiagrégants plaquettaires, sur les critères sévères ainsi que sur la structure et la fonction vasculaires.
Arterial stiffness is an independent risk factor for the development of cardiovascular morbidity and mortality. When arterial “destiffening” strategies emerged, they were originally based on the use of antihypertensive drugs; however, in the last decade, alternative strategies not based upon blood pressure lowering have been developed. This article reviews the major recent developments in this field, discussing a diverse range of drug classes with respect to their destiffening properties. These drug classes include nitric oxide (NO) donors, lipid-lowering drugs, antidiabetic agents, angiotensin II type 2 receptor agonists, anti-inflammatory drugs, antiviral and antibiotic drugs, hormone replacement therapy, and drugs influencing calcium and phosphate metabolism. While the evidence for some of these drugs rests only upon studies in experimental animals, for other therapies there is convincing clinical evidence. However, further developmental studies are needed. With the important cardiovascular risk associated with arterial stiffening, the clinical need for effective destiffening therapies remains. The most promising areas to develop future arterial destiffening drugs appear to include NO donors, drugs interfering with the arterial extracellular matrix, anti-inflammatory drugs, and agents reducing arterial calcification.

New pharmacological approaches targeting arterial stiffness

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Arterial stiffness has emerged as a risk factor for cardiovascular morbidity and mortality. Initially, it was particularly associated with hypertension, but research over the past two decades has revealed its importance in other diseases, such as coronary heart disease, diabetes, and metabolic syndrome (for a review, see reference 1). The important role of arterial stiffness in the etiology of cardiovascular and metabolic diseases raises the question whether arterial stiffness can be a target for drug- or nutrition-based interventions. Other articles in this journal issue describe the various indices used to assess arterial stiffness. Some of these indices (e.g., arterial distensibility) are blood pressure–dependent, whereas others give a measure of the material properties of the arterial wall. That distinction is important when discussing the effects of pharmacological interventions on arterial stiffness. For instance, a drug-induced reduction in blood pressure may influence arterial distensibility without a direct effect on the material properties of the arterial wall. This article will focus on the blood pressure–independent effects of drugs on arterial stiffness. As the effects of non-antihypertensive drugs have already been reviewed by Boutouyrie et al5 in 2011, I will focus on more recent data concerning the effects of different non-antihypertensive drugs on arterial stiffness.
Nitric oxide donors
Most antihypertensive vasodilators selectively dilate small resistance arteries and arterioles, thereby reducing blood pressure. Notable exceptions are the organic nitrates, which are selective dilators of muscular conduit arteries. In a recent study, Omar et al showed that nitrite in near physiological concentrations selectively dilates conduit arteries and reduces central blood pressure. This effect involves cyclic guanosine monophosphate (cGMP) production. Similar evidence for a role of cGMP in influencing arterial stiffness comes from a study by Aversa et al who showed that vardenafil—a selective inhibitor of phosphodiesterase 5, an enzyme which catalyzes the breakdown of cGMP—improves arterial stiffness in patients with erectile dysfunction. Furthermore, a study by Isabelle et al in spontaneously hypertensive rats showed that long-term reduction in nitric oxide (NO) levels increases aortic stiffness. In addition to the enhanced production of cGMP by NO donors, a normalization of the formation of advanced glycation end products (AGEs) has been proposed as a mechanism of sodium nitrite “destiffening” of large arteries. Altogether, these data make NO donors as well as the emerging synthetic soluble guanylate cyclase stimulators attractive candidates for arterial destiffening.

Lipid-lowering drugs
In their 2011 review, Boutouyrie et al discussed the controversies concerning a number of studies on the effects of statins on aortic stiffness. They concluded that these effects, if any, are not clinically significant. A systematic review of the early published trials on statins and arterial stiffness showed that when pulse wave velocity (PWV) was used, only 2 of 4 trials showed destiffening with statins. However, when peripheral indices of arterial stiffness were used, 4 out of 5 trials showed positive results. In two recent studies, fluvastatin and atorvastatin were shown to reduce carotid arterial stiffness.

As suggested by Boutouyrie et al, statin-induced improvement in arterial stiffness may be more marked in the context of inflammation. Furthermore, Wallace et al have shown that simvastatin reduces inflammation-induced aortic stiffening and endothelial dysfunction. More recently, Wang et al observed an improvement in arterial stiffness through reduction in oxidative stress damage in elderly hypertensive patients after 6 months of atorvastatin therapy.

Antidiabetic drugs
Diabetes mellitus is associated with increased arterial stiffness, independently of blood pressure changes. Various cardiovascular risk factors have been implicated in the increased stiffness in diabetes, such as increased sympathetic tone, increased activity of the renin-angiotensin system, and the formation of AGEs.

**Inhibition of AGE formation**
AGEs are nonenzymatically derived glycation products of proteins, in particular, collagen. This leads to the formation of collagen cross-links and arterial stiffening. Early evidence for a role of AGE formation came from a study in diabetic rats in which aminoguanidine—an inhibitor of AGE formation—increased elasticity of large arteries. In this experimental model of diabetes, the same group later showed that the collagen cross-link breaker alagebrium (ALT 711) decreases large artery stiffness. These animal studies were confirmed by clinical observations in hypertensive patients with diabetes. In a rat model for aging, alagebrium reduced arterial stiffness, in particular when combined with regular physical exercise. However, these data could not be confirmed in normotensive, nondiabetic elderly humans. Recent support for the potential of AGEs as a target for arterial destiffening comes from observations on the soluble receptor for AGEs (sRAGE). High plasma levels of sRAGE are associated with incident fatal and nonfatal cardiovascular disease and all-cause mortality in individuals with type 1 diabetes. sRAGE-associated aortic stiffening may partially explain this association.

**Glitazones**
Other drugs used in the treatment of diabetes have been investigated with respect to their arterial destiffening activity. Boutouyrie et al have reviewed the early evidence that the glitazones in particular can decrease aortic stiffness. They proposed that this effect could be related to the increase in adiponectin in both diabetic and hypertensive patients. Recent studies have confirmed that pioglitazone improves aortic stiffness in patients with rheumatoid arthritis.

**Modulation of incretin-receptor signaling**
Drugs interacting with incretin-receptor signaling have recently been studied. Sitagliptin, when added to metformin-treated type 2 diabetes patients, did not significantly affect arterial stiffness. Also, the glucagon-like peptide-1 receptor agonist liraglutide, on top of metformin therapy, did not cause a change in arterial stiffness parameters. Earlier studies had already shown that metformin can reduce aortic stiffness in young women with polycystic ovary syndrome. The new class of
sodium glucose transport inhibitors, including dapagliflozin and empagliflozin, has been shown to have a favorable effect on arterial stiffness in diabetic subjects.

**Angiotensin II type 2 receptor agonists**

Most of the well-known effects of angiotensin II (Ang II) are mediated via the Ang II type 1 (AT₁) receptor. Increasing evidence over the past years suggests that Ang II type 2 (AT₂) receptors mediate vasculoprotective actions via vasodilation, NO production, and inhibition of cell growth and fibrosis. Recent studies in spontaneously hypertensive rats show that the selective AT₂ receptor agonist Compound 21 (C21) reduces arterial stiffness as well as aortic medial and myocardial collagen content, and aortic fibronectin. In Nω-nitro-L-arginine methyl ester hydrochloride (L-NAME)–treated hypertensive rats, C21 prevented aortic stiffening and collagen accumulation without preventing the development of hypertension. It has been suggested that extracellular matrix metalloproteinas (MMPs) play an essential role in AT₂ receptor–mediated effects on cardiac and vascular stiffness. Further clinical studies are needed to confirm a potential role of AT₂ receptors in arterial stiffness in humans.

**Anti-inflammatory drugs**

Inflammation may be an essential mechanism of increased arterial stiffness in diseases such as rheumatoid arthritis or inflammatory bowel disease. Some authors have suggested a role for chronic low-grade inflammation in the increased arterial stiffness in hypertension. In early evidence for arterial destiffening by anti-inflammatory drugs, reviewed by Boutouyrie et al., antibodies against tumor necrosis factor α (TNF-α) were shown to improve arterial stiffness, independently of any change in blood pressure, in patients with different chronic inflammatory diseases. Recent studies confirmed this positive effect of anti–TNF-α in a wide range of chronic inflammatory diseases. Furthermore, Angel et al. showed that anti–TNF-α therapy improved the L-arginine to asymmetric dimethylarginine ratio in patients with inflammatory arthropathies. This raises the interesting possibility that similar mechanisms may reduce the inflammatory process occurring in atherosclerosis. Previous studies had already suggested that statins exhibit destiffening properties only in the presence of inflammation. Additional studies including the effect of classical nonsteroidal anti-inflammatory drugs would offer a more complete picture of the effect of anti-inflammatory drugs on destiffening.

**Antiviral and antibiotic drugs**

**Antiviral therapy**

Individuals infected with the human immunodeficiency virus (HIV) have an increased risk of atherosclerosis and cardiovascular disease, which has been attributed to higher prevalence of traditional cardiovascular risk factors, HIV itself, as well as antiviral therapy. Emerging evidence suggests that HIV-induced T-cell activation, which remains abnormally elevated even after viral suppression with highly active antiretroviral therapy, is associated with an increase in arterial stiffness. Activated T cells are markers of inflammation, and this may contribute to arterial stiffening, as discussed above. When antiretroviral therapy is initiated in HIV-infected subjects at the moment of high nadir T-cell counts, a reduction in arterial stiffness is observed. Since antiretroviral drugs are typically prescribed in cocktails of 3 different drugs, it is difficult to establish the role of specific agents in the development of arterial stiffness. One of the most frequently used antivirals, azidothymidine, was shown to increase arterial stiffness in mice.

**Antibiotic therapy**

There are no systematic studies on the effects of different antibiotic drug classes on arterial stiffness. Some authors reported that low-to-moderate–dose anthracycline-based chemotherapy increases arterial stiffness. However, there are several reports that doxycycline protects against the structural vascular alterations associated with hypertension, including arterial stiffness (for a review, see reference 48). Doxycycline acts at low doses to inhibit matrix MMPs. In view of the important role of MMPs in vascular remodeling, further studies on the effects of doxycycline and related MMP inhibitors are needed.

**Hormone replacement therapy**

In their review, Boutouyrie et al. summarized the results of 13 relevant randomized controlled trials on hormone replacement therapy and arterial stiffness. Negative results were observed with all modalities of hormone replacement therapy: estrogen alone or in combination with the selective estrogen receptor modulator raloxifene. In a recent comprehensive multicenter trial, Gompel et al. showed that hormone replacement therapy in postmenopausal women is associated with lower values of carotid artery intima-media thickness, central pulse pressure, and aortic stiffness, independently of age at menopause and the time since menopause. Matsui et al. reported that ultra-low-dose estradiol (0.5 mg) and hydrogesterone (5 mg) every day for 1 year decreased brachial-ankle PWV and vascular inflammatory markers. A recent trial on the sex hormone precursor dehydroepiandrosterone (DHEA) in older adults showed that DHEA reduced the carotid augmentation index and carotid-femoral artery PWV. This effect was accompanied by a decrease in serum inflammatory cytokines. Altogether, the issue whether hormone replacement therapy has a favorable effect on arterial stiffness remains enigmatic with various confounding factors, eg, dose, duration, and nature of the therapy.

**Drugs influencing calcium and phosphate metabolism**

**Calcium metabolism modulation**

Since calcification of the arterial wall is an important event in arterial aging and stiffening, targeting calcium metabolism looks to be an attractive therapeutic option. The literature on cardiovascular consequences of calcium supplementation is
full of controversies, some claiming beneficial effects, others claiming the opposite (for a review, see reference 53). Since vascular calcification is more common in hemodialysis patients, it has been suggested that repeated episodes of hypercalcemia can increase the risk of vascular calcification and arterial stiffening. Bisphosphonates are considered first-line therapy in osteoporosis. They inhibit bone resorption by an action on osteoclasts in which they form tight complexes with calcium in the bone matrix. Recent studies suggest their potential to reduce atherosclerosis owing to a similar effect on calcium release in the vessel wall. A recent study shows that bisphosphonate treatment in women with postmenopausal osteoporosis reduces arterial stiffness. This interesting observation needs follow-up.

Phosphate metabolism modulation
Phosphate is another mineral that plays an important role in skeletal remodeling, with particular action in the chronic kidney disease–mineral and bone disorder (CKD-MBD), in which increased vascular stiffness is a main feature. Recent studies have shown that sevelamer, a non–calcium-based phosphate binder has a favorable effect on arterial stiffness in patients with chronic kidney disease and in mice with chronic renal failure.

Other drugs
In addition to the above described drug classes, incidental observations were made in experimental animal models on destiffening effects of the cardiac pacemaker current (I(F)) inhibitor ivabradine and the 5-lipoxygenase inhibitor caffeic acid phenethyl ester. Also, clinical observations suggest that uric acid–lowering therapy with allopurinol or febuxostat reduces arterial stiffness. However, these incidental observations need further confirmation.

Conclusion
In conclusion, whereas the original approach to arterial destiffening was primarily focused on antihypertensive drugs, we now see various leads to drugs that lower arterial stiffness without affecting blood pressure. The most promising leads are in the area of NO donors and drugs that interfere with the arterial extracellular matrix, eg, inhibitors of AGE formation and drugs interfering with the metabolism of MMPs. Other potential areas that need further study are anti-inflammatory drugs and drugs affecting arterial calcification. Given the important cardiovascular risk associated with arterial stiffening, the clinical need for destiffening therapies remains significant.

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Destiffening arteries – Struijker-Boudier


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Keywords: arterial stiffness; destiffening; diabetes; drug treatment; extracellular matrix; hypertension
La rigidité artérielle est un facteur de risque indépendant du développement de la morbi-mortalité cardiovasculaire. Lorsqu’elles apparaissent, les méthodes « d’assouplissement » artériel viennent des médicaments antihypertenseurs mais ces 10 dernières années, des stratégies autres que celles basées sur les antihypertenseurs se sont développées. Cet article aborde les principales avancées récentes dans ce domaine en analysant les différentes classes médicamenteuses selon leurs propriétés d’assouplissement. Parmi celles-ci : les donneurs de monoxyde d’azote (NO), les hypolipidémiants, les antidiabétiques, les agonistes du récepteur de type 2 de l’angiotensine II, les anti-inflammatoires, les antiviraux et les antibiotiques, le traitement hormonale substitutif et les médicaments influant sur le métabolisme phosphocalcique. Les données de certains de ces médicaments en sont encore au stade animal expérimental mais d’autres montrent des résultats cliniques convaincants. Des études supplémentaires de développement sont néanmoins indispensables. Le risque cardiovasculaire important associé à la rigidité artérielle rend nécessaires les traitements d’assouplissement efficaces. Les donneurs de NO, les médicaments interférant avec la matrice artérielle extracellulaire, les anti-inflammatoires et les produits diminuant la calcification artérielle sont les plus prometteurs dans le domaine futur de l’assouplissement artériel.
Differences in the rates of stroke and coronary complications with hypertension are explained by pathogenesis: stroke occurs as a direct consequence of hypertension, while coronary complications are a manifestation of atherosclerosis. Antihypertensive treatments reduce most cardiovascular events, and reductions in stroke and cardiovascular events are proportional to blood pressure reduction. Hypertension management could be improved by enhancing diagnosis, evaluating arterial stiffness, and initiating treatment earlier.

The question

What is the major remaining need in hypertension management: reduction of stroke or reduction of coronary events?

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Hypertension has long been known as one of the risk factors for coronary heart disease and stroke. An epidemiologic study showed that an increase in systolic or diastolic blood pressure after the age of 20 is associated with increased cardiovascular morbidity and mortality. A meta-analysis of individual data for 1 million adults from 61 prospective observational studies showed that blood pressure is strongly and directly related to vascular mortality. A 10 mm Hg reduction in systolic blood pressure is associated with a 40% lower risk of stroke death and a 30% lower risk of death from ischemic heart disease or other vascular cause.

The development of stroke and coronary events is a complex process, resulting from the presence of classic risk factors, such as hypertension, obesity, diabetes, smoking, and dyslipidemia. These conditions often present as comorbidities in the same patient, with synergistic interactions between these risk factors. Hypertension and other risk factors are associated with endothelial dysfunction, increased oxidative stress, inflammation, and formation of atherosclerosis. These pathological mechanisms increase the likelihood of coronary artery disease and cerebrovascular disease that will develop into myocardial and cerebral ischemia. Further development leads to coronary and cerebral thrombosis, with the manifestation of myocardial infarction and stroke.

There are a number of risk factors that contribute to the development of coronary heart disease, but persistent high blood pressure is one of the most important, with a stronger relation to systolic blood pressure above 140 mm Hg. A study of the effect of modifiable risk factors in 52 countries (INTERHEART) showed that approximately 50% of the population-related risk of myocardial infarction is caused by dyslipidemia and 25% of the risk is associated with hypertension. For stroke worldwide, approximately 54% can be attributed to high blood pressure values in both genders and in all ages. These findings show that hypertension is the most significant risk factor for stroke and an important risk factor for coronary events.

The goal of hypertension management is not only to lower blood pressure, but also, more importantly, to: reduce target organ damage; reduce cardiovascular, cerebrovascular, and all-cause morbidity as well as mortality; and improve the quality of life of hypertensive patients.

A meta-analysis of 9 major prospective observational study also showed that a reduction in diastolic blood pressure of 5 mm Hg, 7.5 mm Hg, and 10 mm Hg corresponds with reductions in stroke risk of 34%, 46%, and 56%; and reductions in coronary events of 21%, 29%, and 37%, respectively. Newer studies have also shown that blood pressure reduction leads to greater reduction in stroke than in coronary events. These findings prove that lowering blood pressure reduces the risk of stroke more than the risk of coronary events.

The action of lowering blood pressure per se is generally more important than the choice of antihypertensive agent used to do this, but some classes of antihypertensives can provide direct nephroprotective benefits, such as renin-angiotensin-aldosterone system inhibitors, calcium channel blockers, and thiazide diuretics. These agents represent the three classes of antihypertensive agent with the most desirable effects in primary stroke prevention.

In conclusion, the management of hypertension should be accompanied by the concomitant management of other risk factors in order to protect hypertensive patients from all target organ damage, including coronary events as well as strokes.

References
The relationship between blood pressure (BP) and cardiovascular events is continuous, consistent, and independent of other risk factors. In a meta-analysis of 61 studies including nearly 1 million subjects, BP was related to fatal coronary artery disease for BP values ranging from 115/75 to 185/115 mm Hg, independent of age. Each BP increase of 20/10 mm Hg doubles the risk of a fatal coronary event. Other epidemiological studies have revealed that high BP is the main determinant of stroke risk, which is nearly linear, starting at quite low systolic and diastolic BP levels.

Effective antihypertensive therapy greatly reduces the risk of cardiovascular disease in patients with hypertension, a fact demonstrated in many randomized trials. The improved availability and use of antihypertensive treatments are credited for the impressive reduction in cardiovascular morbidity and mortality in the past 50 years. Concerning stroke, reduction of BP in hypertension is the most important factor in the remarkable reduction in stroke death rates.

Generally, antihypertensive treatment is associated with a 35%-40% decrease in stroke, 20%-25% reduction in myocardial infarction, and over 50% reduction in heart failure. For example, reductions of 10 mm Hg in usual systolic BP or 5 mm Hg in usual diastolic BP are related to a 50%-60% lower risk of stroke death and to an approximately 40%-50% lower risk of death due to coronary artery disease or other vascular causes. Furthermore, a 12 mm Hg decrease in systolic BP results in the prevention of 1 death for every 11 patients treated. More recently, a meta-analysis analyzed the effects of antihypertensive treatment in more than 15,000 patients with mild hypertension and no known cardiovascular disease. Those who were randomized to BP-lowering therapy had a 25% lower risk of cardiovascular death, a 28% lower risk of stroke, and a 22% lower risk of all-cause death compared with patients on no treatment, over a 5-year follow-up.

These benefits of BP reduction on all-cause mortality and cardiovascular events are observed throughout the last half of a patient’s life, irrespective of gender. In older people >80 years, there is a significant association between lower BP and fewer stroke deaths and less heart failure, but no significant association with an inferior rate of myocardial infarction.

There are differences in the effect of antihypertensive therapy on different cardiovascular outcomes, according to the BP target obtained with treatment. In the recent ACCORD (Action to Control CardioVascular Risk in Diabetes) trial, a target systolic BP <120 mm Hg was not associated with a reduced risk of a composite of cardiovascular events (heart attack, stroke, or cardiovascular death) compared with a target systolic BP <140 mm Hg. Stroke was significantly lowered in the intensively treated group.

