### ACE Inhibition as a Cornerstone of Hypertension Treatment

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. Laurent, France</td>
<td>Editorial ACE inhibition as a cornerstone of hypertension treatment. L'inhibition de l'enzyme de conversion de l'angiotensine, Pierre Angulaire du traitement de l'hypertension</td>
<td>3</td>
</tr>
<tr>
<td>C. J. Pepine, USA</td>
<td>Pleiotropic effects of ACE inhibitors</td>
<td>9</td>
</tr>
<tr>
<td>B. I. Lévy, France</td>
<td>Are there differences between the RAAS inhibitors?</td>
<td>16</td>
</tr>
<tr>
<td>R. Ferrari, Italy</td>
<td>Do ACE inhibitors differ, and in which way?</td>
<td>24</td>
</tr>
<tr>
<td>G. M. London, France</td>
<td>Arterial compliance, central aortic blood pressure, and ACE inhibition</td>
<td>32</td>
</tr>
<tr>
<td>P. Rossignol and F. Zannad, France</td>
<td>Combination strategy based on perindopril for the treatment of hypertension: what are the options?</td>
<td>38</td>
</tr>
<tr>
<td>P. Sever, United Kingdom</td>
<td>Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm (ASCOT-BPLA): evidence for the use of an amlodipine-perindopril combination</td>
<td>43</td>
</tr>
<tr>
<td>G. Grassi and G. Mancia, Italy</td>
<td>Treating diabetic hypertensive patients: new insights from the ADVANCE trial</td>
<td>51</td>
</tr>
</tbody>
</table>

Contents continued overleaf...
## Contents continued from cover page

### ACE Inhibition as a Cornerstone of Hypertension Treatment

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. de la Sierra, Spain</td>
<td>Controversial Question: What determines your choice between free and fixed combinations in the management of your hypertensive patients?</td>
<td>57</td>
</tr>
<tr>
<td>M. Rosas Peralta, Mexico</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R. R. Azar, Lebanon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>J. Chin Tay, Singapore</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T. Eder, Turkey</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Tykarski, Poland</td>
<td></td>
<td></td>
</tr>
<tr>
<td>J. Chalmers, Australia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Z. D. Kobalava, Russia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. Trimarco, Italy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P. Ramachandran, India</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O. A. Aseeva, France</td>
<td>Coversyl: at the core of cardiovascular disease prevention and treatment</td>
<td>69</td>
</tr>
<tr>
<td>J. C. Tardif and K. Najem, Canada</td>
<td>Interview: ACE inhibition and atrial fibrillation</td>
<td>77</td>
</tr>
<tr>
<td>F. M. Turnbull, Australia</td>
<td>Focus: Inhibition of the renin-angiotensin system — insights from the Blood Pressure Lowering Treatment Trialists’ Collaboration</td>
<td>81</td>
</tr>
<tr>
<td>A. S. Hall, United Kingdom</td>
<td>Update: What is new in the genetics of the renin-angiotensin-aldosterone system?</td>
<td>87</td>
</tr>
<tr>
<td>C. Régnier, France</td>
<td>A Touch of France: Spices, diamonds, and Ayurvedic medicine: French physicians in 17th-century Mughal India</td>
<td>92</td>
</tr>
<tr>
<td>D. Camus, France</td>
<td>A Touch of France: West meets East: Pondicherry and the French East India Company</td>
<td>100</td>
</tr>
</tbody>
</table>
ACE inhibition as a cornerstone of hypertension treatment

by S. Laurent, France

ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS WERE introduced in clinical practice in the 1980s for the treatment of hypertension as the first agents able to block the renin-angiotensin aldosterone system (RAAS). Their effectiveness in reducing elevated blood pressure (BP) and preventing cardiovascular complications in hypertensive patients is solidly documented. The first morbidity-mortality trials of ACE inhibitors in hypertension, such as the Swedish Trial in Old Patients with Hypertension–2 (STOP-HT2) and Captopril Prevention Project (CAPPP) evidenced similar benefits with first-generation ACE inhibitors in comparison with earlier established antihypertensive agents like the β-blockers and diuretics. Subsequently, the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) reported similar effects with an ACE inhibitor and a thiazide diuretic, despite a greater BP reduction with the later. The Blood Pressure Lowering Treatment Trialists’ Collaboration meta-analysis, which included 18,229 patients from six trials of ACE-inhibitor–based therapy, showed significant reductions in risk of total major cardiovascular events in patients assigned to ACE-inhibitor treatment, with risk reductions of 28% in stroke, 20% in coronary heart disease, 22% in major cardiovascular events, 18% in heart failure, 20% in cardiovascular death, and 12% in total mortality, in comparison with placebo.

Pharmacodynamic studies in hypertensive patients have shown that ACE inhibitors are able to reduce target-organ damage. In particular, ACE inhibitors reduce left ventricular hypertrophy, albuminuria, and arterial damage, which are established intermediate end points for cardiovascular events. Because structural and functional changes in large and small arteries in hypertension, even at the early stages, may affect one or several end organs like the brain, heart, and kidney, contributing to cardiovascular morbidity and mortality, modern treatment strategies should not only target BP reduction, but also seek to normalize vascular structure and function. Several randomized, double-blind, parallel studies, conducted in accordance with Good Clinical Practice guidelines, have established the efficacy of ACE inhibition with perindopril in reducing BP, reversing vascular structure and function abnormalities in patients with essential hypertension, and ultimately preventing cardiovascular events. A positive relationship between arterial wall hypertrophy reduction and BP reduction in small resistance arteries has been evidenced following long-term treatment with perindopril, but not atenolol. Of particular interest is how the improvement in small artery function in response to structural changes impacts on the coronary circulation. Indeed, in the coronary arterioles, perindopril achieves an increase in coronary blood flow and coronary reserve, in parallel with a regression of periarteriolar and interstitial collagen. In large arteries, long-term treatment with perindopril reduces carotid and radial artery wall hypertrophy, as well as carotid artery internal diameter. These structural changes result in an improvement in large artery function, with an increase in carotid and brachial arterial distensibility, and normalization of coronary arterial dilation in response to the cold-pressor test or an increase in blood flow.

In addition to their antihypertensive effect, ACE inhibitors exert direct vascular and cardioprotective effects, which appear to be independent of hemodynamic changes. ACE inhibitors act by improving the balance between the production of angiotensin II, a potent vasoconstrictor, and the prevention of bradykinin degradation, a potent stimulator of nitric oxide release. Nitric
oxide plays a crucial role in attenuating endothelial dysfunction, an early manifestation of atherosclerosis. The effects of ACE inhibitors on smooth muscle cell growth and proliferation, fibrinolysis and thrombogenesis, and endothelial apoptosis may result in antiatherogenic benefits. The currently available ACE inhibitors exhibit important differences regarding chemical structure, potency, bioavailability, plasma half-life, distribution, and elimination. Their BP-independent effects vary depending on their activity on tissue RAAS and their affinity for bradykinin binding sites versus angiotensin I binding sites. This could explain that ACE inhibitors differ in their effects on nitric oxide production and endothelial apoptosis rate reduction, for a same BP reduction. ACE inhibitors are also known to reduce insulin resistance and improve insulin sensitivity, thereby contributing to prevent new-onset diabetes, and thus reduce the risk of micro- and macroangiopathy.

Several long-term follow-up trials have shown that ACE inhibition exerted BP-independent effects on large and small arteries. For instance, the Diabetes Artery Perindopril Hypertension Normalization Excess stiffness (DAPHNET) study in hypertensive patients with type 2 diabetes showed that a 6-month treatment with perindopril 8 mg increased carotid distensibility to a greater extent than perindopril 4 mg, for a similar reduction in ambulatory BP. In hypertensives, a 1-year treatment with perindopril normalized the media-to-lumen ratio of small arteries, whereas atenolol did not. These BP-independent effects of ACE inhibitors could confer additional efficacy in terms of prevention of cardiac, cerebrovascular, and renal outcomes.

According to the latest European Society of Hypertension–European Society of Cardiology (ESH-ESC) Guidelines for the management of arterial hypertension (2007), ACE inhibitors are recommended as first-line treatment in a vast range of hypertensive patients, especially those with subclinical organ damage (left ventricular hypertrophy, asymptomatic atherosclerosis, microalbuminuria, or renal dysfunction); cardiovascular events (previous myocardial infarction (MI), heart failure, recurrent atrial fibrillation, end-stage renal disease or proteinuria); and various clinical conditions (metabolic syndrome, diabetes mellitus). ACE inhibitors display the highest range of proven benefits in terms of long-term total risk of cardiovascular morbidity and mortality, which, according to the ESH/ESC guidelines is the primary goal of antihypertensive treatment.