Recent reviews have confirmed the benefits of renin-angiotensin-aldosterone system inhibitors for cardiovascular prevention. Angiotensin-converting enzyme (ACE) inhibitors are superior to angiotensin receptor blockers (ARBs) for cardiovascular and all-cause mortality prevention, probably due to the effects of ACE inhibitors on bradykinin release and endothelial function. ACE inhibitors should therefore be considered before ARBs for preventing death, strokes, and heart disease. The substitution of an ARB for an ACE inhibitor is, however, supported on grounds of tolerability. Overall, in view of the high prevalence of hypertension in the general population, prevention of cardiovascular diseases, particularly coronary events, stands out as an important goal of antihypertensive treatment.

References

Hypertension is an important public health challenge worldwide. More than a quarter of the world’s adult population had hypertension in 2000, and this proportion will increase to 29% by 2025. The high prevalence of hypertension worldwide has contributed to the present pandemic of cardiovascular disease. Hypertension is the leading risk factor for mortality and ranked third as a cause of disability-adjusted life years. Treatment of hypertension is a major achievement of medicine in the second half of the 20th century. Major reductions in cardiovascular morbidity and mortality over the past 50 years have been attributed to the increased availability and use of pharmacological treatment for hypertension. The risk of cardiovascular disease in patients with hypertension is greatly reduced with effective antihypertensive therapy. All major types of cardiovascular events—stroke, coronary artery disease, heart failure, and cardiovascular death—and all-cause death are significantly reduced by blood pressure-lowering treatment, particularly stroke and heart failure. Reductions of stroke, major cardiovascular events, and cardiovascular death are proportional to reduction in blood pressure, suggesting that the main benefits of antihypertensive treatment are due to the reduction of blood pressure itself, regardless of the drugs employed. Absolute risk reduction with blood pressure lowering increases as the level of baseline cardiovascular risk increases. So-called “residual risk”, the rate of cardiovascular events occurring despite treatment, tends to be higher; the higher the risk level at baseline. Preexisting high risk might have a “ceiling effect” for treatment benefits, limiting the benefits of late intervention in different clinical settings. This would maximize the benefits of blood pressure reduction, especially in subjects at increased risk of side effects from indiscriminate blood pressure reduction. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers are now well-proven drugs for achievement of this “additional” cardiovascular protection. One such drug is perindopril, which has been shown to reduce cardiovascular and cerebrovascular events and mortality in several intervention trials, both alone and when combined with other drugs, such as indapamide or calcium channel blockers (CCBs). Combination antihypertensive therapy with ACE inhibitors and dihydropyridine CCBs, in particular, has been demonstrated to be effective in reducing cardiovascular and cerebrovascular mortality and morbidity in high-risk patients with hypertension. This effect is in part independent of blood pressure reduction, as the favorable effects observed are not entirely explained by control of blood pressure.

In conclusion, the major remaining need in hypertension management is the further improvement of the prevention of stroke and coronary events in hypertensive patients. This can be achieved by initiating therapeutic intervention in the earliest phases of hypertension and by maximizing protection in subjects with established vascular damage using more adequate antihypertensive treatments, as “lower” is not always “better”.

References
Is reduction in stroke more important than coronary events in hypertension?

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It is beyond any doubt that antihypertensive treatment lowers the risk of both stroke and coronary heart disease (CHD). In a classic paper, McMahon and colleagues combined the results of five placebo-controlled trials performed in elderly hypertensives. They showed that active treatment significantly reduced the incidence of both strokes by 34%—and CHD—by 19%—during the mean follow-up of five years.1 Stronger decrease of stroke, found in the majority of hypertension trials, is due to the tight association of blood pressure (BP) with strokes whereas in CHD, other factors also play an important role. These data illustrate the enormous success of hypertension management; further progress, however, is needed as the incidence of cardiovascular (CV) events is still much higher in hypertensive subjects than in normotensive subjects.

Should we focus our treatment on either stroke or CHD prevention? In my opinion, we should focus on neither, for two reasons:

1. Epidemiologic data clearly show that hypertension is associated with practically all forms of CV disease (CVD): in a recent study, the strongest associations were found for hemorrhagic strokes, ischemic strokes, stable angina, and myocardial infarction, but highly significant associations were also found for heart failure, peripheral arterial disease, and abdominal aortic aneurysm.2 We should prevent all these types of CVD, rather than focusing on one type in particular.

2. There is no special drug treatment for preventing a specific form of CVD. A meta-analysis comparing the first-line treatments of hypertension in placebo-controlled studies3 showed that calcium channel blockers had the strongest effect on stroke risk (RR, 0.58 compared to placebo), but it was counterbalanced by a higher incidence of heart failure (of about 20%). Angiotensin-converting enzyme (ACE) inhibitors and diuretics were the best in CHD prevention. Regarding the prevention of all CV events together, β-blockers were weaker (RR, 0.89), whereas the effects of diuretics, ACE inhibitors, and calcium channel blockers were similar (RR, 0.70; RR, 0.76; RR, 0.71; respectively); angiotensin-receptor blockers were not evaluated as there were no placebo-controlled studies in hypertension. These data bring arguments for the most modern therapeutic approach—combination therapy—that has an impact on all forms of CVD. Diuretics, ACE inhibitors, and calcium channel blockers are logically the first-choice drugs for such treatment.

What can be done better in hypertension management?

1. Proper diagnosis of hypertension

Classically, the diagnosis is based on office BP measurement. Mancia et al followed a cohort of subjects where office BP ambulatory BP, and home BP measurements were performed at baseline.4 They found that CV risk increased gradually with the number of pathologic BP values assessed by these three types of measurement: the best prognosis was found when all the methods gave normal BP. This approach should be studied further and, whenever possible, multiple methods of BP measurement should be used in clinical practice.

2. Evaluation of arterial stiffness

Physicians are accustomed to evaluating patients’ CV risk, but an important parameter is usually neglected: central artery stiffness. High stiffness is relatively specific for hypertension and is a strong prognostic factor over and above traditional CV risk factors.5 Long-term treatment has been shown to decrease aortic stiffness.6 Its introduction into clinical practice would reveal the high-risk patients who need special attention.

3. Early initiation of treatment

Data on early treatment and prevention of hypertension are scarce. The only prospective trial, TROPHY (TRial Of Preventing Hypertension),7 has shown that the onset of hypertension is delayed if antihypertensive treatment is started in subjects with high-normal BP. Early treatment would probably prevent development of severe hypertension, which is difficult to manage. Correct timing of treatment initiation is a challenge for future research.

References

Is reduction in stroke more important than coronary events in hypertension?

An emerging issue is the importance of lifetime risk and, in particular, the influence of individual cardiovascular risk factors on lifetime risk. A longitudinal study on lifetime risks in people over 30 years who were initially free from cardiovascular disease was published recently. This study included 1.25 million people and during the median follow-up of 5.2 years, 83,098 cardiovascular disease presentations were recorded. The lifetime risk of people with hypertension at the age of 30 years was 63.3% (95% CI, 62.9%-63.8%) compared with 46.1% (95% CI, 45.5%-46.8%) for normotensive people at a similar age. For myocardial infarction, the lifetime risk was 8.0% (95% CI, 7.8%-8.3%) in hypertensives compared to 5.5% (95% CI, 5.3%-5.8%) in normotensives. This difference occurred despite modern treatment of hypertension. The study also demonstrated that blood pressure may have different effects on different types of cardiovascular disease. For example, systolic blood pressure had the strongest association with intracerebral hemorrhage and stable angina, but the weakest association with abdominal aortic aneurysm.

In the largest meta-analysis of the treatment effects of hypertension, Thomopoulos et al recently calculated the absolute risk reductions of 68 clinical trials and showed the absolute risk reductions of cardiovascular events: stroke was reduced by 17 (95% CI, 13-20) cases per 1000 patients treated for 5 years as compared to a reduction of CHD of only 7 (95% CI, 4-10) cases per 1000 patients treated for 5 years, all for a standardized blood pressure reduction of 10 mm Hg in systolic and 5 mm Hg in diastolic blood pressure. Although CHD events were significantly reduced by blood pressure lowering, CHD events were not reduced to the same degree with blood pressure reduction as compared to stroke. The reason for this difference between stroke and CHD remains largely unexplained.

Treating elevated blood pressure leads to proportional reductions in stroke and CHD, but the absolute risk reduction is much larger for stroke than CHD. This difference in outcome emphasizes an unmet need for antihypertensive treatment. Many important questions still remain partially unanswered. Do we need different drugs to treat hypertension? Is effective antihypertensive treatment simply a question of compliance? Should we start the treatment of hypertension much earlier to prevent the maximum number of CHD events? Are specific antihypertensive drug combinations the answer? With regard to this last question, in ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) and ACCOMPLISH (Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension), there were better reductions in CHD with some combinations than others.

References
Here is no unequivocal answer to this question, as it is closely interrelated with numerous issues affecting arterial hypertension management. Among the most important, we should note: (i) our ability to predict a specific event in an individual patient; (ii) the different degree of blood pressure (BP)-dependency of stroke and coronary heart disease; (iii) the different potentials of major drug classes and their combinations to reduce specific event rates; (iv) demographic features of the population; and (v) the individual clinical situation.

Despite all our efforts, the type of event to which a patient is more at risk, and thus to be preferentially prevented, remains unknown. BP has an independent, continuous relationship with the incidence of both stroke and coronary events in all ages and ethnic groups, but stroke is recognized as being a more BP-dependent complication of arterial hypertension. In the latest European guidelines on arterial hypertension management, stroke mortality was suggested as a surrogate of hypertension status because of its close relationship with prevalence of arterial hypertension, BP control rates, and mortality. Rates of coronary events are less dependent on BP lowering, but strongly affected by statin use.

In patients with controlled arterial hypertension, we should be aware of residual risk. Here, pleiotropic properties of antihypertensive drugs and combinations are of greater importance. We should also keep in mind the so-called “stroke paradox,” the greater rate of strokes than myocardial infarctions recorded in some major randomized clinical trials on arterial hypertension. The potential exists to change the ratio of cerebrovascular and coronary complications in well-treated hypertensive patients.

Meta-analyses occasionally reveal superiority of one class of agents over another for some outcomes (eg, strokes or coronary events), but selection bias plays a role. Meta-analyses evaluating drugs’ effect on total mortality are thought to have fewer limitations and be more trustworthy. A strong message comes from a recent pooled analysis of 20 cardiovascular morbidity-mortality trials including 158,998 patients published in the European Heart Journal in 2012. Treatment with an ACE inhibitor resulted in a significant further reduction in all-cause mortality in hypertensive patients, and this finding was mainly driven by results from 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). All these trials, which studied the angiotensin-converting enzyme (ACE) inhibitor perindopril in combination with indapamide or amlodipine, had the largest, statistically significant mortality reductions. ASCOT-BPLA also provided support for the beneficial interaction between an ACE inhibitor/calium channel blocker combination and a statin.

Thus, we have evidence for the use of ACE inhibitor–based therapy and for combinations of at least two drugs (ACE inhibitor/thiazide diuretic and ACE inhibitor/calium channel blocker) to reduce both stroke and coronary events and to improve survival in hypertensive patients. In a short time, we will gain experience about the use of a fixed combination of indapamide and amlodipine, which is deemed to be especially beneficial in elderly patients. From 10% to 20% of patients require three drugs to control their BP effectively, and a combination of an ACE inhibitor, thiazide diuretic, and calcium channel blocker seems to be a promising choice.

Thus, we now have a ready-made answer to the question, “What is the major remaining need in hypertension management: reduction of stroke or reduction of coronary events?”, as a large number of confounding factors should be taken into consideration. The use of drugs providing a “circular defense” seems to represent a simple and pragmatic strategy.

References
Is reduction in stroke more important than coronary events in hypertension?

Arterial hypertension is a major risk factor for stroke and coronary heart disease. Reducing cuff blood pressure levels by treating hypertension using antihypertensive drugs has typically served as a reliable proxy for the primary prevention of blood pressure–related target-organ complications. This has been particularly true for stroke prevention. However, ischemic heart disease is common, and the management of hypertension in these patients remains difficult. It has been shown that, in terms of absolute risk, coronary heart disease is better prevented with antihypertensive drugs in high cardiovascular risk patients than low cardiovascular risk patients. However, residual risk also remains very high in the population with high cardiovascular risk. Some of the greatest challenges in hypertension are to determine the optimal cuff blood pressure goal and the best type of antihypertensive therapy in the coronary heart disease population.

The relationship between blood pressure achieved on treatment and cardiovascular morbidity and mortality in coronary heart disease patients seems to have a J-curve shape, with an optimal value of 130 mm Hg for the systolic component of blood pressure. A recent post hoc analysis of ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) in hypertensive coronary heart disease patients even shows that a low systolic blood pressure (<130 mm Hg) substantially decreases stroke risk, but without significantly increasing coronary heart disease risk.

These findings support the concept that patients with extensive vascular disease have a greater benefit of antihypertensive therapy at the level of the brain than the heart. Treatments that lower systolic blood pressure and simultaneously lower diastolic blood pressure too much may compromise myocardial perfusion. A recent analysis of Framingham Heart Study showed that recurrent cardiovascular events were more likely to occur with a diastolic blood pressure goal <70 mm Hg compared with 70-89 mm Hg, especially when pulse pressure was >68 mm Hg.

We need a better understanding of the respective roles of blood pressure components in cardiovascular risk, particularly in coronary heart disease risk. This could be tested in coronary heart disease patients with systolic hypertension, using different combinations of antihypertensive drugs (including angiotensin-converting enzyme inhibitors, calcium channel blockers, and diuretics) and at tighter and less strict goals of systolic blood pressure and diastolic blood pressure. Their impact on the development of new cardiovascular (especially coronary) complications should be measured, with concurrent attention paid to the potential role played by brachial pulse pressure, nocturnal blood pressure, and blood pressure variability.

The holy grail of antihypertensive treatment is to persistently reduce blood pressure to optimal goal levels with drug regimens that maximize target organ protection. The study designs outlined above could help answer this question.

References
The modern-day decline in cardiovascular age-adjusted death rates in developed countries constitutes a major improvement in population health. Efforts to control hypertension appear to have influenced both the decline in stroke and coronary heart disease (CHD) mortality rates; smoking cessation programs and control of high cholesterol and diabetes, particularly when combined with antihypertensive treatment, have also aided.¹

Despite improvements, cardiovascular disease (CVD) still remains the most common cause of death worldwide, and arterial hypertension continues to be the most important risk factor for stroke, coronary events, and premature death (13.5% of deaths, 54% of stroke, and 47% of CHD each year can be attributed to hypertension). Uncontrolled hypertension is a precursor of these poor outcomes.²

Presently in developed countries, nearly one in every three adults has hypertension. Although lowering elevated blood pressure (BP) is undoubtedly an effective way of reducing cardiovascular risk, only a quarter to a third of people receiving treatment for hypertension achieve adequate BP control,³,⁴ despite numerous guidelines and education programs.

Unfortunately, the actual situation—in insufficient BP control and prevalent hypertension-related morbidity and mortality—may worsen in future. With increasing life expectancy and burdens of comorbidities in developed countries, the prevalence of hypertension and its contribution to CVD will increase.⁵ Accordingly, hypertension management will become even more vital for population health. Numerous epidemiologic studies and clinical trials have demonstrated the importance of BP control in the global reduction of CVD-related mortality and have shown that the reduction in the incidence of stroke has been greater than the reduction in the incidence of myocardial infarction: 35% to 40% versus 20% to 25%, respectively.⁶ Although estimates vary, different models of risk prediction suggest that additional large reductions in stroke and CHD mortality are still feasible.

In pathophysiological terms, it is widely accepted that hypertension is a multifactorial and highly complex entity, where the endothelium and smooth muscle cells of the vasculature, and their responses to hypertension, play a central role. Patients who develop hypertension are known to have vasculature that behaves abnormally in response to vasoconstrictive stimuli. So, in essence, chronic hypertension is a vascular disease. In hypertensive patients, changes in vascular wall thickness cause increased arterial stiffness and augment the reflection of waves back to the aorta, resulting in increased systolic BP (increased central aortic BP) and widened pulse pressure. The main factors influencing the development of complicated hypertension are: decreased coronary perfusion pressures; increased myocardial oxygen consumption; left ventricular hypertrophy; and compromise of the cerebral and renal circulations. Some antihypertensive drugs can modify vascular remodeling in chronic hypertension, which may explain why these drugs improve outcomes in terms of secondary cardiovascular events.

With what we have learned in recent times, the major remaining need is the improvement of hypertension management: treating hypertension earlier, achieving BP control more rapidly, and obtaining better control rates. Implementing timely interventions with drugs that have proven efficacy will bring about the desired reductions in stroke and coronary events, as these are closely interrelated.

Important aspects of the epidemiology of BP and BP lowering provide support for: (i) the continuous, positive log-linear association between BP and vascular risk; (ii) absolute benefits of BP lowering are greatest in the presence of other vascular risk factors; (iii) deciding to lower BP based on cardiovascular risk, not just BP levels; and (iv) randomized trials showing the benefits of BP-lowering drugs in hypertensive and non-hypertensive patients.⁷

References
The latest meta-analysis of the benefits of blood pressure lowering showed that the major significant beneficiary in lowering blood pressure is reduction in heart failure (43%), followed by stroke (36%), cardiovascular death (18%), coronary heart disease (16%), and total mortality (11%). This meta-analysis, which looked at a total of 245,885 patients from studies published in both the English and non-English literature from 1960 to 2013, is arguably the most comprehensive and probably the most authoritative to date. In terms of number-needed-to-treat over 5 years (5-year NNT), this analysis showed that one has to treat only 59 patients to prevent 1 stroke. Analysis from a fiercely independent group, called the NNT Group (2010-2015), concluded that the 5-year NNT for primary prevention in moderate hypertension (blood pressure >160/100 mm Hg) is 67 for stroke and 100 for myocardial infarction. It is a well-known fact in the Asia-Pacific region that hypertension contributes more to stroke than it does to myocardial infarction. Up to 39% of ischemic heart disease (IHD) in the region can be attributed to hypertension, while the figure for stroke is almost twice that of IHD at 66%. A recent study looking into the perceptions of doctors and hypertensive patients in 7 countries across the Asia-Pacific region found that stroke as a consequence of hypertension is of most concern to these Asian patients. Worldwide, the most recent World Health Organization (WHO) report highlighted that IHD and stroke were two of the three leading causes of years of life lost (the other being lower respiratory tract infection).

It is also now well established that treatment of hypertension is able to prevent strokes as predicted from observational studies, but when it comes to IHD there is a shortfall compared with what is predicted. It is therefore obvious that although more can be done to prevent stroke (given that the relationship between blood pressure and stroke is almost linear), the major unmet (in other words “remaining”) need in hypertension treatment is for coronary event reduction. Coronary event reduction with blood pressure lowering has long been bogged down with lingering uncertainties. Foremost is the so-called J-curve phenomenon, which refuses to go away. Although this was first described in patients with established IHD and hypertension, it has since been suggested (though not confirmed) in studies looking at high-risk hypertensives, including diabetics. No such signal was seen with stroke and hypertension treatment across a spectrum of high-risk hypertensives. It is thus plausible that for coronary prevention, attention to other risk factors over and above blood pressure is the way forward. The most important of which is the control of hyperlipidemia, which has a primary prevention 5-year NNT of 60 for nonfatal myocardial infarction and a very impressive corresponding secondary prevention 5-year NNT of 39.8,7

In conclusion, the major remaining (unmet) needs in hypertension management indeed lie with reduction in coronary events. The answer may not center on more aggressive blood pressure reduction, but rather includes paying attention to other concurrent risk factors, the most well-studied and evidenced-based being optimal management of concurrent dyslipidemia. In the era of intense research into the “polypill”, a novel compound with properties to lower both lipids and blood pressure may be an important step forward.

References
Arterial hypertension is the most prevalent cardiovascular risk factor and constitutes the number one cause of death in the general population. The absence of adequate blood pressure control translates into progressive risk of developing cardiovascular disease in the heart, brain, and large arteries and also of developing chronic kidney disease. Both cardiovascular disease and chronic kidney disease are intimately bound together, and their origin and progression have many common risk factors. As an example, the finding of an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² has to be considered one of the five most frequent causes of acute coronary syndrome. In a recent publication, we described the existence of cross-talk between cardiovascular disease and chronic kidney disease. Treatment of cardiovascular disease often simultaneously protects against chronic kidney disease; in other words, prevention of coronary and cerebrovascular events is accompanied by a diminished progression of renal damage. One of the studies where this relationship between cardiovascular disease and chronic kidney disease protection was shown to be simultaneous was the ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation) trial, where simultaneous cardiovascular and renal protection was shown to occur with the administration of the combination of perindopril/indapamide. This protection was reinforced when a calcium channel blocker was added in third place to the angiotensin-converting enzyme inhibitor/diuretic combination. It is generally accepted that the control of blood pressure simultaneously prevents coronary and cerebrovascular events, but the relationship between blood pressure and events is stronger for stroke than for myocardial infarction. This explains why stroke is more prevalent in elderly hypertensives, in whom elevation of systolic blood pressure is highest due to the development of isolated systolic hypertension with aging. Coronary events are more prevalent at younger ages, but in elderly hypertensives they can also be seen; the cardiac consequence most frequently seen in the elderly with high blood pressure is heart failure. Adequate control of blood pressure in the elderly is followed by a significant decrease in the prevalence of stroke and heart failure, even at ages above 80 years, as shown in HYVET (Hypertension in the Very Elderly Trial). When chronic kidney disease develops, age has an influence on the possibility of developing end-stage renal disease. In younger patients, this possibility is greater; in the elderly, the result is often death, predominantly of cardiovascular origin, which is why the appearance of end-stage renal disease is less frequent. Blood pressure control together with adequate therapy for the remaining cardiovascular risk factors is ultimately mandatory to diminish the risk of both cardiac and cerebral events.