Whether ACE inhibitors provide better cardiovascular protection than angiotensin-receptor blockers (ARBs) has been intensely debated. Four years ago, Verma and Strauss challenged the protective effects of ARBs against coronary events in general and myocardial infarction (MI) in particular, and suggested that ARBs may increase MI. These authors reviewed various data suggesting that the deleterious effect of ARBs could occur through AT2 receptor stimulation, which, under certain circumstances, could mediate growth promotion, fibrosis, and hypertrophy, as well as proatherogenic and proinflammatory effects. The first direct, head-to-head comparison between an ACE inhibitor and an ARB was the recent ONGOing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET). This study showed that despite a more specific blockade of RAAS, ARBs are not superior to ACE inhibitors in reducing fatal and nonfatal cardiovascular events. The most recent meta-analysis, performed on 6 large clinical trials including the ONTARGET trial, and gathering 49 924 patients, showed that ARBs were as effective as ACE inhibitors regarding the risk of MI.

ACE inhibitors with a long duration of action and an improved tolerability profile, such as ramipril, perindopril, and trandolapril, ensure effective and well-tolerated long-term treatment both in monotherapy and in combination. The resulting long-term BP lowering is a major factor in the reduction in cardiovascular events in several major morbidity-mortality trials, such as the Heart Outcomes Prevention Evaluation (HOPE) study, the European trial on Reduction Of coronary events with Perindopril in stable coronary Artery disease (EUROPA), and the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial. An indirect demonstration of the major role played by the improvement in large artery function in the reduction in cardiovascular events has been reported in patients with end-stage renal disease. In these patients, perindopril decreased pulse wave velocity independently of BP changes, resulting in a highly significant relative risk reduction in all-cause and cardiovascular mortality. In addition, the multifactorial antiatherosclerotic profile of perindopril suggests a beneficial effect not only in hypertensive patients, but also in patients with established coronary heart disease or previous stroke as has been demonstrated in the EUROPA and the Perindopril pROtection aGainst Recurrent Stroke Study (PROGRESS) trials.

In the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA), modern combination treatment, based on amlodipine/perindopril, was shown to be significantly more effective in reducing all-cause and cardiovascular mortality, stroke, total cardio-
vascular events and procedures, and in the prevention of new-onset diabetes, in comparison with conventional treatment based on a β-blocker and a thiazide diuretic.²⁰ The Conduit Artery Function Evaluation (CAFE) substudy of ASCOT-BPLA sheds light on the pathophysiological mechanisms that underlie the differences in clinical outcomes.²¹ In CAFE, treatment with amloidipe/perindopril resulted in a significantly greater reduction in central aortic pressures in comparison with β-blocker/thiazide diuretic treatment, despite a similar reduction in brachial pressure. In turn, central aortic pressures appears to better correlate with cardiovascular outcomes than peripheral, including brachial, pressures. This finding underscores the importance of not only targeting brachial BP reduction, but also normalizing vascular structure and function, which, when impaired, affect end organs (brain, heart, kidneys) and contribute to cardiovascular morbidity and mortality.

More recently, in the Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation (ADVANCE) trial in patients with diabetes mellitus, perindopril in combination with a metabolically neutral diuretic indapamide showed a reduction in total and cardiovascular mortality, a composite end point of macro- and microvascular events, as well as in coronary and renal outcomes.²² These effects of the perindopril/indapamide combination were not confounded by initial BP levels or concomitant use of other treatments.

As most hypertensive patients need more than one drug to achieve their BP target, ACE inhibitors, which are effective antihypertensive drugs with pleiotropic effects, should be considered as a cornerstone of combination treatment. As such, perindopril both in monotherapy and in combination with indapamide or amlodipine, can claim the largest number of large clinical trials showing a significant reduction in cardiovascular events in a vast range of hypertensive patients.¹⁶,¹⁹,²²

REFERENCES


Keywords: renin-angiotensin-aldosterone system; angiotensin-converting enzyme inhibitor; perindopril; pleiotropic effects; guidelines; evidence-based medicine
L’inhibition de l’enzyme de conversion de l’angiotensine, pierre angulaire du traitement de l’hypertension