References
Since the beginning of the 1990s, we have known that antihypertensive therapy in patients with elevated blood pressure (BP) can prevent cardiovascular and cerebrovascular complications and death. It is also well known that the effect depends on the degree of BP lowering. A recent comprehensive meta-analysis by Thomopoulos et al confirmed these statements conclusively, with a stroke reduction rate above 30% and a reduction rate for coronary events around 20%. Explanation for the difference in the rates lies in the pathogenesis of these complications: stroke is a direct consequence of elevated BP, while coronary events are manifestations of atherosclerosis; for coronary events, arterial hypertension is just an accelerating risk factor.

The second observation from several meta-analyses is that all first-line antihypertensive drugs reduce cardiovascular and cerebrovascular complications to the same degree (with a small exception being for old β-blockers with stroke). However, meta-analyses have also shown that particular classes of drugs can reduce specific complications much more than other drugs. An elegant meta-analysis by Verdecchia et al showed that angiotensin-converting enzyme (ACE) inhibitors can reduce coronary events by 14% more than other antihypertensive drugs and that this effect was not BP-dependent. Similarly, calcium channel blockers (CCBs) can reduce the risk of stroke by 12%, also in a BP-independent manner. After publication of these data, some experts proposed so-called “effective prevention strategies” for some countries and regions.

It is well known that in majority of antihypertensive trials, the ratio of development of stroke and myocardial infarction was 1:1. However, this ratio varies in some countries, according to national medical statistics. For example, in Ukraine the ratio of stroke:myocardial infarction was 2:5:1. According to the proposed “effective prevention strategy”, the use of CCBs should in theory be more effective for prevention than the use of ACE inhibitors. However, these ideas do not consider the possibility that official statistics might only reveal a part of the truth. In Ukraine, some forms of acute coronary syndrome do not appear in official statistics because of documentation particularities and misdiagnosis as well. If we standardize these elements, we would obtain another set of statistics that resemble the data from trials more closely.

Recent European Society of Hypertension/European Society of Cardiology guidelines strongly recommend more frequent prescription of combinations, especially in high-risk patients. From real-life observational studies, it is well known that two thirds of patients receive ≥2 antihypertensive drugs. Considering all the arguments mentioned above, the use of ACE inhibitor and CCB combinations would be effective at preventing both stroke and myocardial infarction simultaneously. This has been proven in large-scale trials like ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) and ACCOMPLISH (Avoiding Cardiovascular events through COMBinatory therapy in Patients Living with Systolic Hypertension). Retrospective data from other studies, like EUROPA (European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease) and ADVANCE (Action in Diabetes and Vascular disease: Preterax and Diamicron MR Controlled Evaluation), have also shown that adding CCB to ACE inhibitor dramatically reduced the rates of cardiovascular and cerebrovascular end points.

So, we have to stop debating to what extent stroke prevention or myocardial infarction prevention is the priority. We have to realize that we can effectively prevent them both by prescribing ACE inhibitor and CCB combinations more often from the start.

References
Observational studies have demonstrated a linear relationship between blood pressure (BP) and the risk of cardiovascular events. Randomized controlled trials have found that lowering BP by as little as 10 mm Hg in patients with hypertension can reduce a person’s lifetime risk for cardiovascular and stroke death by 25% to 40%.1

In persons older than 50 years, systolic BP of more than 140 mm Hg is a much more important cardiovascular disease risk factor than diastolic BP. The risk of cardiovascular disease (CVD), beginning at 115/75 mm Hg, doubles with each increment of 20/10 mm Hg. Individuals who are normotensive at 55 years of age have a 90% lifetime risk for developing hypertension. Individuals with a systolic BP of 120 to 139 mm Hg or a diastolic BP of 80 to 89 mm Hg should be considered as prehypertensive, and they require health-promoting lifestyle modifications to prevent CVD.2

CVD is considered to be one of the major causes of death in Saudi Arabia according to the World Health Organization in its 2011 report,3 which also states that death from cardiovascular disease accounted for 46% of total deaths, ranking Saudi Arabia #32 in the world with a cardiovascular disease prevalence of 5.5% of the total population.

From the perspective of cardiologists, the major need is for the reduction of coronary events, because the reduction of stroke incidence is proportionally related to BP control, irrespective of the agent used to obtain BP control. At the same time, reducing BP does not necessarily lead to a reduction in coronary events or even cardiovascular outcomes, as many antihypertensive trials have failed to present a clear relation between these two parameters.

The goals of treatment should be to prevent the progression of underlying vascular changes and to act on all blood parameters simultaneously, as shown in ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial)4 in more than 19,000 patients with hypertension. In this trial, a combination of perindopril/amlodipine reduced major events, thanks to the synergy between angiotensin-converting enzyme inhibitor and calcium channel blocker (CCB) that affected all blood parameters and the vasculature.

Various substudies of ASCOT, like CAFE (Conduit Artery Function Evaluation),5 have provided further information on the superior efficacy of the amlodipine and perindopril strategy. The BP variability results with ambulatory blood pressure monitoring in ASCOT also help explain the unique outcomes obtained with the amlodipine and perindopril strategy, whose benefits are not limited to BP lowering alone.

The optimal clinical synergy between these medications has been confirmed in a post hoc analysis of EUROPA (EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease)6 in a stable coronary artery disease population with normal BP. Treatment with perindopril plus CCB reduced cardiovascular mortality, hospitalization for heart failure, and myocardial infarction by 41%, 54%, and 28%, respectively, compared with CCB alone. Comparison of hazard ratios suggests the presence of a clinical synergy between perindopril and CCB, with an overall effect greater than the sum of individual effects.

In conclusion, it is not “enough” to lower BP alone. The goals of treatment should be to prevent the progression of underlying vascular changes and to act on all blood parameters, which will reduce major complications and improve longevity. I think that if we take a wider view of these interesting goals, we will find that we still need to reduce coronary events further by modifying environmental factors or using drugs. We have a huge responsibility in terms of increasing our treatment standards in order to tackle and reduce all BP complications.

References
When initiating antihypertensive treatment, most hypertension guidelines have the goal of preventing cardiovascular disease. However, treated hypertensive patients, even when controlled, have significant levels of residual cardiovascular risk; in other words, lowering blood pressure per se is not sufficient. As pharmacological classes, and molecules within them, differ significantly from each other, it seems logical to adopt a tailored approach for each patient based on the progression of disease. Perindopril has compelling evidence supporting its initiation early in the diagnosis of hypertension, as its ability to reduce angiotensin II while preserving bradykinin protects patients from the progressive stiffening of large arteries and further alteration of the microcirculation. Bradykinin is involved in the fundamental mechanism of the additive, dose-dependent benefit of angiotensin-converting enzyme inhibitors for both blood pressure reduction and vascular protection. Bradykinin preservation may help explain the difference between renin-angiotensin-aldosterone system blockers in blood pressure reduction and coronary protection. However, many hypertensive patients already have stiffened arteries and substantial rarefaction of the microcirculation when diagnosed. Treatment with a combination of vasodilatory agents, such as thiazide-like diuretic and a calcium channel blocker (CCB), eg, indapamide and amlodipine, decreases wave reflection in the peripheral circulation and lowers systolic blood pressure. As such, CCB/diuretic is effective at decreasing the risk of stroke, a predominant risk in the elderly. A greater understanding of disease progression is essential for proposing the best treatment solutions to hypertensive patients.
Tailored-treatment approaches for the management of hypertension – Clavreul

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**The fundamentals of individualized treatment of hypertension**

Hypertension is the result of a process of aging of the cardiovascular system. As such, it should be considered as a progressive disease with multiple steps corresponding to different stages of alteration of blood vessels and organs.

Large arteries absorb the pulsatility of the blood ejected by the heart, by deforming themselves during systole and restoring the energy during diastole, in order to convert this pulsatility into a steady flow allowing peripheral organ perfusion. These properties rely on elastic fibers, which allow large arteries to distend, and collagen fibers, which act as the structural “backbone” of the artery. The pool of elastin is often considered to be established by birth; the process of aging, due to repeated pulsatile constraints, leads to a continuous fragmentation of these proteins, which have a very low rate of replacement. Metalloproteases, which are progressively upregulated, have been identified as important contributors to this phenomenon by degrading matrix proteins. Metalloproteases also favor the deposition and accumulation of collagen in the media, which is reorganized as a matrix, and lower its capacity to distort. As a consequence, intima-media thickness increases, with a progressive enlargement of proximal arteries, but not of distal arteries, which are more muscular.

In summary, with age large arteries lose their elastic properties and become stiffer. Risk factors such as obesity, dyslipidemia, or high glucose levels favor systemic inflammation that promotes endothelial dysfunction, through the generation of oxidative stress, and that decreases the bioavailability of the natural vasodilator nitric oxide. In addition to structural modifications, arteries also lose their mechanical capacity to vasodilate. A large number of mechanisms have been proposed to promote arterial wall stiffness, but the renin-angiotensin-aldosterone system (RAAS) seems to be particularly involved in this phenomenon.

The first consequence of large artery remodeling and endothelial dysfunction is an increase in the pressure necessary to stretch arteries during systole when blood is ejected into the ascending aorta. In addition, this dilatation of the aortic wall generates a pressure wave that moves along the arterial tree. The velocity of this pressure wave gives a measurement of arterial compliance, which is now widely recognized as an important independent marker of cardiovascular events and mortality. However, with progressive arterial stiffening, pressure waves move down the arteries faster, and this increased...
pulse wave velocity causes the reflected wave moving back toward the heart to overlap with incident wave during systole. This overlapping contributes to an increase in central systolic blood pressure due to a higher afterload on the ventricle. At the other end of the system, capillaries—especially those in the heart, brain, and kidneys—are the main source of blood pressure regulation, as they are responsible for most of the peripheral vascular resistance: about 50% for small arteries and arterioles (>350 μm in lumen diameter) and about 30% for capillaries (>7 μm in lumen diameter). They act as a filter to protect organs from damage by preventing large fluctuations in blood pressure from penetrating the microcirculation too deeply. However, when central blood pressure increases as a result of large artery stiffening, small arteries will undergo remodeling to comply with this increase in order to preserve their function as a protective filter. This remodeling is mostly qualified as eutrophic, with development of a thicker media in an inward direction, meaning blood flow is reduced. With time, this leads to wall rupture and microinfarcts due to the weaker structure of the microcirculation, fatigue, and uneven fragmentation of elastin. The consequent thrombosis can block blood flow and cause small vessels to collapse. This is the phenomenon of capillary rarefaction. Based on preclinical models, this phenomenon is considered to start with functional rarefaction—that is, blood vessels do not allow correct blood flow anymore—and lead to structural rarefaction, when actual blood vessels disappear. Both have been observed in hypertensive patients: primarily in the skin, but also in the myocardium. The immediate consequence is an increase in peripheral resistance as there are less small vessels to absorb central blood flow, and therefore blood pressure rises. In addition, due to this higher peripheral resistance, reflected waves that return to the heart are greater in amplitude and, as pulse wave velocity is already higher, add to the first systolic peak enhancing pulse pressure. Tissue perfusion is eventually reduced causing ischemic events. At the level of the heart, the diastolic blood pressure responsible for myocardial tissue perfusion becomes suboptimal. In addition, large artery stiffness is reinforced by capillary rarefaction of the nutritive blood vessels of the aorta. Interestingly, a recent analysis of the Framingham population has proven that development of arterial stiffness could precede the development of true hypertension by years. This means that upon diagnosis, vascular modifications have already been occurring and should be considered when initiating treatment. Furthermore, pharmacological strategies, though still effective, seem to have difficulty in lowering residual risk in patients with complicated hypertension. This could be a reflection of the advanced state of arterial modifications and the increased difficulty in reversing them. These two phenomena illustrate that, beyond blood pressure reduction, therapeutic strategies must address either the stiffness of large arteries to lower pulse wave velocity or enable vasodilation of the capillaries to prevent wave reflection in order to offer full, efficient protection from cardiovascular disease. Pharmacological strategies Pharmacological classes have been shown in numerous meta-analyses to be different to each other, with differences in specific beyond–blood pressure–lowering effects. Indication may also differ between molecules within a class. For instance, angiotensin-converting enzyme (ACE) inhibitors were shown, using meta-regression, to provide protection against coronary events even when not lowering blood pressure. Calcium channel blockers, on the other hand, are particularly good at preventing stroke. Another illustration comes from a recent meta-analysis by Thomopoulos et al that reported that for a similar blood pressure reduction of 10/5 mm Hg, ACE inhibitors would reduce coronary events by 35%, stroke by 48%, and heart failure by 53%, while ARBs would only reduce stroke and heart failure by 20% and 25%, respectively (Figure 1). This apparent absence of coronary event reduction with ARBs has been the subject of long-lasting debates since 2006, when the so-called “MI paradox” was first proposed. Debate about the paradox was recently resuscitated with the presentation of a meta-regression of randomized trials studying RAAS blockers. In this analysis, in the absence of any blood pressure reduction, the net effect of ARBs was to increase the rate of coronary events by 13%, while ACE in-
hibitors reduced these events by 9% (with the ACE inhibitor perindopril reducing events by 13%). In another meta-analysis in more than 100,000 patients, Savarese et al reported that perindopril did indeed prevent myocardial infarction better than other ACE inhibitors, with a 43% better reduction in the risk compared with ramipril, for instance.

In a previous meta-analysis of mortality in hypertensive patients, perindopril was shown to significantly reduce all-cause mortality by 13% and cardiovascular mortality by 22%, while the benefit of other ACE inhibitors and ARBs versus comparator was not obvious. In fact, in a large registry of more than 15,000 patients, it was demonstrated that newly treated hypertensive patients initiated on perindopril had a 8% lower risk of all-cause mortality and 15% lower risk of cardiovascular mortality compared with lisinopril. The rate of hospitalization for diabetes was also lower with perindopril. This illustrates that not only do pharmacological classes act differently, yielding different rates of outcomes, but also that within each class, molecules can differ significantly.

Based on the previous description of the development and progression of arterial disease, treatment strategy can be adapted with the objectives of stopping, or even reversing, the progression of large artery stiffness and of lowering wave reflection at the microcirculation level.

**Blockade of the RAAS**

As previously stated, the RAAS is intrinsically involved in the process of the stiffening of large arteries, as well as in the remodeling and progressive disappearance of small arteries and capillaries (Figure 2). Renin itself has been shown to promote the generation of reactive oxygen species via NADPH oxidase, by binding to the recently identified renin receptor. Nevertheless, angiotensin II is by far the most important mediator of impaired vascular function. Binding of angiotensin II to the AT$_2$ receptors has been shown to promote cardiac hyper trophy, and fibrosis, as well as a proatherogenic and proinflammatory state. For instance, in cardiac myocytes, stimulation of the AT$_2$ receptors is associated with cellular growth, hypertrophy, and fibrosis, despite a similar reduction in brachial blood pressure with both regimens. The prognostic value of reducing pulse wave velocity with perindopril has been demonstrated in patients with end-stage renal disease over a 10-year follow-up. In two groups of patients with similar brachial blood pressure reduction, those whose pulse wave velocity remained persistently high despite treatment were at significantly greater risk of mortality.

In addition, treatment with RAAS blockade has also been shown to improve myocardial capillary density in different models of hypertensive rats. Perindopril promoted new formation of blood vessels, which led to an increase in microcirculatory density and improved muscle perfusion. In hypertensive patients, coronary flow reserve has also been shown to improve consistently.

For ARBs, it was recently proposed that their positive effect on arterial stiffness and remodeling due to the reduction in angiotensin II binding to the AT$_1$ receptor was counterbalanced by unopposed stimulation of AT$_2$ receptors. Stimulation of AT$_2$ receptors is associated with cellular growth, hypertrophy, and fibrosis, as well as a proatherogenic and proinflammatory state. For instance, in cardiac myocytes, stimulation of the AT$_2$ receptors has been shown to promote cardiac hypertrophy. This pharmacological specificity may help explain the absence of reduction in coronary events associated with the use of ARBs, which was reported in the large meta-analysis that revealed the MI paradox in 2006. Interestingly, in vitro studies have revealed that the benefit of RAAS blockade on vascular stiffness or remodeling requires the presence of endothelial cells. This strongly suggests that the principal
mode of action of RAAS blockade is the preservation of the bioavailability of nitric oxide, a vasodilating and anti-inflammatory agent. Nitric oxide is massively scavenged by reactive oxygen species, whose production is stimulated by angiotensin II in hypertensive patients. Preservation of nitric oxide allows vascular smooth muscle to relax and prevents the expression of adhesion molecules and penetration of inflammatory cells. At the perivascular level, inhibition of the RAAS translates into lower metalloproteinase activity and reduction in collagen deposition. Preclinical models in hypertensive rats have shown that prolonged treatment with perindopril can improve vascular function, by decreasing pulse wave velocity, reducing markers of oxidative stress, and protecting against arterial remodeling.20

◆ Bradykinin, the essential partner in cardiovascular protection

Hypertension is characterized by an imbalance in the homeostasis between angiotensin II and bradykinin, the active mediator of the kallikrein-kinin pathway. Under normal conditions, bradykinin can oppose most of the deleterious vascular effects of angiotensin II: it is a potent vasodilator, but it also has anti-inflammatory and antiatherosclerotic properties that help maintain arterial compliance (Figure 2). In addition, bradykinin promotes the elimination of electrolytes and fluid by the kidney, which lowers cardiac output and enhances blood pressure reduction.24

Bradykinin is synthesized by endothelial cells and is stored as a precursor at their surface, being released upon stimulation. It binds locally to the bradykinin receptor and promotes the synthesis of the vasodilatory agents nitric oxide and prostacyclin.25 In hypertensive patients, the level of bradykinin has been reported to be abnormally low, and it has been clearly demonstrated that these patients have impaired vascular function, meaning a lack of nitric oxide response, which predisposes them to cardiovascular disease.31

It therefore seems logical to set up strategies that enable the restoration of normal endogenous levels of bradykinin and nitric oxide signaling to slow, or even reverse, the process of arterial stiffening. At the moment, there is no specific stimulator of the bradykinin receptor, and the most efficient way to do so is by using ACE inhibitors.33 ACE inhibitors have been shown to enhance bradykinin secretion at lower doses and before any therapeutic effect related to the reduction of angiotensin II occurs. Differences exist between the agents in this class, and Ceconi et al have shown that perindopril has the highest level of affinity for the bradykinin site of ACE compared with other ACE inhibitors.32 In practical terms, for the same reduction in angiotensin II, perindopril will have a greater effect on bradykinin preservation. The highly lipophilic profile of perindopril confers it with the ability to penetrate deeper into tissue, helping it exert this bradykinin-protecting effect. The EUROPA (EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease) trial is considered a good illustration of the pleiotropic effects of perindopril on blood vessels, especially endothelial function.22 Because blood pressure decreased only marginally in this population with coronary artery disease, the significant 20% reduction in cardiovascular morbidity and mortality must be explained by other factors, bradykinin being one of the first. In PERTINENT (PERindopril-Thrombosis InflammatioN, Endothelial dysfunction and Neurohormonal activation Trial), one year of treatment with perindopril 10 mg in patients with coronary artery disease significantly increased the level of bradykinin compared with placebo (+17%; P<0.05), with a direct enhancement of the nitric oxide pathway since the activity of endothelial nitric oxide synthase was upregulated versus placebo (+27%; P<0.05).24 In contrast, other ACE inhibitors failed to demonstrate the same vasculoprotective effect in large randomized trials: quinapril in QUIET (QUinapril Ischemic Event Trial) and trandolapril in PEACE (Prevention of Events with Angiotensin Converting Enzyme inhibition) both failed to reach their primary end point in a similar population.35,36 Preclinical studies confirmed that perindopril had the ability to protect...
endothelial cells of normotensive rats from apoptosis, while quinapril and trandolapril had no significant effect. As previously mentioned, a recent study in a large population of more than 15,000 patients also reported that newly diagnosed hypertensive patients initiated on perindopril rather than lisinopril had a significantly lower rate of all-cause mortality (-8%) and cardiovascular mortality (-15%) over a mean follow-up of 15 years.21

Another important aspect of bradykinin signaling is its pharmacologic response to ACE inhibitors, especially perindopril. Preclinical studies examining the effect of dose escalation with perindopril on both angiotensin II and bradykinin bioavailability in plasma revealed that upon administration of the ACE inhibitor, angiotensin II would rapidly decrease and become almost undetectable even with low dosages. Meanwhile, the concentration of bradykinin would gradually increase with higher dosages of perindopril, with no apparent plateau being reached at pharmacological dosages.37 This dose-dependent effect of perindopril on plasma bradykinin was further confirmed in healthy volunteers, where a single-dose administration of perindopril rapidly increased concentrations of this peptide in a linear, dose-dependent manner up to 20 mg. Plasma generation of angiotensin II was inhibited by 80% with the lowest dose of 2.5 mg of perindopril.38

From a mechanistic perspective, this sounds a rational explanation for the potentially greater effect on blood pressure reduction and blood vessel protection with ACE inhibitors compared with ARBs. Although both ACE inhibitors and ARBs downregulate angiotensin II signaling, only ACE inhibitors dose-dependently preserve bradykinin, a mechanism that becomes predominant at higher dosages and seems to be responsible for most of the cardioprotective effect of this class (Figure 3). Therefore, early administration of an ACE inhibitor with high selectivity for the bradykinin degradation site of angiotensin-converting enzyme is a prerequisite for obtaining the full benefits. Perindopril is an example of a RAAS blocker that at high dosage lowers blood pressure better than other RAAS blockers and of an effective cardioprotective agent, thanks to its antiremodeling properties (Figure 4).

◆ Vasodilation of small arteries: when stroke matters…

As previously described, hypertension is essentially the result of the aging process, and its diagnosis can happen at any stage of development of the disease. In developing countries, high blood pressure remains critically underdiagnosed, and early treatment with a vasculoprotective ACE inhibitor is not always possible.

When large arteries have stiffened to a high degree and a substantial proportion of the microcirculation has started to collapse, systolic blood pressure becomes critically high due to the joint effect of earlier wave return and increased wave reflection at the capillary level.10 Patients are therefore exposed to a particularly high risk of stroke, whose rate is linearly dependent on systolic blood pressure and which dramatically increases with age.39 For these patients, the most urgent step is to rapidly lower systolic blood pressure and because large arteries lack compliance, the best way to do this might be to promote vasodilation at the capillary level. This immediate-

![Figure 4. Schematic representation of perindopril-based strategies according to the stage of hypertension. In young hypertensives, perindopril (combined with indapamide or amlodipine when needed) will prevent early arterial remodeling and further consequences of arterial stiffness and raised central blood pressure at the capillary level. In aging hypertensive patients, for whom the risk of stroke is key, combination indapamide and amlodipine actively reduces wave reflection via peripheral vasodilation and is the most efficient strategy at reducing systolic blood pressure. Abbreviations: BP, blood pressure; PWV, pulse wave velocity.](image)
ly lowers the amount of wave reflection (Figure 4). Diuretics and calcium channel blockers are both powerful peripheral vasodilator agents. In these two classes of antihypertensive agents, indapamide and amlodipine have been shown to be among the most effective agents at lowering systolic blood pressure, and the recent EFFICIENT (Efficacy of a Fixed Combination of Indapamide sustained-release with amlodipine on blood pressure in hypertension) study confirmed the potency of the combination of indapamide and amlodipine for lowering systolic blood pressure and pulse pressure. A recent meta-analysis by the group of Messerli recently reported that combining these two classes proved to be systematically more efficient at reducing stroke in large randomized trials than other strategies (-23%).

Combining indapamide and/or amlodipine with perindopril has also been demonstrated in large trials to reduce stroke and mortality. In HYVET (Hypertension in the Very Elderly Trial), elderly patients receiving the combination of perindopril/indapamide experienced a significant 39% reduction in death from stroke \( (P=0.046) \), as well as a 21% reduction in all-cause death \( (P=0.02) \). In high-risk patients, the recent subanalysis of ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation) revealed that the relative risk of all-cause mortality fell by 28% in patients on calcium channel blocker at baseline who received combination perindopril/indapamide in addition, a new piece of evidence in the era of multiple combinations, as underlined in an editorial by Prof Barkris.

◆ The earlier, the better

The recent publication of ADVANCE-ON (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation–ObservatioNal study), the follow-up study over ten years of the ADVANCE trial that compared the perindopril/indapamide combination to standard treatment in diabetic patients, reported long-term preservation of the benefits provided by ACE inhibitor–based treatment. Indeed, while patients in both arms became rapidly equally treated, reaching the same blood pressure level, after the end of the randomized phase of the trial (4.5 years), a significant 9% reduction in all-cause mortality remained after 10 years in patients who received perindopril/indapamide at baseline versus standard therapy. These new results in particular highlight the long-term benefits of the well-known properties of perindopril on blood vessels, ie, protection of endothelial cells from apoptosis, preservation of the microcirculation at the organ level, and reversal of wall stiffness in large arteries. This example is a perfect illustration that starting with the right treatment early gives patients greater benefits in the future because the ability to reverse vascular remodeling is greater at a younger age.

An interesting preclinical study confirmed the benefit of using perindopril as early as possible. A strain of rats that spontaneously developed hypertension between the ages of 10 and 14 weeks were treated for a limited period either before or after the onset of raised blood pressure. When treatment was stopped, blood pressure rose again in the animals with the late, post-onset treatment, while the rats that received early treatment with perindopril never became hypertensive. In clinical practice, in major randomized trials such as EUROPA, ADVANCE, or PROGRESS (Perindopril pROtection aGainst REcurrent Stroke Study), patients treated with perindopril experienced the greatest benefit in terms of cardiovascular event reduction when they received treatment early on, with the lowest hazard ratio in patients under 60 years of age.

Time to blood pressure control is an important aspect of treatment success as well. A recent retrospective analysis of 1762 patients who received initial antihypertensive treatment confirmed that those who had received a combination from the beginning had a better rate of blood pressure control over the one-year follow-up period (median time to achieve blood pressure control of 9.7 versus 11.9 months; \( P=0.004 \)) and

![Figure 5. Benefit of faster blood pressure control.](image-url)
had a 34% lower risk of cardiovascular events (Figure 5).49 ACE inhibitors, even though a gold standard treatment for initiation of antihypertensive therapy for the reasons developed above, may need to be combined from the beginning to achieve this goal. A recent study comparing a new strategy for newly diagnosed hypertensive patients based on a combination of perindopril 3.5 mg and amlodipine 2.5 mg, which was then uptitrated by systematically doubling doses, was superior to a stepped-care strategy based on valsartan and amlodipine. In fact, the rate of blood pressure control was 23% and 27% higher in the perindopril/amlodipine group after 1 and 2 months of treatment, respectively.50

Together with the ADVANCE-ON study, this suggests that optimized combination treatment with perindopril will shift the odds in favor of patients, both by achieving blood pressure control earlier and by preserving the vascular structure of patients from further remodeling. An important feature of ACE inhibitors that allows their easy first-line administration is their excellent tolerability and the absence of dose-related adverse effects. With ARBs, individual trials as well as meta-analyses have reported a significant increase in the risk of kidney injury (+48%; \( P<0.001 \)), hyperkalemia (+57%; \( P=0.008 \)), and hypopotasmin (+56%; \( P<0.001 \)); the last of these is probably related to their mode of action, which is completely dependent on the abrupt blockade of the angiotensin pathway.51

Conclusion

Compelling evidence now supports the need to address the residual risk of hypertensive patients as much as their elevated blood pressure. An approach based on a thorough understanding of the pathophysiological development of the disease seems justified to maximize the potential of each pharmacological treatment. The cardiovascular protective properties of perindopril have been well demonstrated. Its early initiation in hypertensive patients allows a more efficient counteraction of the progressive remodeling of large arteries and, therefore, prevention of further alterations to the microcirculation, especially at the coronary level. Combining perindopril with amlodipine right from initiation in newly diagnosed hypertensive patients allows even faster blood pressure control. In patients with advanced vascular stiffness and capillary rarefaction, like the elderly for instance, the combination of indapamide and amlodipine allows the risk of stroke to be reduced by decreasing wave reflection, which lowers systolic blood pressure.

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Keywords: bradykinin; RAAS blockade; vasodilatation; early treatment; perindopril; indapamide; amlodipine

UN TRAITEMENT SUR MESURE POUR LA PRISE EN CHARGE DE L’HYPERTENSION

Au début d’un traitement antihypertenseur, le but de la plupart des recommandations sur l’hypertension est de pré-
venir la maladie cardio-vasculaire. Il existe cependant des risques cardio-vasculaires résiduels non négligeables chez
les patients hypertendus traités, même contrôlés ; autrement dit, abaisser la pression artérielle per se ne suffit pas.
Les classes pharmacologiques, et les molécules qui en font partie, diffèrent significativement les unes des autres, il
semble logique d’adopter un traitement sur mesure pour chaque patient, basé sur l’évolution de la maladie. Le pé-
réindopril, prescrit très tôt après le diagnostic de l’hypertension, présente des preuves irréfutables : grâce à son aptitude
diminuer l’angiotensine 2 tout en préservant la bradykinine, il protège les patients de la rigidité progressive des
grosses artères et de l’altération ultérieure de la microcirculation. La bradykinine est impliquée dans le mécanisme
fondamental de l’effet bénéfique supplémentaire dose-dépendant des inhibiteurs de l’enzyme de conversion de l’an-
giotensine, à la fois sur la diminution de la pression artérielle et sur la protection vasculaire. La préservation de la
bradykinine peut aider à expliquer la différence entre les antagonistes du système rénine-angiotensine-aldostère
e face à la diminution de la pression artérielle et à la protection coronaire. De nombreux patients hypertendus ont ce-
pendant déjà une rigidité artérielle et une raréfaction substantielle de la microcirculation au moment du diagnostic.
Un traitement composé d’une association de produits vasodilatateurs comme un diurétique thiazidique et un anta-
goniste calcique (AC), par exemple l’indapamide et l’amlodipine, diminue la réflexion de l’onde dans la circulation
périphérique et abaisse la pression systolique. C’est ainsi que l’association AC/diurétique est efficace pour diminuer
le risque d’AVC, principal risque chez les personnes âgées. Il faut absolument que l’évolution de la maladie soit mieux
comprise pour recommander les meilleures solutions de traitement aux patients hypertendus.
Some factors that can influence the adherence of patients to treatment (like those related to the health system) may be difficult to address or modify. However, by developing good relationships with patients, physicians and other members of the health-care team can address “human” factors like motivation (eg, by discussing and raising awareness of the level of cardiovascular risk associated with hypertension), and this can help to improve adherence. Other “human” factors, like emotional state, can also have major effects on adherence/compliance.

Despite increasing knowledge about hypertension and its available treatments, blood pressure control remains suboptimal, in part due to poor treatment adherence. Poor treatment adherence in hypertension remains a daily challenge for patients and is of considerable concern given the high number of patients that may be affected. This includes patients who discontinue treatment completely as well as those who take their treatment irregularly or interrupt treatment repeatedly. Health-care systems could make significant savings (financial and in terms of prevention of adverse outcomes) by promoting the benefits of good adherence. An improvement in patient awareness and motivation, and new tools, are required to fight poor treatment adherence in hypertension. Among these tools, the assessment of the psychological status of patients, the transtheoretical model, motivational interviewing, and multidisciplinary health-care team–based approaches could be of interest and should be promoted. All of the above have shown promise in improving treatment adherence in hypertension, and further studies should be undertaken to elucidate how further benefits could be obtained. Ultimately, better blood pressure control for our hypertensive patients will be the reward for these efforts.

Hypertension is today the leading cause of diseases and death with about 1 billion people affected in the world. Despite efficient ways of detecting it and multiple treatments available, the rate of diagnosis and blood pressure (BP) control remain critically low. This partly contributes to the fact that hypertension was a primary or contributing cause of 9.4 million (95% uncertainty interval [UI], 8.6-10.1 million) deaths in 2010. In addition to death, elevated BP is also associated with major disability, such as that caused by nonfatal strokes and heart attacks. As such, elevated BP is a leading risk factor for global disease burden in terms of global disability-adjusted life years (DALYs). In 1990, elevated BP was the fourth leading risk factor for global disease burden (5.5% [95% UI, 4.9%-6.0%] of DALYs), while in 2010, elevated BP was ranked as the number one risk factor for disability and accounted for 7.0% (95% UI, 6.2%-7.7%) of global DALYs.1

Different hypertension guidelines, eg, the 2013 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines,2 have been issued by various societies to assess BP goals in different types of patient population. These guidelines have established management tools to control BP by the use of pharmaco-
logical or nonpharmacological tools. Despite this, over the last two decades various studies and surveys have shown that the proportion of patients with controlled BP is suboptimal in many European countries and that less than 50% of treated patients attain goal BP. Overall, across all countries in the EURIKKA (EURopean study on cardiovascular risk prevention and mAnagemen in usual daily practice) study, the proportion of treated hypertensive patients who had attained goal BP was 34.8%.

**How does adherence affect BP control in clinical practice?**

The 2013 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines have identified causes for poor BP control in clinical practice:

1. Poor patient adherence to treatment is of considerable concern given the high number of patients who may be affected. This includes “discontinuers” (patients who discontinue treatment completely) and “bad users” (those who take their treatment irregularly or interrupt treatment repeatedly). Healthcare systems need to pay greater attention to the management of chronic diseases and must appreciate that significant savings (financial and prevention of adverse outcomes) can be made by promoting the benefits of adherence.

2. The reluctance or failure of physicians to initiate or intensify treatment in appropriate situations, which has been linked to several factors:
   - Doubts about the risk represented by high BP (particularly in the elderly).
   - Fear of morbidity/mortality due to a reduction in vital organ perfusion when BP is reduced too much (the J-curve phenomenon).
   - Concern about side effects.

Many countries have their own treatment guidelines, and within countries certain regions and even cities with large populations may produce their own treatment guidelines. The existence of different guidelines increases complexity and may be a potential source of confusion for physicians, who may be uncertain over which guidelines to follow.

Hence there is a need to develop new strategies to increase patient adherence, compliance, and persistence and to overcome clinical inertia. This suggests that there is a need for physician education, which should include the following topics in educational programs:

- The need for BP control to avoid sequelae associated with hypertension such as myocardial infarction, stroke, left ventricular hypertrophy, and microalbuminuria.
- Criteria for treatment intensification, particularly for patients receiving combination therapy who may already take other medication for comorbidities.
- The benefits of home and nurse BP testing, including obtaining information on diurnal variations in BP and avoidance of “white coat” hypertension.
- Information on the potential consequences of even modest elevations in BP.

**What factors can influence treatment adherence?**

The importance of adherence as a key factor in BP control is demonstrated by the fact that the 2013 ESH/ESC guidelines contains a section dedicated to the improvement of BP control in hypertension, and this section pays considerable attention to adherence and its improvement.

The 2013 ESH/ESC guidelines not only stress the importance of improving patient adherence in order to improve BP control, but also advise physicians on how they can monitor and attempt to improve patient management on several levels. Some factors that can influence the adherence of patients to treatment (like those related to the health system) may be difficult to address or modify. However, by developing good relationships with patients, physicians and other members of the healthcare team can address “human” factors like motivation (eg, by discussing and raising awareness of the level of cardiovascular risk associated with hypertension), and this can help to improve adherence. Other “human” factors, like emotional state, can also have major effects on adherence/compliance. Misperception of cardiovascular risk is an issue, since a “perception gap” exists, which can result in patients with an intermediate or high level of cardiovascular risk mistakenly perceiving themselves to be at low risk.

A large, prospective, community-based study investigated whether anxiety and five major components of personality could identify individuals likely to present with white coat or masked hypertension. There was a significant interaction between anxiety and use of antihypertensive medications in predicting white-coat effect ($P=0.0005$); in patients treated with antihypertensive medication, anxiety was associated with a 39% higher risk of pseudoresistant hypertension due to white-coat effect (Table I). Masked hypertension was not associated with any personality factor, although higher conscientiousness was associated with a lower risk of masked uncontrolled hypertension (odds ratio [OR], 0.70; 95% confidence interval [CI], 0.49-0.99). This study emphasizes that
and BP control. Physicians from hospital-based hypertension intervention to improve antihypertensive medication adherence. Pladevall and colleagues used a multifactorial in-patients and take into account stage of change and patient personalities. Pladevall and colleagues used a multifactorial intervention to improve antihypertensive medication adherence. Physicians who were more motivated had a more confident and optimistic approach towards hypertension. Importantly, physicians who were more motivated also appeared to be more empathetic and supportive towards patients and were characterised by having higher rates of patients with controlled BP (range 32% to 42%; \( P=0.01 \) for trend).18 Finally, research has also shown that a team-based approach to patient management can have a favorable effect on adherence and BP control. Hypertension management teams can comprise primary care physicians, nurses, and others (like pharmacists) who may have an especially important role to play. Some health-care professionals, like nurses, may be able to spend more time with patients than physicians and may also be able to make home visits and develop relationships with significant members of the patient’s social circle (such as relatives, close friends, or neighbors). For this reason, health-care professionals like nurses may be of particular importance in helping patients to implement important-but-challenging lifestyle changes beyond BP control, like smoking cessation or weight loss, and to adhere to their treatment.21,22 This type of team-based care has been associated with a reduction in systolic BP of \( \approx 10 \) mm Hg and an increase in BP control of \( \approx 22\% \). More generally, nurse- and pharmacist-based programs have been shown to reduce cardiovascular disease risk versus usual care.

**Does motivational interviewing improve adherent behavior?**

Motivational interviewing is a patient-centered, directive therapeutic approach that can be used to help patients embrace change, alter their behavior by exploring feelings and attitudes, and resolve areas of ambivalence. It is more focused and goal-directed than nondirective methods like counseling, in which therapists attempt to influence clients to consider making changes. Motivational interviewing works by enabling and engaging intrinsic motivation within patients to help them change their behavior, and it can be used to help patients improve adherence to medication. Studies have assessed the use of motivational interviewing

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pseudoresistant hypertension due to white coat effect</th>
<th>Masked uncontrolled hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1: Anxiety</td>
<td>1.39 (1.01-1.91)*</td>
<td>1.02 (0.72-1.43)</td>
</tr>
<tr>
<td>N: Neuroticism</td>
<td>1.02 (0.75-1.41)</td>
<td>0.82 (0.58-1.15)</td>
</tr>
<tr>
<td>E: Extraversion</td>
<td>1.02 (0.76-1.39)</td>
<td>0.94 (0.68-1.29)</td>
</tr>
<tr>
<td>O: Openness</td>
<td>1.11 (0.82-1.50)</td>
<td>0.89 (0.64-1.23)</td>
</tr>
<tr>
<td>A: Agreeableness</td>
<td>1.26 (0.93-1.72)</td>
<td>0.84 (0.60-1.17)</td>
</tr>
<tr>
<td>C: Conscientiousness</td>
<td>1.01 (0.74-1.40)</td>
<td>0.70 (0.49-0.99)*</td>
</tr>
</tbody>
</table>

Table 1. Association between different personality traits and the phenomena of white coat or masked uncontrolled hypertension in patients taking antihypertensive medication. *\( P<0.05 \)

Abbreviation: CI, confidence interval.

in the management of hypertensive patients and shown that it is possible to increase patients’ motivation to adhere and comply with their treatment. Various studies have assessed the use of motivational interviewing in the management of pa-
tients with hypertension. For example, in a randomized clin-
cial trial in 190 hypertensive African Americans (88% female; mean age 54 years), practice-based motivational interviewing counseling was compared with usual care, and the primary outcome was adherence measured by electronic pill moni-
tors. A steady maintenance of treatment adherence was ob-
served in those receiving motivational interviewing counsel-
ing compared with a decline in adherence in those receiving usual care (Figure 1). Furthermore, the between-group dif-
fferences in systolic BP and diastolic BP were −6.1 mm Hg (P=0.065) and −1.4 mm Hg (P=0.465), respectively, in favor of the motivational interviewing group.

Conclusion

In summary, treatment adherence in hypertension remains a daily challenge for patients. Despite increasing knowledge about hypertension and its available treatments, BP control remains suboptimal, in part due to poor adherence. This calls for an improvement in patient awareness and motivation to fight this disease with the use of new tools. Among them, the assessment of the psychological status of patients, motivation-
al interviewing, and transtheoretical modeling could be of inter-
est and should be promoted in the health-care community.

Figure 1. Motivational interviewing counseling resulted in steady maintenance of medication adherence compared with usual care after 12 months. Based on data from reference 22.