par S. Laurent, France

Les inhibiteurs de l’enzyme de conversion de l’angiotensine (IEC), qui sont apparus en pratique clinique dans les années 1980 pour le traitement de l’hypertension, ont constitué les premiers médicaments permettant de bloquer le système rénine-angiotensine-aldostérone. Leur efficacité dans la réduction de l’hypertension et la prévention des complications cardio-vasculaires est abondamment documentée. Les premiers essais de morbidité et de mortalité menés sur les IEC dans l’hypertension, par exemple l’étude STOP-HT2 (Swedish Trial in Old Patients with Hypertension–2) et l’étude CAPPP (CAPtopril Prevention Project), ont montré que les IEC de première génération induisaient des bénéfices similaires à ceux obtenus par les agents antihypertenseurs précédemment établis, tels les bétabloquants et les diurétiques. Par la suite, l’étude ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial) a mis en évidence la comparabilité des effets entre un IEC et un diurétique thiazidique, malgré la réduction plus importante de la pression artérielle (PA) obtenue avec ce dernier. La méta-analyse Blood Pressure Lowering Treatment Trialists’ Collaboration, qui a porté sur 18 229 patients ayant participé à 6 études effectuées sur des traitements à base d’IEC, a montré des réductions significatives des risques d’événements cardio-vasculaires majeurs chez les patients recevant un traitement à base d’IEC. Les réductions des risques par rapport au placebo ont été de 28 % pour les accidents vasculaires cérébraux, 20 % pour les coronaropathies, 22 % pour les événements cardio-vasculaires majeurs, 18 % pour l’insuffisance cardiaque, 20 % pour les décès cardio-vasculaires et 12 % pour la mortalité totale.

Les études pharmacodynamiques menées chez des patients hypertendus ont montré que les IEC permettaient de réduire les lésions des organes cibles. Plus particulièrement, les IEC ont réduit l’hypertrophie ventriculaire gauche, l’albuminurie, et les lésions artérielles, qui sont des critères intermédiaires établis pour les événements cardio-vasculaires majeurs chez les patients recevant un traitement à base d’IEC. Dans la mesure où les altérations structurelles et fonctionnelles des artères de grand et de petit calibre dans l’hypertension, même dès les stades précoce, risquent d’affecter un ou plusieurs organes cibles comme le cerveau, le cœur et le rein, aggravant la morbidité et la mortalité cardio-vasculaires, les stratégies thérapeutiques modernes doivent non seulement cibler une réduction de la PA, mais également viser à normaliser la structure et de la fonction vasculaires. Plusieurs études parallèles randomisées et en double aveugle effectuées conformément aux directives des Bonnes Pratiques Cliniques ont établi l’efficacité de l’inhibition de l’enzyme de conversion par le perindopril pour la réduction de la PA, la correction des anomalies structurelles et fonctionnelles vasculaires chez les patients atteints d’hypertension essentielle et, finalement, la prévention des événements cardio-vasculaires. Une relation positive entre la réduction de l’hypertrophie des parois artérielles et la réduction de la PA dans les artères à faible résistance a été mise en évidence après un traitement à long terme par le perindopril, mais n’a pas été retrouvée avec l’aténolol. Il est particulièrement intéressant de considérer l’impact sur la circulation coronaire de l’amélioration de la fonction des petites artères en réponse aux changements structurels. Ainsi, il apparaît que, dans les artérioles coronaires, le perindopril entraîne une augmentation du débit sanguin coronaire et de la réserve coronaire, parallèlement à une régression du collagène périarteriel et interstitiel. Dans les artères de grand diamètre, un traitement à long terme par le perindopril réduit l’hypertrophie de la paroi des artères carotides et radiales, ainsi que le diamètre in-

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terme des artères carotides. Ces changements structurels entraînent une amélioration de la fonction des grandes artères, qui s’accompagne d’une augmentation de la distensibilité des artères carotides et brachiales et d’une normalisation de la dilatation des artères coronaires en réponse à l’épargne à droite ou à une augmentation du débit artériel.5


Plusieurs études de suivi à long terme ont montré que l’inhibition de l’enzyme de conversion exerçait des effets indépendants de la PA sur les artères de faible et de grand calibre. Ainsi, l’étude DAPHNET (Diabetes Artery Perindopril Hypertension Normalization Excess sTiffness) effectuée chez des patients hypertendus atteints de diabète de type 2 a montré qu’un traitement de 6 mois par le perindopril à la posologie de 8 mg augmentait de façon plus importante la distensibilité des carotides qu’à la posologie de 4 mg, pour une réduction similaire de la PA ambulatoire.7 Chez les sujets hypertendus, un traitement d’un an par le perindopril a permis de normaliser le rapport média/lumière des petites artères, ce qui n’a pas été le cas de l’aténolol.10 Ces effets indépendants de la PA exercés par les IEC pourraient conférer une efficacité supplémentaire quant à la prévention des événements cardiaques, vasculaires cérébraux et rénaux.