**P=0.94; ***P=0.027 versus usual care group.

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vention to improve antihypertensive medication adherence and blood pres-


Keywords: treatment adherence; patient compliance; hypertension; motivational interviewing; transtheoretical model; personality
Nouvelles stratégies pour améliorer l’adhésion au traitement dans l’hypertension

L’hypertension et ses traitements sont de mieux en mieux connus mais pourtant la pression artérielle demeure mal contrôlée, en partie à cause d’une mauvaise adhésion au traitement qui reste un obstacle quotidien pour les patients et un problème considérable compte tenu du nombre élevé de patients atteints. Cela concerne les patients qui arrêtent complètement leur traitement comme ceux qui le prennent irrégulièrement ou qui l’interrompent de façon répétée. Promouvoir les avantages d’une bonne adhésion pourrait engendrer des économies significatives pour le système de santé (financiers et en termes de prévention des effets secondaires). Combattre cette faible adhésion au traitement antihypertenseur nécessite d’améliorer la sensibilisation et la motivation du patient et de nouveaux outils. Parmi ces derniers, l’évaluation de l’état psychologique du patient, le modèle transthéorique, l’entretien de motivation et les approches en équipe multidisciplinaire sont intéressants et devraient être encouragés. Ils ont tous été prometteurs en termes d’amélioration de l’adhésion au traitement antihypertenseur et d’autres études sont nécessaires pour savoir comment obtenir des bénéfices supplémentaires. Enfin, ces efforts seront récompensés par un meilleur contrôle de la pression artérielle de nos patients hypertendus.
Over the last few years, the concept of early vascular aging (EVA) has supported research and clinical applications that aim to initiate preventive efforts early enough to influence the risk of cardiovascular disease. For example, young members of families at increased cardiovascular risk that are diagnosed with arterial stiffness and negative changes in hemodynamic control could be candidates for preventive efforts. Such efforts may be based on improved lifestyle habits and even early drug treatment if the absolute risk is considered to be high enough. However, how should EVA be defined? This question is yet to be settled, but one way is to target subjects with a carotid-femoral pulse wave velocity that is more than 2 standard deviations from that of the background population stratified for age and gender.

There is still no direct treatment of EVA, only recommendations for conventional cardiovascular risk factor control. However, new interventions are being developed, not only new antihypertensive drugs, but also resveratrol and new vasculoprotective drugs, eg, the selective angiotensin II type 2 (AT2) receptor agonist named Compound 21 (C21). Human studies are awaited. In France, the ongoing SPARTE study (Stratégie de Prévention Cardiovasculaire Basée sur la Rigidité Arterielle) aims to elucidate whether an intervention strategy targeting arterial stiffness is more beneficial in patients with hypertension than conventional and guidelines-directed treatment.

Medicographia. 2015;37:454-460 (see French abstract on page 460)
ment of central hemodynamics and arterial stiffness, components of great importance for understanding EVA, as summarized in a 2006 review in the European Heart Journal. It is believed that arteriosclerosis precedes the development of atherosclerosis, even if the two conditions tend to develop in parallel in adult life and in the elderly.

Arterial stiffness as the core of vascular aging
Arterial aging starts early in life and is a process that spans from normal aging to pathological aging and the profound changes related to atherosclerosis. This aging process involves all three layers of the arterial wall: (i) the intima, with endothelial dysfunction, decrease in nitric oxide (NO) production, local inflammation, and later on, fatty streaks as early signs of atherosclerosis; (ii) the media, with decreasing levels of elastin and a relative increase in collagen content with cross-linkages enhanced by detrimental effects of protein glycosylation; and finally (iii) the adventitia, with impairment of innervation and neuronal control, a less functional vasa vasorum and development of perivascular fat deposits that may increase local inflammatory actions that can negatively impact vasodilation.

Thus, arterial aging should be understood as a general process involving many different components of the entire arterial wall, as shown in Figure 1. Furthermore, this aging process involves not only the large elastic arteries (with their elastic content of the media), but also other parts of the entire vascular system, for example, remodeling of small arteries due to an increase in blood pressure. There is also a negative impact on the microvasculature of stiff large arteries when the pulse wave energy is transmitted to the microcirculation, causing damage. Thus, the EVA concept goes beyond both atherosclerosis and arterial aging for a more holistic view on the vascular system undergoing aging with superimposed disease processes. This cross-talk between the macro- and microcirculation is evident in the origin of vascular brain damage and impaired cognitive function. Finally, it should be noted that structural changes in the vasculature correspond with a number of hemodynamic changes associated with aging, what can be called hemodynamic aging in relation to EVA.

How should EVA be defined?
Arterial aging was first named and systematically studied in Italy by Taddei et al and in the United States by Lakatta et al in the BLSA study (Baltimore Longitudinal Study of Aging). During the same period, and having already begun in the 1980s, researchers in Maastricht (Struijker-Bourdier, Stehouwer, et al), Ghent (Van Bortel, Rietzschel, Segers, et al), and Paris (Safar, London, Laurent, Benetos, Boutouyrie, Bla-

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**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>BLSA</td>
<td>Baltimore Longitudinal Study of Aging</td>
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<tr>
<td>c-f PWV</td>
<td>carotid-femoral pulse wave velocity</td>
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<tr>
<td>C21</td>
<td>Compound 21</td>
</tr>
<tr>
<td>CKD</td>
<td>chronic kidney disease</td>
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<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
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<tr>
<td>ESH</td>
<td>European Society of Hypertension</td>
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<tr>
<td>EVA</td>
<td>early vascular aging</td>
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<tr>
<td>LDL</td>
<td>low-density lipoprotein</td>
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<tr>
<td>RAS</td>
<td>renin-angiotensin system</td>
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<tr>
<td>SCORE</td>
<td>Systemic COronary Risk Evaluation</td>
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<tr>
<td>SD</td>
<td>standard deviation</td>
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<tr>
<td>SNS</td>
<td>sympathetic nervous system</td>
</tr>
<tr>
<td>SPARTE</td>
<td>Stratégie de Prévention Cardiovasculaire Basée sur la Rigidité Arterielle</td>
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</table>
cher, et al\textsuperscript{23-26} contributed important findings to describe arterial stiffness and changes in central wave reflections shaping the hemodynamics of aging, as well as changes in the microcirculation. In recent years, Dzau, Safar, and O’Rourke coined the term “the cardiovascular aging continuum” to describe the long road from risk factors to cardiovascular events and post-event complications.\textsuperscript{26}

The EVA concept, which emerged in 2008,\textsuperscript{2,6} is now being extensively studied in different population-based cohorts in Europe, Asia, Africa, and Latin America, but still no general definition has been agreed upon. A number of risk markers constitute the background knowledge of EVA, with arterial (aortic stiffness) as the core variable (Table I). One way to define EVA could therefore be to select the outliers according to the normal range of carotid-femoral pulse wave velocity (c-f PWV), ie, more than 2 standard deviations (SD) above the normal distribution of c-f PWV based on data from the European reference group.\textsuperscript{27} Another way to describe EVA is based on statistical methods when arterial stiffness (measured by c-f PWV)—a central aspect of EVA—is used as the dependent variable in multiple regression analyses, and a number of risk markers or characteristics are used as independent variables, based on data from population-based studies. As the influence of hemodynamic changes and sympathetic nervous system (SNS) stimulation on the arterial tone is substantial, the data are normally adjusted for mean arterial pressure (MAP) and heart rate, the latter being a marker of SNS activity. Such investigations in a population-based study of elderly subjects (n=3700; mean age, 71 years) in Malmö, Sweden, has revealed that markers of glucose metabolism and dyslipidemia (elevated triglycerides, low high-density lipoprotein [HDL] cholesterol levels), as well as waist circumference (a marker of active abdominal fat tissue with inflammatory action), are significantly associated with arterial stiffness (c-f PWV), but not LDL cholesterol, smoking, or cystatin-C, a marker of impaired renal function.\textsuperscript{28} The findings thus point to two different clusters of cardiovascular risk factors involved in development of arteriosclerosis and atherosclerosis, respectively. Levels of arterial stiffness were also higher in subjects with known or newly detected diabetes, as compared with nondiabetic subjects. In another set of analyses from the same cohort, it was shown that arterial stiffness, at least at the higher end of the distribution, is associated with impaired cognitive function as measured in a cross-sectional analysis, especially concerning testing of “speed and executive” function.\textsuperscript{29} Vascular aging is thus linked to brain and cognitive aging.

In northern Portugal, in the Gumarães study, Cunha and colleagues have screened more than 2500 local inhabitants from an area known for a high stroke incidence, one of the highest in the western part of Europe.\textsuperscript{30} In that study, the authors wanted to screen for the proportion of subjects with characteristics of EVA in that stroke-prone population. The method they used to define EVA subjects was the one based on c-f PWV more than 2 SDs above normal in the European database. The findings were remarkable, with a very high proportion defined as EVA subjects in the young, especially in young men.\textsuperscript{30} The causes are unknown; however, that finding calls for screening and treatment of cardiovascular risk factors, including blood pressure control and improved lifestyle, in these subjects.

Also, in the Belgian Asklepios study, arterial aging has been determined in a healthy population by use of measures of arterial stiffness and ultrasound examinations of large arteries.\textsuperscript{31} The findings showed that femoral arterial stiffness was higher in men than in women, but did not change with age and no age-gender interaction was evident. Carotid arterial stiffness increased with age and showed a significant age-gender interaction, with carotid stiffness increasing more rapidly in women than in men, crossing over around the age of 45 years. Aortic pulse wave velocity did not differ between men and women, but did increase with age. No age-gender interaction was evident. The authors concluded that the relation with age and gender of local and central stiffness measures is not the same over the age range of 35-55 in apparently healthy men and women. Whether age-gender effects, as evident in the carotid artery, are found centrally depends on the central stiffness parameter used.\textsuperscript{31}

It is thus of great importance to have a number of population-based studies to compare between, especially for characteristics of EVA and the prevalence rates in different age groups. Studies from other ethnic groups are also very much needed.

**Prediction of cardiovascular disease based on arterial stiffness**

Stiffening of the large arteries known as arterial stiffness (arteriosclerosis) has been shown to be an important risk marker for future cardiovascular events and mortality beyond well-known cardiovascular risk factors, based on two updated meta-analyses.\textsuperscript{32,33} The prediction of total mortality hints that arterial stiffness could be a marker of aging and frailty in gen-

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**Table I. Proposed components (criteria) for definition of the early vascular aging syndrome.**

<table>
<thead>
<tr>
<th><strong>Primary criterion</strong></th>
<th><strong>Secondary criteria</strong></th>
</tr>
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<tbody>
<tr>
<td>– Arterial stiffness (aortic pulse wave velocity), more than 2 SDs above values in the background population</td>
<td>– Chronic inflammation, general and perivascular</td>
</tr>
<tr>
<td></td>
<td>– Impaired glucose metabolism, including insulin resistance</td>
</tr>
<tr>
<td></td>
<td>– Dyslipidemia (high TG and low HDL cholesterol levels)</td>
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<tr>
<td></td>
<td>– Telomere shortening/attrition</td>
</tr>
<tr>
<td></td>
<td>– Cognitive dysfunction and brain aging</td>
</tr>
<tr>
<td></td>
<td>– Disturbances of the microcirculation</td>
</tr>
</tbody>
</table>

Abbreviations: HDL, high-density lipoprotein; SD, standard deviation; TG, triglycerides.
eral, including increased risk of many causes of mortality. Measurement of arterial stiffness is preferably performed by use of c-f PWV, with a risk threshold of 10 m/s according to an updated consensus document from 2012 published in the Journal of Hypertension. This can be achieved by both direct and indirect methods, which are reasonably well correlated with each other in most cases, even if the direct measurement (c-f PWV) is preferred. Arterial stiffness is known to be strongly associated with age and hypertension, findings also confirmed in a longitudinal study from the United States. The arterial aging is tightly intercorrelated with blood pressure and causes the increase in pulse pressure seen in aged individuals. In some individuals, the arterial stiffening seen with increasing age is more pronounced and occurs earlier in life, a marker of EVA. In fact, a number of nonhemodynamic components are thought to affect arterial aging, such as hyperglycemia and dyslipidemia. Several cross-sectional studies have shown an association between arterial stiffness and diabetes as well as with markers of impaired glucose metabolism. This is also evident in subjects with end-stage renal disease (ESRD) with an increased central arterial stiffness. However, results from studies investigating the association between arterial stiffness and other and milder stages of chronic kidney disease (CKD) have presented conflicting results. For example, hypercholesterolemia—and that the degree of albuminuria is a marker of this increased risk, easy to quantify. More studies are needed for evaluation of vascular calcification as an important part of the arterial aging phenomenon in CKD patients.

How can we build awareness and interest in knowing one’s vascular age?

It is a common human finding that most people are interested in their health and would like to avoid disease if possible, especially for members of families at increased risk of cardiovascular metabolic disorders. Attempts have been made to develop models to show cardiovascular risk estimation; one example is based on the European Systemic COronary Risk Evaluation (SCORE). In both SCORE and the Framingham project, another model has been proposed, one that calculates the so-called cardiovascular risk age, where conventional risk factors for coronary heart disease are used, not arterial stiffness (PWV) itself.

In recent years, many manufacturers of modern devices that estimate, either directly or indirectly, the stiffness of the aorta have launched models to calculate vascular age based on stiffness estimation. As the gold standard methods (Complior, Sphygmocor) for direct assessment of c-f PWV have until now been expensive to use—though becoming less so with time—other devices with various ways of indirect measurement have been marketed (Arteriograph, Mobil-O-Graph, the CAVI system [cardio-ankle vascular index], etc). The increasing attention to arterial stiffness and vascular aging, not only among physicians, but also among patients and lay people has led to the development of various ways to calculate the vascular age based on algorithms where background factors (age, sex, body mass index, blood pressure, smoking) are entered together with some kind of measure of aortic stiffness or central hemodynamics. In the end, it is possible to show an individual’s vascular age in relation to chronological age, or at least an approximation. If elevated, this sends a strong message that a discrepancy is present and that signs of early aging are detected. Patients may understand this to reflect not only vascular aging, but in a more general sense, biological aging, which may trigger different reactions, perhaps even fear and anxiety. However, if the physician-patient relationship is good and based on mutual trust and understanding, this can lead later on to positive changes in lifestyle. It may also encourage patients to accept new drug treatment for risk factors, for example, elevated blood pressure.

Poor adherence to preventive drug therapy is a well-described problem. If new pedagogical models can improve adherence, this could translate into a more solid cardiovascular risk reduction, for example, if somebody decides to quit smoking or to restart previously abandoned therapy for hypertension and hyperlipidemia. The estimates of vascular aging (arterial stiffness) can even be followed over time at repeat visits. That can provide the patient with useful feedback information further reinforcing healthy lifestyle changes and adherence to drug therapy. A similar, well-known approach is used with diabetic patients, who are taught and encouraged to follow their own fasting glucose levels via home measurements and to keep a diary of habits and plasma glucose levels, as well as their glycated hemoglobin A1c (HbA1c) levels.

In preventive cardiology, we need to find new ways to increase interest in cardiovascular risk and awareness to promote healthy changes. At the same time, we have to be cautious not to overexaggerate findings for risk markers that could be influenced by technical shortcomings. Due to methodological variation, which clinicians are very accustomed to and understand, it is better to rely on repeated measures rather than to put too much emphasis on single measurements.

Treatment of arterial stiffness

Different methods have been proposed to treat or retard the process of arterial stiffening as a reflection of vascular aging, and a number of suggested interventions are shown in Table II. So far, one observational analysis of 294 patients with a prolonged follow-up period has shown that, beyond blood pressure control, prolonged control of hypertension reverses early vascular changes and has a long-term beneficial influence on arterial stiffness with decreasing c-f PWV levels over time. It is suggested that blocking the renin-angiotensin system (RAS) or using calcium antagonists could be of special relevance, based both on experimental and clinical studies.
Focus

Table II. Potential treatment modalities for early vascular aging (and its core component, arterial stiffness).

- **Specific**
  - Not established

- **Experimental**
  - Resveratrol
  - Elastase inhibitors
  - MMP inhibitors
  - AGE breakers (ie, thiazolidine)
  - Anti-inflammation (ie, TNF-α antagonists)
  - Sirtuins (ie, PARP-1 inhibitors)
  - GH/IGF-1 supplementation

- **Conventional**
  - Lifestyle improvement (exercise, caloric restriction, Mediterranean diet, smoking cessation)
  - Blood pressure control via antihypertensive drugs (in particular by use of RAS blockers, calcium antagonists)
  - Statins
  - L-arginine
  - Hormonal therapies

Only one large intervention study addressing arterial stiffness (as the core component of EVA) is currently ongoing. This is the randomized controlled SPARTE study (Stratégie de Prévention Cardiovasculaire Basée sur la Rigidité Arterielle) in France, aiming to compare a treatment strategy for reduction of arterial stiffness (c-f PWV) by different means, including drugs that specifically influence the RAS, with another treatment strategy (control) for controlling conventional risk factors, including blood pressure, as suggested in guidelines. The SPARTE study is planned to continue for a number of years, until a sufficient number of cardiovascular end points has accumulated in order to show potential differences in outcomes between the treatment arms. Recruitment is ongoing, eventually also for patients outside of France in collaboration with the European Society of Hypertension (ESH).

It is important to note that a number of new antihypertensive drugs are under development at various stages of preclinical and clinical studies, as reviewed by Laurent et al in the Lancet.

**Multiple cardiovascular risk factor control for EVA**

As increased c-f PWV has been documented to be an independent risk marker for future cardiovascular events and total mortality in recent meta-analyses, there is a need to target it with multiple-risk-factor control, aiming for a c-f PWV measure under 10 m/s, the current threshold for increased risk. Whether this also holds true in patients with established type 2 diabetes is currently unknown. However, it is plausible and very likely that it takes a multidrug intervention to achieve positive results in these patients, because of the advanced stage of vascular disease and the combination of atherosclerosis, atherosclerosis, and chronic inflammation further enhanced by hyperglycemia and insulin resistance. This strategy is also emphasized in the recent European guidelines on risk factor control in patients with diabetes, prediabetes, or impaired glucose metabolism. In clinical practice, this means that cardiovascular risk patients should be offered antihypertensive and lipid-lowering drugs (statins) as well as antidiabetic drugs if needed, but they should also stop smoking (facilitated by drugs if necessary) and take aspirin, the latter only in secondary prevention.

The treatment should also be patient-centered and based on motivation, information, and effective systems for clinical follow-up.

**New and emerging therapies**

There exist a number of potential therapeutic alternatives for treatment of vascular aging, but still no specific treatment directed against arterial stiffness itself (Table II). Recently, new discoveries for better understanding the RAS have led to the development of a selective angiotensin II type 2 (AT2) receptor agonist called Compound 21 (C21). This rather small molecule increases the physiological defense mechanism in the vascular system, providing some vascular protection based on anti-inflammatory and antiremodeling effects on the arterial wall. Still, only data from animal experiments are available, but these have shown a reduction in arterial stiffness in experimental models of induced hypertension. The interesting aspect is that the blood pressure effect is rather limited, so this could be a way to selectively improve arterial compliance. Other beneficial actions of C21 include neuroprotection and improved glucose metabolism. This means that the drug will also be tested in other animal models of disease. If these intervention effects can also be repeated in humans and with a positive tolerance profile, the drug could be used for vascular protection in combination with more conventional antihypertensive and lipid-lowering drugs. So far, the safety profile seems to be beneficial in animal experiments, even at supranormal dosages of C21. Human studies are planned to begin during 2015 or 2016.

There have been high hopes for dietary modification of vascular aging, for example, by use of resveratrol, an extract from red wine flavonoids. The benefits of the Mediterranean diet are well known, and one Dutch study showed beneficial influences in adolescence and early adulthood. The authors concluded that this kind of diet may be an important means of preventing arterial stiffness in adulthood.

**Summary**

EVA as a new concept for research and early prevention has sparked interest among many physicians, and offers new perspectives. Current medical and surgical therapies will be ex-
panded in the future for better control of the pathological processes involved, even for the control of arterial aging. If stiffness of large arteries can be controlled, this may also benefit the microvasculature, as the transmission of pulse wave energy to the periphery will decrease. New interventions are needed to address the role of blood glucose and advanced glycation end products for worsening EVA, as are methods to counteract this detrimental influence on the arterial wall. A better control of arterial stiffness and central hemodynamics could eventually translate into improved prognosis and reduced risk of CVD events. What can be done now is to aim for an effective 24-hour blood pressure control, both for brachial and central blood pressure. This requires drug combination therapy in many patients, where RAS blockers and calcium antagonists should be preferred. If patients can be convinced that arterial and vascular aging is of concern to them, this will increase understanding and adherence to therapy, thereby contributing to cardiovascular prevention: the earlier, the better!

Acknowledgments. This review was supported by two grants from the Research Council of Sweden for research on early vascular aging and cardiovascular risk factors.

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**Keywords:** aging; arterial stiffness; blood pressure; C21; drugs; family; glycemia; hypertension; vascular

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**ÂGE VASCULAIRE : COMMENT LE DÉTERMINER ?**

**Quelles applications en pratique clinique ?**

Ces dernières années, le concept de vieillissement vasculaire précoce (VVP) a appuyé la recherche et les applications cliniques afin de mettre en place une prévention suffisamment précoce pour influer sur le risque de maladie cardio-vasculaire. Un exemple de candidats à la prévention pourrait être les jeunes membres d’une famille à risque cardio-vasculaire augmenté, diagnostiqués pour une rigidité aortique et des modifications négatives du contrôle hémodynamique. Ces efforts pourraient porter sur une amélioration du style de vie et même un traitement médicamenteux plus précoce en cas de risque absolu suffisamment élevé. Cependant, comment définir le VVP ? La question n’est pas encore réglée mais on pourrait cibler les sujets ayant une vitesse de l’onde de pouls carotido-fémorale supérieure à 2 déviations standard de celle de la population de référence stratifiée pour l’âge et le sexe. Le traitement spécifique du VVP n’existant toujours pas, les recommandations pour le contrôle du facteur classique du risque cardio-vasculaire sont la seule possibilité. De nouveaux traitements sont néanmoins en développement et pas seulement de nouveaux antihypertenseurs, mais aussi le resvératrol et de nouveaux médicaments vasculoprotecteurs comme le composé 21 (C21), agoniste sélectif du récepteur de l’angiotensine II de type 2 (AT2). Des études chez l’homme sont attendues. En France, l’étude en cours SPARTE (Stratégie de Prévention cardiovasculaire basée sur la rigidité AR-TEnelle), cherche à savoir si traiter la rigidité artérielle est plus bénéfique pour les patients hypertendus qu’un traitement classique selon les recommandations.
Chronic kidney disease (CKD) is common, affecting more than 10% of the adult population, and has been clearly demonstrated to be a strong risk factor for cardiovascular events. Developing effective treatment strategies for this population is therefore important. A range of processes are likely to be key in mediating this excess cardiovascular risk, including atherosclerosis, arteriosclerosis, left ventricular hypertrophy, atrial fibrillation, and others. Different of approaches are therefore likely to be required to abrogate the excess cardiovascular risk in CKD. Blood pressure elevations are common in CKD, and are likely to be important in most or all of the mechanisms causing elevated cardiovascular risk in CKD. The available data suggest that blood pressure lowering substantially reduces the risk of cardiovascular events in CKD, and that agents acting via the renin-angiotensin system are preferred due to their coexistent renoprotective benefits. Lipid lowering prevents atherosclerotic cardiovascular events in early CKD, but other mechanisms may be more important as kidney function declines. Recent studies suggest that strategies targeting metabolic bone disease may modulate the risk of cardiovascular events, but more studies are required to define the optimal approach. Other approaches have been disappointing to date, highlighting the need for continued effort and innovation in this area.

Reducing the excess vascular risk associated with chronic kidney disease

by M. G. Wong and V. Perkovic, Australia

Chronic kidney disease (CKD) is common, affecting more than 10% of the adult population, and has been clearly demonstrated to be a strong risk factor for cardiovascular events. Developing effective treatment strategies for this population is therefore important. A range of processes are likely to be key in mediating this excess cardiovascular risk, including atherosclerosis, arteriosclerosis, left ventricular hypertrophy, atrial fibrillation, and others. Different of approaches are therefore likely to be required to abrogate the excess cardiovascular risk in CKD. Blood pressure elevations are common in CKD, and are likely to be important in most or all of the mechanisms causing elevated cardiovascular risk in CKD. The available data suggest that blood pressure lowering substantially reduces the risk of cardiovascular events in CKD, and that agents acting via the renin-angiotensin system are preferred due to their coexistent renoprotective benefits. Lipid lowering prevents atherosclerotic cardiovascular events in early CKD, but other mechanisms may be more important as kidney function declines. Recent studies suggest that strategies targeting metabolic bone disease may modulate the risk of cardiovascular events, but more studies are required to define the optimal approach. Other approaches have been disappointing to date, highlighting the need for continued effort and innovation in this area.

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Arteriosclerosis progressively and substantially increases in people with chronic kidney disease. This has been demonstrated from both an anatomical perspective, with a rapid increase in the risk of vascular thickening and calcification in the presence of reduced kidney function, and a functional perspective, with an increase in markers of arterial stiffness. These factors are likely to be important contributors to the increased risk of left ventricular hypertrophy and heart failure in chronic kidney disease.”
Despite the well-documented increase in cardiovascular risk with kidney disease, current risk prediction tools do not currently incorporate kidney disease markers in risk estimation equations, leading to underestimation of risk and suboptimal prevention measures in patients with CKD. Cardiovascular disease is frequently underdiagnosed and undertreated in patients with CKD. This group of patients should, therefore, be acknowledged as having high cardiovascular risk that needs particular attention at an individual level.

A growing number of studies and clinical trials, either conducted specifically in CKD populations or through analyses of CKD subgroups, and systematic reviews have shed light on the processes involved in elevating cardiovascular risk in CKD and on strategies for the prevention of cardiovascular events in people with CKD.

### Pathophysiological mechanisms

Increased cardiovascular risk in individuals with CKD is due partly to the high prevalence of traditional risk factors, such as hypertension and diabetes, which increase the risk of the development and progression of atherosclerosis. The associations of kidney function with cardiovascular risk and albuminuria with cardiovascular risk are, however, independent of these traditional cardiovascular risk factors. Thus, non-traditional kidney-specific mechanisms make notable contributions to cardiovascular risk, and a number of recent studies have highlighted the role of factors such as arteriosclerosis and vascular calcification in the risk of adverse cardiovascular outcomes in CKD. Evidence currently available suggests that both probably play a role.

A broad range of risk factors are likely to be important in this regard. Hypertension, a well-known and strong risk factor for cardiovascular disease in the general population. Additionally, CKD is associated with a range of metabolic abnormalities, the so-called milieu of uremic toxicity, and involvement of the neurohormonal axis, including the renin-angiotensin system, vitamin D receptors, and altered bone metabolism (eg, phosphatase, parathyroid hormone, fibroblast growth factor 23, and others), all of which may contribute to accelerated damage to the heart and vasculature. Finally, the dialysis procedure itself may have a direct toxic effect on the myocardium.

Dyslipidemia and low-grade inflammation are also more common in the presence of CKD. In patients with impaired kidney function and severe albuminuria, lipid profiles become atherogenic owing partly to the defective function of high-density-lipoprotein cholesterol and excessive oxidation of low-density-lipoprotein cholesterol. The mechanisms of increased systemic inflammation in CKD are unclear, but increased production of inflammatory mediators has been attributed to raised oxidative stress and accumulation of posttranslation modified proteins and toxins that are ordinarily cleared with normal renal function.

### Reducing cardiovascular risk in kidney disease

#### Lifestyle modification

Lifestyle modification is the cornerstone of prevention strategies for cardiovascular disease in the general population. Although the effects of lifestyle modifications, such as smoking cessation, a low-sodium diet, exercise, and weight loss, have not been greatly studied in the CKD population, it appears reasonable to extrapolate the results from non-CKD populations and recommend similar approaches in the CKD population. Detailed discussion of these approaches is beyond the scope of this review.

#### Blood pressure lowering

There is no question regarding the benefit of BP lowering in reducing cardiovascular events in both the general and CKD populations. The Blood Pressure Lowering Treatment Trials’ Collaboration assessed over 30 randomized trials involving approximately 30,000 people with early stage CKD (mostly stage 3a) out of 160,000 participants in total. These showed that treatment with angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers produced almost identical 17% reductions in the risk of cardiovascular events in participants with or without CKD with a 5 mm Hg reduction in systolic BP. The effects were consistent across a

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**Selected abbreviations and acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</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>
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<tr>
<td>BP</td>
<td>blood pressure</td>
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<tr>
<td>CKD</td>
<td>chronic kidney disease</td>
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<tr>
<td>DCOR</td>
<td>Dialysis Clinical Outcomes Revisited</td>
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<tr>
<td>eGFR</td>
<td>estimated glomerular filtration rate</td>
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<tr>
<td>ESKD</td>
<td>end-stage kidney disease</td>
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<tr>
<td>EVOLVE</td>
<td>Evaluation Of cinacalcet hydrochloride therapy to Lower cardiovascular eVents</td>
</tr>
<tr>
<td>KDIGO</td>
<td>Kidney Disease Improving Global Outcomes</td>
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<tr>
<td>SHARP</td>
<td>Study of Heart And Renal Protection</td>
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When eGFR is lower than 30 mL/min/1.73 m², around 50% of patients develop left ventricular hypertrophy, which is predominantly caused by hypertension, with additional contributions from renal anemia and increased vascular stiffness due to arteriosclerosis. Hypertension is also a contributor to the risk of atherosclerosis, arteriosclerosis, and left ventricular hypertrophy, each of which leads to reduced coronary reserve.

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Excess vascular risk and chronic kidney disease – Wong and Perkovic
range of cardiovascular outcomes, and no overall differences were identified between different classes of agents (ACE inhibitors vs calcium channel blockers vs diuretics or β-blockers).

The evidence in people with advanced kidney failure receiving dialysis is much more limited. However, a systematic review pooling several small trials of limited quality showed a significantly reduced risk of cardiovascular events and death in people receiving BP-lowering therapy compared to controls.

BP lowering is therefore a key element of strategies to prevent cardiovascular events in people with CKD. While evidence available from trials suggests that different classes of agents have similar effects on cardiovascular events, ACE inhibitors and angiotensin receptor blockers (ARBs) are recommended by guidelines as the preferred BP-lowering agents for people with CKD due to their proven benefits in preventing kidney failure more effectively than other classes of agents in this population. An additional consideration is the role of β-blockers in the presence of cardiac failure in people with CKD. These agents are routinely recommended in people with cardiac failure in the general population, and the limited data available in people with CKD suggest they have similar benefits in this population.

Optimal BP target has been a matter of controversy in both the general population and in people with CKD. Observational analyses have raised concerns about the possibility of a J-curve, with an increased risk of cardiovascular events at lower BP levels, but these analyses have a high risk of confounding with incorrect conclusions being the result. A number of randomized trials have assessed the impact of different BP targets in both these groups, and they have effectively excluded the likelihood of a J-curve at commonly observed BP levels. A systematic review of a number of trials found that intensive BP lowering in people with CKD was no more beneficial than standard BP lowering in terms of cardiovascular event reduction. In participants with CKD and proteinuria, however, intensive BP lowering may be of benefit.

The KDIGO (Kidney Disease Improving Global Outcomes) BP guidelines recommend BP lowering in people with CKD, with a regimen incorporating ACE inhibitors or ARBs are recommended by guidelines as the preferred BP-lowering agents for people with CKD due to their proven benefits in preventing kidney failure more effectively than other classes of agents in this population. An additional consideration is the role of β-blockers in the presence of cardiac failure in people with CKD. These agents are routinely recommended in people with cardiac failure in the general population, and the limited data available in people with CKD suggest they have similar benefits in this population.

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The KDIGO (Kidney Disease Improving Global Outcomes) BP guidelines therefore recommend BP lowering in people with CKD, with a regimen incorporating ACE inhibitors or ARBs, and a systolic BP target below 140 mm Hg (or below 130 mm Hg for people with CKD and proteinuria).

**Lipid-lowering therapy**

The lack of a clear relationship between cholesterol levels and the risk of cardiovascular events and death in advanced kidney disease has led to substantial debate about the efficacy and safety of lipid lowering in CKD. The largest individual study in the area is the SHARP (Study of Heart And Renal Protection) trial involving approximately 9500 participants with CKD. This trial showed that participants randomized to combined simvastatin and ezetimibe had a 17% reduction in the risk of major atherosclerotic events (coronary death, myocardial infarction, nonhemorrhagic stroke, or any revascularization) compared to those randomized to placebo. The results of the SHARP trial are supported by post hoc analyses of CKD subgroups of randomized trials of statin versus placebo in the general population, which reported that statins reduce the relative risk of cardiovascular events to a similar degree in patients with or without CKD. The use of statins in CKD, particularly early on, is therefore now widely recommended by guidelines.

The role of statins in ESKD is less certain, with meta-analyses of results of randomized trials clearly demonstrating that there is less reduction in relative risk compared with people with preserved kidney function, although absolute risk reduction is likely to be similar.

This may well be due to a similar effect on atherosclerotic events being drowned out by a larger number of nonatherosclerotic cardiovascular events. While BP lowering, especially using ACE inhibitors or ARBs, is likely to reduce the incidence and progression of atherosclerosis, arteriosclerosis, and left ventricular hypertrophy, lipid lowering is only likely to substantially impact atherosclerotic events.

Concerns that the well-documented side effects (rhabdomyolysis, myalgia, and abnormal liver function test) with statin use may be more frequent in patients with CKD, especially when high doses are used, have proven unfounded. Recent evidence has confirmed there is no difference in side effect profiles between statins and placebo even in patients with reduced kidney function.

Fewer data exist for other lipid-lowering agents. Fibrates have been shown to prevent cardiovascular events in the general population, with particular benefit in preventing coronary events. Secondary analyses of trial subsets with CKD suggest similar benefits may exist in the CKD population, but the total amount of data available is limited. Fibrates transiently and reversibly increase serum creatinine levels, which has limited their use in CKD. Nevertheless, trial data suggest that this does not translate into renal harm, and that there may in fact be protection of kidney function.

Recently, a number of novel agents for the treatment of dyslipidemia, including alirocumab and evolocumab (proprotein convertase subtilisin/kexin type 9 inhibitors), have been developed and are being studied in large clinical trials. In a large, long-term study (n=4465) comparing monthly subcutaneous evolocumab injection plus standard therapy versus standard therapy alone, the addition of evolocumab to standard therapy reduced low-density-lipoprotein levels by 61% (P<0.001) and lowered the incidence of cardiovascular events (hazard ratio, 0.47; 95% confidence interval [CI], 0.28–0.78; P=0.003). However, neither this study or the alirocumab study has to date published data on subgroup analyses according to kidney function.
◆ Antiplatelet agents

People with CKD appear to have a thrombogenic profile, with an increased risk of venous thromboembolism identified in large observational studies. The risk of atrial fibrillation has also been shown to increase in the presence of reduced kidney function, and the risk of thromboembolic complications in people with atrial fibrillation is also increased in people with CKD compared to those with normal kidney function. Conversely, the risk of bleeding has also been shown to increase in CKD, particularly when antiplatelet or anticoagulant therapy is used. Data are sparse regarding the efficacy of aspirin in advanced CKD.

A recent Cochrane systematic review of antiplatelet agents for chronic kidney disease included 44 studies (21,460 participants) comparing an antiplatelet agent with placebo or no treatment and 6 studies (5679 participants) directly comparing one antiplatelet agent with another. The authors showed antiplatelet agents reduced the risk of myocardial infarction compared with placebo (relative risk, 0.87; 95% CI, 0.76-0.99), but not the risks of all-cause mortality, cardiovascular mortality, or stroke.

Post hoc subgroup analyses of randomized trials suggested that the protective effect of daily aspirin may be increased in individuals with an eGFR <45 ml/min/1.73 m², but these studies also showed a higher incidence of bleeding (major and minor) in CKD patients. These data suggest that antiplatelet agents should be used in a similar fashion in CKD patients as they are in the general population, but with greater caution as CKD patients are at increased risk of bleeding. Additional studies in this area are urgently required.

There are no randomized controlled trial data regarding the safety and efficacy of warfarin therapy in people with CKD, causing much uncertainty regarding the balance of risks versus benefits of this therapy in the CKD population. More recent studies of the novel anticoagulants in people with CKD and atrial fibrillation suggest that these agents might reduce thromboembolic complications and have a better risk profile than warfarin.

◆ Arteriosclerosis

Arteriosclerosis progressively and substantially increases in people with CKD. This has been demonstrated from both an anatomical perspective, with a rapid increase in the risk of vascular thickening and calcification in the presence of reduced kidney function, as well as a functional perspective, with an increase in markers of arterial stiffness (eg, pulse wave velocity, augmentation index, pulse pressure, and others). These factors are likely to be important contributors to the increased risk of left ventricular hypertrophy and heart failure in CKD.

While some BP-lowering agents (ACE inhibitors, ARBs, calcium channel blockers) appear to reduce vascular stiffness, other BP-lowering agents appear to have no effect on markers such as pulse wave velocity, suggesting a potential additional rationale for considering the use of these drug classes ahead of others.

Given the central role of calcification in these processes and the documented relationship between vascular calcification and bone metabolism in people with CKD, there has been much interest in the effects on the risk of cardiovascular events of agents that modulate mineral metabolism.

Phosphate levels increase ubiquitously in people with ESKD, and also commonly in those with advanced CKD. Phosphate levels predict the risk of cardiovascular events and death in CKD, leading to interest in the use of oral phosphate binders to reduce serum phosphate levels in blood along with the risk of cardiovascular events and death. The most commonly used phosphate binders were originally aluminium-based. These, however, have been effectively abandoned due to the risks of aluminium absorption and brain, blood, and bone toxicity. Calcium-based phosphate binders subsequently became the standard of care. Again, there were safety concerns; this time relating to the potential for these agents to increase the risk of vascular calcification due to calcium absorption from the gut. This led to a drive to develop alternative agents.

The most commonly used noncalcium-based phosphate binder is sevelamer, a nonabsorbed phosphate binder that appears to be associated with lower calcium levels and a lower risk of vascular calcification compared to calcium-based phosphate binders.

The largest trial comparing sevelamer to calcium-based phosphate binders was the Dialysis Clinical Outcomes Revisited (DCOR) trial, which enrolled over 2000 people with ESKD. This trial failed to show any difference overall, but was limited in its ability to do so by the large proportion of participants who discontinued randomized therapy and also by the number lost to follow-up. Subgroup analyses suggested mortality benefits for individuals over the age of 65 years and those receiving treatment for 2 years or more, but these analyses were not conclusive in the presence of a negative overall result. Other studies have suggested mortality benefits for noncalcium-based phosphate binders compared to calcium-based phosphate binders, but the optimal strategy has yet to be defined. Nonetheless, phosphate management appears to be useful, and further studies in this area are required.

An additional factor highly relevant to metabolic bone disease in CKD is parathyroid hormone. Parathyroid hormone levels are commonly and substantially elevated in CKD and have been associated with an increased risk of cardiovascular events in some, but not all, observational studies. While surgical parathyroidectomy has traditionally been the treatment of choice for hyperparathyroidism, the introduction of calci-
mimetic hormones that lower parathyroid hormone levels led to optimism that the widespread use of these agents might help prevent cardiovascular events in advanced CKD. The EVOLVE (Evaluation Of cinacalcet hydrochloride therapy to Lower cardiovascular evEnts) trial compared the effect of cinacalcet versus placebo on cardiovascular events and death in people with ESKD requiring dialysis and increased parathyroid hormone levels.43 The primary results of the study revealed a small and nonsignificant reduction in the risk of cardiovascular events, but baseline risk imbalances and high drop-out and drop-in rates appear likely to have contributed to a false negative result for this study.44 Overall, the available data suggest that interventions to lower parathyroid hormone levels led to a false negative result for this study.44

Other strategies

A range of other strategies have been studied for the prevention of cardiovascular events in CKD. Normalizing hemoglobin levels using erythropoietin has clearly been shown to be harmful, and this has now also been suggested as a therapeutic strategy in CKD.45

Homocysteine lowering is ineffective and is similarly no longer recommended for cardiovascular protection in CKD.46

New CKD-specific strategies, along with a better understanding of the effects of therapies that are effective in the general population, are urgently required.

Conclusion

People with kidney disease have been clearly and unequivocally proven to be at increased risk of cardiovascular events, and effective preventive strategies are urgently required. BP lowering and lipid lowering clearly have an important protective role in this population, and antiplatelet therapy is also likely to be useful for some people with CKD. Available data suggest that strategies targeting mineral metabolism and metabolic bone disease may also have a role in cardiovascular prevention in CKD. More effective strategies are urgently required.

References

15. Cuzzolin M, Ketteler M, Zehnder D. The vitamin D system: a crosstalk between mimetic hormones that lower parathyroid hormone levels. the primary results of the study revealed a small and nonsignificant reduction in the risk of cardiovascular events, but baseline risk imbalances and high drop-out and drop-in rates appear likely to have contributed to a false negative result for this study.44 Overall, the available data suggest that interventions to lower parathyroid hormone levels may have an important role in preventing cardiovascular events in advanced CKD, but more data are clearly required.

Excess vascular risk and chronic kidney disease – Wong and Perkovic

**Keywords:** cardiovascular risk; chronic kidney disease; end-stage kidney disease; risk reduction; risk factor

**Diminuer le sur-risque vasculaire associé à l’insuffisance rénale chronique**

L’insuffisance rénale chronique (IRC), maladie courante touchant plus de 10 % de la population adulte, est un facteur avéré de risque élevé d’événements cardio-vasculaires. Le développement de stratégies thérapeutiques efficaces pour cette population est donc primordial. Une série de processus dont l’athérosclérose, l’artériosclérose, l’hypertrophie ventriculaire gauche, la fibrillation auriculaire et autres, semblent participer à ce sur-risque cardio-vasculaire pour lequel un éventail de traitements est nécessaire. L’élévation de la pression artérielle, courante dans l’IRC, est vraisemblablement majeure dans la plupart, si ce n’est dans tous les mécanismes responsables d’un risque cardio-vasculaire élevé. D’après les données disponibles, abaisser la PA diminue considérablement le risque d’événements cardio-vasculaires de l’IRC, de préférence à l’aide de produits agissant sur le système rénine-angiotensine en raison de leurs effets rénoprotecteurs coexistants. Diminuer le taux de lipides prévient les événements cardio-vasculaires de l’IRC, de préférence à l’aide de produits agissant sur le système rénine-angiotensine. À ce jour, d’autres stratégies se sont révélées décevantes, soulignant le besoin de poursuivre les efforts et l’innovation dans ce domaine.
A TOUCH OF FRANCE

The Aveyron department, tucked away at the southern edge of the Massif Central, has stunning landscapes, like the Tarn valley, tremendous food, like Roquefort cheese, beautiful Romanesque churches, picturesque paths on the ancient St James pilgrimage route, a welcoming people with a warm accent that “rolls the r’s,” a shibboleth no Anglophone can match. Our two Touch of France articles look at the Aveyron from the vantage point of “communication”: one contemporary, with the Millau Viaduct for automobiles, the world’s tallest and most breathtaking bridge; the other historical, with the discovery of a feral child in 1799, Victor the Wild Boy, and the attempts to teach him to speak, an event that riveted the whole Europe.

World’s tallest bridge spans ancient pilgrimage routes in France

P. Jodidio, Switzerland
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The Naturalist, the Doctor, and the Wild Boy

C. Régnier, France
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One of the seven cable-stayed pylons of the Millau Viaduct.
© Murat Taner/Corbis.
World’s tallest bridge spans ancient pilgrimage routes in France

by P. Jodidio, Switzerland

High above the banks of the Tarn River in the Aveyron region of France, a singular bridge called the Millau Viaduct, designed by the French engineer Michel Virlogeux and the British architect Norman Foster, carries automobile traffic north and south. In the lands below, the history of France from the Roman or even Barbarian occupation to the pilgrims of the Way of Saint James has played out, leaving monuments as famous as the Abbey Church of Saint-Foy in Conques along the route. Today, the natural beauty of the region, but also products such as the famous cheese of Roquefort-sur-Soulzon, are highlighted by one of the most remarkable works of civil engineering in the world.

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Those who know the history and geography of France will be familiar with the Aveyron. Though it remains one of the least densely populated departments of France, this region, located between Toulouse, Clermont-Ferrand, and Montpellier, retains a natural beauty and a presence of the past that set it apart, even in the rich tapestry of French culture. Nearby sites of interest include the canyon of the Tarn River (Gorges du Tarn), which is 53 kilometers long and between 400 and 600 meters deep. The Aveyron is also home to the town of Roquefort-sur-Soulzon, famous for its eponymous cheese for which the village was given a monopoly in 1411 by King Charles VI. The authenticity of the cheese was rather unexpectedly confirmed in 1961 by the Tribunal de Grande Instance in Millau, which declared that only cheese ripened in the Mont Combalou caves at Roquefort-sur-Soulzon could carry the name Roquefort. Local brands such as Roquefort Papillon and Roquefort Société produce nearly 20,000 tons of the cheese each year, attracting a good number of tourists in the process.
Millau and the Aveyron: a historical nexus

Millau is also near to the Abbatiale Sainte-Foy de Conques, the Abbey Church of Sainte-Foy, a masterpiece of the Romanesque period. The presence of this monument, begun between 1050 and 1065 and completed in 1120, points to another long tradition of the Aveyron, which is crossed by the Puy-en-Velay pilgrimage route of Santiago da Compostela, or the Way of Saint James. One of the four main pilgrimage routes in France, the Puy-en-Velay path leads from the valley of the Rhone toward Spain. Together with numerous other monuments along the ancient route, the Abbey Church became part of the UNESCO World Heritage List in 1998. The UNESCO listing is justified in terms that relate specifically to the Abbatiale Sainte-Foy de Conques:

Criterion (ii): The Pilgrimage Route of Santiago da Compostela played a key role in religious and cultural exchange and development during the later Middle Ages, and this is admirably illustrated by the carefully selected monuments on the routes followed by pilgrims in France.

Criterion (iv): The spiritual and physical needs of pilgrims travelling to Santiago de Compostela were met by the development of a number of specialized types of edifice, many of which originated or were further developed on the French sections.1

UNESCO specifically identifies as “pilgrimage churches” Sainte-Foy at Conques, Saint-Sernin at Toulouse, and the Cathedral of Santiago de Compostela itself “because of their large transepts and apsidal chapels ranged round a spacious ambulatory, designed to meet the liturgical needs of pilgrims.”

The Abbey at Conques was actually founded in 819 when relics of St. James were discovered in Compostela. Seeing that pilgrims headed for Spain were stopping at Agen, where relics of Sainte Foy were kept, the Benedictine monks of Conques conspired to steal her mortal remains. Kept in a golden reliquary statue in Conques, these remains sufficed to shift the pilgrimage route from Agen and to duly enrich Conques, whose new-found wealth was used to build the Abbey Church. The 80-centimeter-high reliquary, made of gold, silver gilt, gems, and cameos over a wooden core, is still conserved in the Treasury of Sainte-Foy, where it continues to attract tourists and pilgrims.

A more modern pilgrimage route of sorts, the A75 highway, also crosses through the Aveyron running 340 kilometers north from the area of Béziers, Narbonne, and Montpellier across the Massif Central to Clermont-Ferrand. The Massif Central is a large mountainous and volcanic (more than 450 extinct volcanoes) plateau region in south-central France, which extends over close to 15% of the country. The motorway passes close to the town of Millau near the confluence of the Tarn and Dourbie Rivers. As is often the case in France, profound historical reasons influence the course of roads. As it happens, a Roman road also led north...
More specifically, the town is located astride the southern part of the Massif Central near the Grands Causses Regional Park. The Grands Causses are a series of high limestone plateaus, valleys, and gorges.

The Millau Viaduct: a joint architectural-engineering project

It is in this unusual geographic setting that it was decided to build one of the most spectacular bridges in the world, the Millau Viaduct, which was completed in 2004. Intended to alleviate excessive holiday traffic heading south or north, four potential routes for the A75 Highway linking the Causse Rouge to the north and the Causse du Larzac to the south were carefully studied. In 1989, the so-called “median” route located a few kilometers to the west of Millau was chosen. From the outset, this route promised to be one of superlatives because of the depth of the Tarn River valley and the 2.46-kilometer span required to travel from one plateau to the other. The completed structure is the highest road bridge deck in Europe, passing 270 meters above the Tarn River.

Between 1993 and 1994, the French government consulted a total of seven architects and eight structural engineers. In 1995 and 1996, five groups associating architects and structural engineers prepared a study defining the issues concerned. In 1996, teamed with the French engineering companies SOGELEERG (Michel Virlogeux), EEG (Europe Etudes from the Languedoc region, crossing the Tarn. Settled on the left bank of the Tarn in the 2nd or 1st century BC, Millau was a place of trade and a victim of numerous invasions, by barbarians and others, which led the townspeople to resettle on the opposite bank of the river in the 4th or 5th century AD. By the 9th century, Millau was already known for the production of lambskin gloves, a tradition that has continued into modern times with the leather and leatherwear industry.

The layering of history seen in Millau finds an intriguing echo in the remains of a medieval bridge, of which only two sandstone and volcanic tuff stone pillars remain, one topped by a more modern mill. Reference is found to a bridge at this location in 1156 when the Count of Barcelona, then Millau’s ruler, granted free passage to monks from the nearby Cistercian Abbey of Sylvanès. Millau was then successively ruled by the King of Aragon in the 12th century, becoming French in 1271 only to fall under English rule during the Hundred Years War in 1361. The town and its region again became French in 1476. The medieval bridge, a 17-span, 218-meter long witness to the long history of trade and movement through the area, fell to flooding in 1758 and was never rebuilt as such. With a population of about 22,000 persons, Millau is set in a predominantly agricultural and rural area, characterized by numerous gorges and ravines.

from the Languedoc region, crossing the Tarn. Settled on the left bank of the Tarn in the 2nd or 1st century BC, Millau was a place of trade and a victim of numerous invasions, by barbarians and others, which led the townspeople to resettle on the opposite bank of the river in the 4th or 5th century AD. By the 9th century, Millau was already known for the production of lambskin gloves, a tradition that has continued into modern times with the leather and leatherwear industry.

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More specifically, the town is located astride the southern part of the Massif Central near the Grands Causses Regional Park. The Grands Causses are a series of high limestone plateaus, valleys, and gorges.

The Millau Viaduct: a joint architectural-engineering project

It is in this unusual geographic setting that it was decided to build one of the most spectacular bridges in the world, the Millau Viaduct, which was completed in 2004. Intended to alleviate excessive holiday traffic heading south or north, four potential routes for the A75 Highway linking the Causse Rouge to the north and the Causse du Larzac to the south were carefully studied. In 1989, the so-called “median” route located a few kilometers to the west of Millau was chosen. From the outset, this route promised to be one of superlatives because of the depth of the Tarn River valley and the 2.46-kilometer span required to travel from one plateau to the other. The completed structure is the highest road bridge deck in Europe, passing 270 meters above the Tarn River.

Between 1993 and 1994, the French government consulted a total of seven architects and eight structural engineers. In 1995 and 1996, five groups associating architects and structural engineers prepared a study defining the issues concerned. In 1996, teamed with the French engineering companies SOGELEERG (Michel Virlogeux), EEG (Europe Etudes...
Gecti), and SERF, Norman Foster won a limited competition against French architects to build a 2.5-kilometer viaduct. Though it is not highly unusual, it was somewhat unexpected that architects played such a prominent role in this process. Many significant bridges have been designed purely by engineers, with architects perhaps taking an increasing role in recent years. Such architects as Zaha Hadid (Sheikh Zayed Bridge, Abu Dhabi, UAE, 1997–2010) or Ben van Berkel (Erasmus Bridge, Rotterdam, The Netherlands, 1996) have successfully delved into this domain, while others such as the architect-engineer Santiago Calatrava have built many bridges. Even as he worked on the Millau Viaduct, Norman Foster was designing and building the very visible Millennium Bridge (London, UK, 1996–2002), a pedestrian span that links Saint Paul's Cathedral on the north bank of the Thames to Tate Modern in Southwark.

Norman Foster, born in Manchester in 1935, is one of the best-known figures in the world of contemporary architecture. He received the RIBA Gold Medal for Architecture in 1983. He was knighted in 1990 and was honored with a Life Peerage in 1999. The American Institute of Architects granted him its Gold Medal for Architecture in 1994, and he received the Pritzker Prize in 1999. Aside from bridges, Foster is no stranger to other technical structures that are usually designed by engineers. His Torre de Colserola communications tower (Barcelona, Spain, 1992) is 288 meters high. Foster is proud of the fact that a more conventional design for a tower of this height would have required a main support more than six times broader than the 4.5-meter-diameter hollow slip-formed reinforced concrete shaft that reduces to just 300 mm to hold a radio mast. In the context of the Millau Viaduct, in a discussion with the author of this article, he stated:

> It is why some things, which appear to be very simple, look better than others, whether it be aircraft or bridges. You don’t have to be an architect to have an eye, and I know lots of architects who don’t have an eye. When you see a bridge that really sings, then you can be sure that that engineer had an eye. When you see one aircraft which is more remarkable than another, the same is true. They are all obeying the laws of nature. There are a whole series of visual options that permit one to achieve an optimal engineering solution, whether it is in designing a building, a bridge, or an aircraft. You are making a choice. You are using an eye.²

In the case of the Millau Viaduct, Foster had a number of associates who were engineers. He explains:

> Bridges are often considered to belong to the realm of the engineer rather than that of the architect. But the architecture of infrastructure has a powerful impact on the environment and the Millau Viaduct, designed in close collaboration with structural engineers, illustrates how the architect can play an integral role in the design of bridges. It follows the Millennium Bridge over the River Thames in expressing a fascination with the relationships between function, technology, and aesthetics in a graceful structural form.

© Murat Taner/Corbis.
The Millau Viaduct, the world's highest bridge, floating on a sea of clouds.

© Jean-Philippe Arles/Reuters.
Despite the very large scale of this project, it achieves a lightness and elegance that does not damage the natural setting and projects an image of modern automobile travel. The co-architects for the project were Chapelet-Defol-Mousseigne, and the consultants were EEG, SOGELERG, SERF, Agence TER, and Michel Virlogeux. Michel Virlogeux, born in 1946 in the Sarthe region of France, went to work for the French Highway Administration (SETRA) in 1974. As head of the Bridge Division, he designed more than 100 bridges. He worked on other significant spans, such as the Normandy Bridge (Honfleur, France, 1994), which at the time was the longest cable-stayed bridge in the world. He left SETRA in 1995 to become a consultant. It is in this capacity that he worked on the Vasco da Gama Bridge (Lisbon, 1997) and on the Millau Viaduct. Although originally overshadowed by the presence of Norman Foster in the communications surrounding the Millau Viaduct, Virlogeux subsequently was understood to have played a leading role in the design. He continues to give credit to the British architect, however. He states,

I am able to see what kind of structure is fitting to the landscape, and what is technically suited to the conditions and constraints of the location. I’m able to develop the global proportions. But I’m not able to do the detailed shaping, and that’s not a minor role. From the global idea, you can form the detailed shape, so that it expresses the flow of forces and can enhance the structural concept. This is something that, personally, I cannot do.  

In June 2000, a contest for the construction contract of the Millau Viaduct was launched, with four invited consortia. In March 2001, Eiffage established a subsidiary called Compagnie Eiffage du Viaduc de Millau (CEVM) and was declared winner of the contest with a steel-deck proposal and awarded the prime contract in August of the same year. This 75-year concession for the financing, design, construction, operation, and maintenance of the Viaduct was confirmed by a French government decree published in the Journal Officiel on October 10, 2001. The concession contract stipulates a “useful project life” for the Viaduct of 120 years. This system allowed the bridge to be built entirely with private funding.

With columns varying in height between 75 and 245 meters, the Viaduct is a multispan cable-stayed design with sections each of no less than 350 meters in length. Making its design and construction even more complex, the Viaduct is curved and has a constant upward slope from north to south of just over 3%. The curve was added to avoid the floating sensation that drivers might have felt in a completely straight de-
sign and also to allow them better visibility. Further difficulty accrued from the potential of high winds, especially given the distance from the road deck to the bottom of the gorge. Wind tunnel tests were conducted at the CSTB in Nantes, taking into account wind effects and potential air turbulence, which resulted in relatively slight design changes. The significance of these studies is underlined by the fact that the wind accounted for 25% of total forces and loads acting on the Millau Viaduct during construction.

Even the construction of the Viaduct was innovative. Rather than cantilevering the road deck outward in small sections from each of the seven pylons as would have been expected, the deck was built on flat sites on either side of the bridge in two large sections. Hydraulic jacks on the tops of the piers were synchronized to move the entire deck out in increments of 600 mm until both sides met over the river. This method required the construction of temporary intermediate piers to avoid buckling of the deck.

Opened in December 2004 after three years of construction, the Viaduct cost approximately 400 million euros to build, and created a certain controversy because it is the tallest bridge in the world, with one mast reaching a height of 336.4 meters (P2 pylon). In this instance, the P2 pylon is 245-meters high and the mast rises a further 87 meters above the deck. Such statistics raised local concern that the Viaduct threatened to dwarf the features of the countryside, and associations such as the World Wildlife Fund actively opposed the project. In fact, the controversy reached the highest levels of the French government. Before construction, Valéry Giscard d’Estaing, the former President of France, went so far as to write to his successor Jacques Chirac:

“This project must elicit the most serious reservations, which is why I ask you to reexamine this question at your earliest convenience... The project envisaged for Millau belongs to the family of cable-stayed bridges, often built near the entries to ports or in the mouths of rivers... In designing a bridge that spans a valley at such a great height, it is necessary to obtain a less opaque profile, which is less oppressive for the surrounding countryside.”

The project was bound to elicit a certain amount of hostility toward Norman Foster among some, but it may be suspected that in this instance it was related to a lingering reticence about the virtues of contemporary architecture and perhaps also to the fact that he was English. In fact, his work was the result of the solution favored by the French Roads Department (AIOA) and the engineers associated with the project, SOGELERG, FFG, and SERF. The influential public works magazine *Le Moniteur* went so far as to openly take position in this controversy in a revealing way:
Piers P2 (height 245 m) and P3 (height 223 m) are the two highest piers ever built in the world. From their base to 90 meters below the deck, the piers rise as a single hollow shaft, then they are divided into two separate parallel shafts, which are each pre-stressed vertically by eight cables.7

Much as had been the case with Ieoh Ming Pei’s Louvre Pyramid, completed in 1989 after bitter, politically-oriented controversy, the completed Millau Viaduct has since imposed itself not only as a local tourist attraction, but as one of the most remarkable technical achievements in France in the late 20th century; each year, a million people visit the viewing platform of the Viaduct.

Local tourist offices claim that what the Eiffel Tower is to Paris, the Millau Viaduct is to the Aveyron. The comparison might be considered particularly apt, not only because of the essentially technical nature of the two structures, but also because the Viaduct was built by Eiffage, the contemporary successor of Gustave Eiffel’s own construction company. The designers were pleased to point out that the steel deck of the Millau Viaduct weighs 36 000 tons, which is to say four times more than the Eiffel Tower. As it happens, Gustave Eiffel himself worked in the region between 1882 and 1884, build-

Far be it from us to deny the talent usually displayed by the winner of this competition, the Englishman Sir Norman Foster. Far be it from us, in the midst of the construction of the European Community, to argue that preference should be given to French candidates, even if the architectural profession in this country is in a state of severe depression. Couldn’t it be imagined, though, that French architects might one day receive such commissions in Italy, England, or Spain?6

As it happens, the completed Millau Viaduct in no substantive way disfigures the landscape more than might have a 17-arch medieval stone bridge, for example. Rather, the involvement of Norman Foster and the will to make the Viaduct fit into its grand natural setting assured a degree of discretion and elegance that is rare in contemporary architecture and engineering. Norman Foster stated in 2011, “We wanted the piers to look as if they had barely alighted on the landscape, light and delicate—like butterflies’ legs.”

A winner of the prestigious 2006 IABSE (International Association for Bridge and Structural Engineering) Outstanding Structure Award, the bridge is indeed a remarkable combination of very large elements and outstanding lightness. The IABSE citation emphasizes the fact that:

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ing the Garabit Viaduct, a railway arch bridge over the Truyère River at Ruynes-en-Margeride (page 476). At the Viaduct’s opening on December 14, 2004, President Jacques Chirac stated:

The Millau Viaduct is a magnificent example, in the long and great French tradition, of audacious civil engineering structures, a tradition begun at the turn of the nineteenth and twentieth centuries by the great Gustave Eiffel.\(^5\)

Though it appears to almost hover over the Tarn River valley in all of its rural splendor, the Millau Viaduct thus in some sense embodies an incredibly rich history that reaches back to the time of the Romans, continuing with the stream of pilgrims headed toward Santiago de Compostela, and brought to modern life with the A75 highway, also called La Méridienne (The Meridian), going north to the center of France. A meridian is of course an imaginary circle, traced on the surface of the globe, leading from one pole to the other. In this case the meridian in a sense bisects the map of France and crosses over its geography and through its history. Descriptions of the Viaduct tend to be rather technical or full of impressive figures, but what strikes those who see it most is its lightness. When the engineer Virogeux stated, “From the global idea, you can form the detailed shape, so that it expresses the flow of forces and can enhance the structural concept,” he was referring to his own collaboration with the architect Norman Foster. In a way, it is also Jacques Chirac who best explained the architectural or engineering significance of the Millau Viaduct, pointing out its affiliation with Gustave Eiffel and his tower or the Garabit Viaduct.\(^5\) The engineer at Millau was indeed French, even if the subtle refinements introduced by Norman Foster surely made the bridge the vision of lightness that it is. Odd that Millau was once British, a land of invasions ruled by the Romans, Aragon, and Barcelona before finally assuming its profoundly French identity. It is the combination of the knowledge of the French engineer and the esthetic, functional sense of the English architect that made the Millau Viaduct one of the most artistic pieces of civil engineering of the early 21st century, and a fitting monument to the rich valley that it passes over.

References
2. Sir Norman Foster in discussion with the author, Châteauneuf-Grasse, France, July 21, 1996
5. Valéry Giscard d’Estaing, “Viaduc de Millau : Giscard écrit à Chirac,” Le Figaro, August 18, 1996. “Ce projet me parait appeler les plus graves réserves, c’est pourquoi je me permets de vous saisir de cette question en vous demandant de réexaminer cette décision... Or le projet envisagé pour Millau appartient à la famille des ponts haubanés, construits pour les entrées de port ou les estuaires des fleuves... Lorsqu’il s’agit, par contre, d’un ouvrage situé à grande hauteur, on doit rechercher un profil moins opaque et moins oppressant pour le paysage.”
8. The viaduc de Millau s’inscrit magnifiquement dans cette longue et grande tradition française d’ouvrages d’art audacieux, tradition ouverte au tournant des XIXe et XXe siècles par le grand Gustave Eiffel, auteur, à quelques dizaines de kilomètres d’ici, du viaduc de Garabit. Tradition poursuivie, plus près de nous, avec les ponts de Tancarville, de l’île de Ré et de Normandie.

LE PLUS HAUT VIADUC DU MONDE S’ÉLANCE AU DESSUS D’ANCIENS CHEMINS DE PÉLERINAGE FRANÇAIS

Enjambant les rives du Tarn, le Viaduc de Millau, conçu par l’ingénieur français Michel Virlogeux et l’architecte britannique Norman Foster, assure la communication routière entre nord et sud dans le département de l’Aveyron. Il domine de sa hauteur l’histoire de cette région de France, depuis l’époque Romaine et Barbare, le Moyen-Âge avec la superbe abbaye de Conques et son reliquaire en or de Sainte Foy, en passant par les pèlerins sur le chemin de Compostelle (toujours présents de nos jours). L’Aveyron, riche de la beauté de ses innombrables sites naturels et culturels, de sa gastronomie, de son célébre fromage de roquefort, a acquis avec ce nouveau viaduc, le plus haut du monde, l’un des ouvrages architecturaux contemporains les plus remarquables qui soient.
The Wild Boy, found in the Woods in Aveyron.
When Itard placed on the table letters to spell out “milk,” while presenting a glass of milk, Victor learned to arrange the letters in the right order to obtain his reward (the milk). But he soon tired of this and during classes had fits of anger and hurled the teaching materials onto the floor. Itard punished the boy for such behavior by locking him inside a dark cabinet or dangling him out of the window. These coercive methods had the desired effect, and Victor picked up the things he had tossed aside.

In the spring of 1797, five years into the French First Republic, which had emerged from years of revolutionary upheaval, a singular tale swept through the land. A naked boy had been sighted scurrying around a forest on all fours gathering acorns and tubers for food, in the mountainous Lacaune region in the southern Massif Central. Two years passed before hunters captured the feral child, who a week later skedaddled and for the next six months strayed around the region, occasionally fed potatoes by local peasants who deemed him a waif.1 This story of the feral child assumed particular importance in revolutionary France. In November 1799, on the pretext of restoring order in Paris and in the assemblies, Napoleon

The Naturalist, the Doctor, and the Wild Boy

by C. Régnier, France

One summer day in 1799, men with dogs laid hands on a feral child in the Massif Central in France. Twelve or thirteen years old, he was living alone in a forest, scampering around on all fours, naked, mute, surviving on fruit, roots, and acorns. The news spread fast. A welcome distraction from years of revolutionary turmoil, the story piqued the public’s curiosity. The government’s too. Here was a timely opportunity to educate a feral child according to the philosophical and philanthropic precepts of the newly founded republic. The wild boy’s discovery prompted naturalists and scholars to indulge in descriptions of natural man, while physicians sought ways to rehabilitate him. Pierre-Joseph Bonnaterre, a priest and a noted naturalist and coauthor of an encyclopedia of the animal world, made the first clinical observations of the child, whom he classified as a whole new hominid species: Juvenis averionensis. Taken to Paris, the boy was pronounced a “hopeless idiot” by the great alienist (archaic term for psychiatrist) Philippe Pinel, while Roch-Ambroise Cucurron Sicard, the director of the National Institute for Deaf-Mutes and, like Bonnaterre, also a priest, soon gave up trying to teach him sign language. In early 1801, Sicard entrusted Jean Itard, a young surgeon attached to his institute, with the child’s rehabilitation, which was to be funded by the Ministry of the Interior. And a certain Madame Guérin was charged with providing for the daily needs of the child, henceforth named Victor. Dr Itard invented various processes to teach Victor language and writing. Six years later, though, the outlook was bleak: Victor could make himself understood, but expressed no needs and had made scant progress. Yet this incredible human adventure enabled Jean Itard to lay the foundations of pediatric psychiatry and to pioneer otology in France through his exploration of the causes of deafness and muteness.

Medicographia. 2015;37:480-490 (see French abstract on page 490)
Bonaparte led a coup d’état, repealed the Constitution, and ended the revolutionary process by establishing the Consulate, an authoritarian regime headed by three consuls, but whose real power lay in the hands of the First Consul, Napoleon Bonaparte himself. Bonaparte and the people around him were nonetheless still attached to revolutionary principles, notably those pertaining to education as enunciated by Enlightenment philosophers, notably philosopher Jean-Jacques Rousseau in his treatise *Emile, or On Education* on the nature of man and of education. Symbolizing the first man, who has never known the “torments” of civilization, the wild child immediately excited the interest (and covetousness) of scientists like Pierre-Joseph Bonnaterre, politicians, educationalists, and physicians like Jean Itard, who was working on the rehabilitation of deaf-mutes.

**Pierre-Joseph Bonnaterre and the first observations of *Juvenis averionensis***

Meanwhile, one cold January morning in 1800, the feral child sought warmth in a dye works, some 45 kilometers north of where he had first been sighted. Alerted by rumors, the commissioner of the Consulate, Jacques-Jean Constands Saint-Estève, hastened there and found the boy sitting near the fire clothed in a shirt, now in tatters, given to him six months before at Lacaune. Constands Saint-Estève recounted his experience: “I did not take long to notice that he was mute. Soon afterwards, I believed him to be deaf when I noted that...”
he made no sign in response to various questions that I put to him, in a loud or in a hushed voice. When I took him affectionately by the hand, to take him to my home, he resisted vigorously. But repeated caresses and in particular two kisses I gave him, plus the smile of friendship, decided him there and then." Constans Saint-Estève offered the child a choice of foods: potatoes, cooked and raw meat, rye bread, wheat bread, apples, pears, grapes, walnuts, chestnuts, acorns, oranges, and parsnips. After having sniffed these different foodstuffs, the child chose potatoes, which he threw into the fire and then ate hot, voicing his pain the while through inarticulate and resonant sounds.3

Constans Saint-Estève had the child transferred to the hospital at Saint-Affrique in the Aveyron. There the wild boy refused to wear any clothing, but did become accustomed to sleeping in a bed. His diet, hitherto limited to potatoes, raw chestnuts, and walnuts, expanded to include bread soaked in soup. He fled the hospital twice, but each time was brought back.1

Constans Saint-Estève wrote the first report on the feral child and sent it to Jean-François Randon, the Central Commissioner of the Aveyron, who had discovered this "really phenomenal event" in an article in the newspaper Les Débats. In his report, Saint-Estève wrote:

This interesting and unfortunate creature invites the care of humanity, perhaps even the attention of a philanthropic observer [i.e., scientist]. I shall inform the government, which doubtless will consider that the child should be placed in the hands of the renowned and respectable Sicard, teacher of the deaf and dumb.

Irrited by having been informed after the event by a subordinate, and to satisfy the demand of Pierre-Joseph Bonnaterre, a celebrated naturalist, Randon had the child sent to Rodez, where he arrived in early February 1800 surrounded by a jostling crowd.4

Bonnaterre was an expert on the nosology of the Swedish physician, botanist, and zoologist Carl Linnaeus (1707-1778), as laid out in his Genera Morborum [Varieties of Diseases], and also adopted Linnaeus’s binomial nomenclature introduced in his Systema Naturae [Nature’s System]. In the latter work, Linnaeus classified animals into families and genera using criteria on their resemblances and distinguishing species by their distinctive features.

Linnaeus designated each organism by two names in Latin, the first (with the first letter capitalized) indicating the genus and the second (in lower case) indicating the species. Enlightenment philosophers criticized the classification for dismissing the experimental approach and for defining species while seeking to reproduce elements of the Biblical creation. In 1792, Bonnaterre fled the Reign of Terror in Paris and once in the Aveyron resumed his career, by founding the botanical gardens in Rodez and teaching at the higher education École Centrale. After the episode of the feral child, Bonnaterre published several works on the flora of the Aveyron, agriculture, and veterinary medicine.5

PIERRE-JOSEPH BONNATERRE: A NATURALIST’S LIFE

Born in 1751 in the Aveyron Department, Pierre-Joseph Bonnaterre studied at a local seminary and was ordained as a priest. An outstanding naturalist, he contributed to a five-volume encyclopedia of plants, animals, and minerals published in Paris (1788-1792) and illustrated by color plates by Robert Bénard, who had already illustrated the Encyclopedia of Diderot and d’Alembert. Bonnaterre wrote the volumes on cetaceans, birds, amphibians, reptiles, insects, and fish (he discovered 25 species). Other contributors to the Encyclopedia included Jean-Baptiste de Lamarck (plant taxonomy) and Louis Daubenton (quadrupeds).

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Bonnaterre was famous for his contributions to the Tableau Encyclopédique des Trois Règnes de la Nature (an illustrated encyclopedia of plants, animals, and minerals) published in...
Table of sign language letters, for the deaf-mute, invented by Abbé Sicard and published in 1803. © BIU Santé.
Paris between 1788 and 1792. Forced to leave the capital to escape revolutionary condemnation, he sought refuge in his native region of the Aveyron, where the feral child had been discovered. Bonnaterre published a short paper on the child, placing him in a historical and scientific context, and reported the cases of a dozen feral children described in the literature since 1544, whose attitudes and behavior were similar to those of the wild boy of Aveyron, whom Bonnaterre categorized as *Juvenis averionensis* in the classification of the human races proposed by Linnaeus. Bonnaterre noted that the child’s body bore 23 scars, of animal bites, scratches, and burns. In particular, Bonnaterre noted at the upper end of the windpipe and in the middle of the glottis a 41-millimeter scar of a wound probably inflicted with a sharp-edged instrument. Bonnaterre speculated whether this scar was the work of a barbarian who, having led the child into the wilderness, wielded a murderous blade to have done with him once and for all.

The child made guttural noises, was wild and grimy, tended to bite, moved around like “certain animals in a menagerie,” heeded no one, seemed indifferent to loud sounds and fetid smells, and had eyes only for the food he was given. Bonnaterre considered that the boy’s strongest senses were smell and taste, followed by vision, hearing, and lastly touch, which seemed poorly developed.

Bonnaterre noted that the boy’s disposition enabled him to perform some tasks: to shell beans, select the good ones, fill a casserole with water to cook them, and fuel the fire with pieces of bean pods. Bonnaterre added:

> This child is not totally devoid of intelligence, thought, or reasoning. However, I must say that when his bodily functions or the need to satisfy his appetite are not called upon, one sees in him purely animal functions […] he thinks about nothing and so has no discernment, mind, or memory.1,4

In February 1800, Lucien Bonaparte, Napoleon’s brother and the Minister of the Interior, asked Randon for the immediate transfer of the child to the capital. Pretexting that the “abandoned” child had found “his family,” and wishing to keep him in his administrative department, Randon delayed his reply. In the end, though, the prefect of the Aveyron deci-
ed to have the child taken to Paris. Accompanied by Bonnaterre, the boy left Rodez on 20 July, contracted chickenpox between Lyon and Moulins, and on 6 August arrived in the capital, where he was taken to the National Institute for Deaf-Mutes run by Roch-Ambroise Cucurron Sicard. An article in the newspaper Les Débats prompted a flood of visitors keen to see the wild boy of the Aveyron. Sicard and Bonnaterre later presented the boy to the Minister of the Interior, who “caressed and kept him for nigh on half an hour.”

By coincidence, the Society of Observers of Man, a short-lived, but important learned society, had just announced the subject of study for its annual prize. Through daily observation of one or more children from birth, the task was to establish the order in which the physical, intellectual, and moral faculties develop, and to discover to what degree this development is helped or hindered by the influence of the objects, and more importantly, in the child's environment. With its sixty or so naturalists, doctors, philosophers, explorers, historians, and writers, the Society of Observers of Man, and Lucien Bonaparte in particular, was close to the center of political power and played a leading role in the child's transfer to Paris.

Sicard, Georges Cuvier the naturalist, and Philippe Pinel, the father of modern psychiatry and author of the influential Traité Médico-Philosophique sur l’Aliénation Mentale, ou la Manie [Medical-Philosophical Treatise on Mental Alienation, or Mania], which served as a reference work for French psychiatry for 20 years, were members of the Society of Observers of Man, which is considered as the cradle of French anthropology. Pinel examined the boy a few days after his arrival in Paris and in his report to the Society pulled no punches: he consigned the wild boy of the Aveyron to the vague category of idiocy and considered his mental deficiency as innate and inalterable. All attempts at rehabilitation, he believed, were doomed to failure. The feral child was a genuine idiot (and not a savage), which was probably why he had been abandoned, likely as a four- or five-year-old.

Interest in the child waned and by November 1800, Sicard had stopped looking after “his wild boy.” The sign method he used for deaf children had been an utter failure. The Ministry of the Interior now paid for the upkeep of the boy, who was entrusted to a housekeeper, Mrs Guérin, and to a young surgeon, Jean Itard.

Jean Itard: on becoming a pediatric psychiatrist

On the last day of 1800, Sicard appointed Jean Itard as resident physician at the French National Institute of Deaf-Mutes. Second-class surgeon at the Val de Grâce Military Hospital, student of Dominique-Jean Larrey, Napoleon’s surgeon-in-chief...
Jean Itard had yet to obtain the title of Doctor of Medicine (he did so in 1803, with a thesis on pneumothorax). Itard was tasked with the exclusive care of the wild boy, who remained at the institute during his “rehabilitation” (six years). Itard had no teaching experience and nothing about him suggested that he would be assigned to such a mission. Deeply imbued as he was by sensualism (the idea that sensations and perception are the truest form of cognition), Itard considered that man makes himself and progressively accumulates knowledge during the awakening of his senses. The linguist and educationalist Joseph-Marie de Gérando, who was a member of the Society of Observers of Man, imparted a philosophical meaning to the education of the feral child, by asserting that to enable him to associate ideas, it was first necessary to give birth to these ideas. And to achieve that, the boy’s attention had to be caught, the only way possible being to appeal to his needs.9-11

Itard lost no time in starting treatment of the feral child, while waging a constant battle against the administration, which was tempted to end what was deemed a costly and pointless exercise. The Minister of the Interior was inclined to consign the child to the lunatic asylum at Charenton, the fate of most idiots.11 Itard used the famous “moral treatment” pioneered by Pinel, who lent him support in his dealings with the administration. Itard set himself five objectives to bring the child out of his “wild state”:
- Draw him into social interactions by making his life more agreeable than it had been hitherto and, above all, with references to the life he’d just left behind.
- Awaken his sensitivity by energetic stimulation and sometimes by strong human affection.
- Extend the range of his ideas by exciting new needs and by multiplying his relations with the people around him.
- Cultivate his use of speech through imitation driven by need.
- Have him apply simple operations of the mind to objects associated with his physical needs.9,11,12

During the ten months after his admission to the National Institute for Deaf-Mutes, the child gradually lost his stereotyped gestures and movements. He no longer swayed about, became calm, but nonetheless made several escape attempts. Apart from moments when hunger drove him to the kitchen, the boy was to be found crouched in some corner of the gar-

It was around this time that the wild boy was christened Victor, following the publication of a novel entitled *Victor, ou l'Enfant de la Forêt* [Victor, or the Child of the Forest] and its hugely successful stage adaptation in Paris, with 392 performances in 1797-1798.

Victor rarely uttered a word, but did manage to pronounce monosyllables like “lait” (milk). However, to Itard’s great disappointment, he articulated such words to express pleasure (at seeing milk poured into his cup) rather than need (wish to drink milk). With Mrs Guérin, Victor was able to understand a certain language of action: if she indicated a pitcher, he would go to fetch water.

When Itard placed on the table letters to spell out “milk,” while presenting a glass of milk, Victor learned to arrange the letters or hidden upstairs. Highly sensitive to changes in the weather and to the full moon, the feral child took pleasure in running in the fields (Itard always accompanied him). He was able to dress himself, took a daily bath, checking its temperature beforehand with his finger, and followed (for a while) some rules of personal hygiene.

In August 1801, Itard presented a report to the Society of Observers of Man. He rejected Pinel’s diagnosis, arguing that the child’s state was not explained by congenital mental deficiency, but rather by a long period of social and emotional deprivation. Thus was born the dichotomy between congenital mental retardation (which would explain why the boy was abandoned in the first place) and acquired mental retardation (which would result from the abandonment and isolation). 4,11 Attempts to teach the boy to speak, however, yielded little.

As the founder of the French school of otology, Itard trained a good many 19th-century ear specialists, like Nicolas Deleau, who pioneered catheterization of the Eustachian tube and insufflation (blowing air into the ear canal), Pierre Bonnafont, who invented the otoscope, and Prosper Ménière, the first to describe the eponymous disease, author of a dissertation on inner ear lesions, and the successor to Itard at the National Institute for Deaf-Mutes. 4,10,15-18

### DR JEAN ITARD, THE FOUNDER OF MODERN OTOHINOLARYNGOLOGY IN FRANCE

Born in 1774 in Oraison in Provence (southeastern France), Jean-Marc-Gaspard Itard was sent by his uncle and father to study medicine at a military hospital so as to avoid conscription into the French army during the Revolution. He later worked at the military hospital in Toulon, where he attended anatomy and surgery lectures given by Dominique-Jean Larrey, surgeon-in-chief under Napoleon and a pioneer in battlefield medicine, whom he followed to the Val-de-Grâce military hospital in Paris in 1796. As fate would have it, during 1800 Itard was summoned by Roch-Ambroise Cucurron Sicard to the National Institute for Deaf-Mutes for a simple medical intervention. He remained there for the rest of his working life.

In 1821 in Paris, Itard published a two-volume treatise on diseases of the ear and of hearing that is considered as the first modern clinical and nosological work on otology. Itard adopted an original classification by separating ear diseases and hearing disorders. The second volume focused on deafness and the education of deaf children. The time of onset of deafness (congenital or around two years of age) was seen as important because it allowed the cause to be determined: neurological disorder or lesions of the hearing organs. Itard also invented two groundbreaking instruments: Itard’s catheter, or the Eustachian catheter, which is used to explore the inner ear by passing through the Eustachian tube; and an audiometer to assess degree of deafness.

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Frustrated, Itard had lost interest in Victor by the end of 1806 and left him to his housekeeper Mrs Guérin’s “affection.” He even tried to forget the child, like a disappointment in love or a mistake, and when, twenty years later, he recalled the time he had spent attempting to teach Victor, he confessed that mostly it had been an uphill and painful struggle. 8

Four years later, Sicard wrote to the Minister of the Interior asking for Victor to be removed from the National Institute for Deaf-Mutes, arguing that he was now over 20 years old, wasn’t deaf, was still asocial, and that his sexual urges were likely to cause problems. Victor left the institution13 with Mrs Guérin, who found lodgings nearby, so that Dr Itard could continue to visit. She received an annuity to cover her salary and Victor’s board and lodging. The institute’s administrators specified that Victor should not be exhibited or allowed to become the object of public inquisitiveness. 3 Soon after, Victor and Mrs Guérin moved into number 4 passage des Feuillantines, an alleyway where, as it happened, the 9-year-

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old Victor Hugo was then living. Thereafter, the young man re-gressed greatly, became obese, indulged in veritable masturbatory frenzies, and resumed his automatic gesturing. Interest in him faded and, soon forgotten, he continued a life of sorts until his death in 1828.3

Many present-day authors see Victor not as an idiot, but as autistic. Others point to epilepsy, as suggested by the spasms and convulsive states reported in the first reports of Bonnaterre and Itard.10

The year Victor died, Itard wrote about infantile psychosis, which hitherto had been confused with deafness-muteness. Emphasizing the emotional detachment of affected children, Itard recommended rehabilitation (based on the model used with Victor), having first established that the patient was at least capable of human intelligence, made manifest by the ability to give an affirmative or negative response, spoken or mimed, enabling the child to accept or refuse, to affirm or deny.11 Itard was therefore the first to express the concept of infantile psychosis outside a setting of profound mental retardation.12

References
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