Les dernières directives de la Société européenne d’hypertension et de la Société européenne de cardiologie (European Society of Hypertension – European Society of Cardiology, ESH-ESC) concernant la prise en charge de l’hypertension artérielle (2007) recommandent d’utiliser les IEC comme traitement de première intention chez une large variété de patients hypertendus, en particulier lorsqu’ils présentent des lésions organiques subcliniques (hypertrophie ventriculaire gauche, athérosclérose asymptomatique, microalbuminurie ou dysfonctionnement rénal) ; des événements cardio-vasculaires (antécédents d’infarctus du myocarde (IDM), insuffisance cardiaque, fibrillation auriculaire récurrente, insuffisance rénale de stade terminal ou protéinurie) ; ou différentes affections cliniques (syndrome métabolique, diabète sucré).11 Les IEC apportent la gamme la plus importante de bénéfices démontrés en ce qui concerne le risque total de morbidité et de mortalité cardio-vasculaires à long terme, qui constitue, selon les directives de l’ESH/ESC, l’objectif principal d’un traitement antihypertenseur.

Il a été longuement débattu pour déterminer si les IEC apportaient une meilleure protection cardio-vasculaire que les antagonistes des récepteurs de l’angiotensine II (ARA). Il y a 4 ans, Verma et Strauss, examinant les effets protecteurs des ARA sur les événements coronaires en général et l’infarctus du myocarde (IDM) en particulier, ont suggéré que les ARA pouvaient augmenter l’IDM.12 Ces auteurs ont analysé un certain nombre de données suggérant que les effets délétères des ARA pourraient résulter de la stimulation des récepteurs AT₂, qui, dans certaines circonstances, assureraient la médiation de la promotion de la croissance, de la fibrose et de l’hypertrophie, ainsi que d’effets pro-athérogènes et pro-inflammatoires.12 La première comparaison bilatérale directe effectuée entre un IEC et un ARA a été la récente étude ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial). Cette étude a montré que, malgré un blocage plus spécifique du système rénine-angiotensine-aldostérone, les ARA n’étaient pas supérieurs par rapport aux IEC pour la réduction des événements cardio-vasculaires fataux et non fataux.13 La méta-analyse la plus récente, effectuée sur 6 études cliniques à grande échelle (y compris l’étude ONTARGET), qui a porté sur 49 924 patients, a montré que les ARA étaient aussi efficaces que les IEC en ce qui concerne le risque d’IDM.14
Les IEC présentant une longue durée d’action et un profil de tolérance amélioré, comme le ramipril, le perindopril et le trandolapril, permettent d’assurer un traitement à long terme efficace et bien toléré à la fois en monothérapie et en association. La réduction à long terme de la PA obtenue est un facteur majeur de réduction des événements cardio-vasculaires, comme cela a été démontré dans plusieurs études majeures de morbidité et de mortalité, notamment l’étude HOPE (Heart Outcomes Prevention Evaluation), l’étude EUROPA (EUropean trial on Reduction Of coronary events with Perindopril in stable coronary Artery disease), et l’étude PEACE (Prevention of Events with Angiotensin Converting Enzyme Inhibition). Une démonstration indirecte du rôle majeur joué par l’amélioration de la fonction des grandes artères dans la réduction des événements cardio-vasculaires a été fournie chez des patients atteints d’insuffisance rénale au stade terminal. Chez ces patients, le perindopril a diminué la vitesse de l’onde du pouls aortique indépendamment des modifications de la PA, entraînant une réduction du risque relatif hautement significative de la mortalité cardio-vasculaire et de toute cause. En outre, le profil anti-athéroscléreux multifactoriel du perindopril suggère l’existence d’un effet bénéfique non seulement chez les patients hypertendus, mais également chez les patients atteints de coronaropathies établies ou présentant des antécédents d’accidents vasculaires cérébraux, comme cela a été démontré dans les études EUROPA et PROGRESS (Perindopril pROtection aGainst Recurrent Stroke Study).

Dans l’étude ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm), une association thérapeutique moderne, regroupant l’amlodipine et le perindopril, s’est avérée être significativement plus efficace pour réduire la mortalité cardio-vasculaire et la mortalité de toute cause, les accidents vasculaires cérébraux, les événements cardio-vasculaires totaux et les procédures, ainsi que dans la prévention des nouveaux cas de diabète, par rapport à un traitement conventionnel utilisant un bétabloquant et un diurétique thiazoïdique. La sous-étude CAFE (Conduit Artery Function Evaluation) de l’étude ASCOT-BPLA a mis en lumière les mécanismes physiopathologiques sous-jacents permettant d’expliquer les différences des résultats cliniques. Dans la sous-étude CAFE, le traitement par l’association amlodipine/perindopril a entraîné une réduction significativement supérieure des pressions artérielles centrales par rapport au traitement par le bétabloquant et le diurétique thiazoïdique, malgré une réduction similaire de la pression de l’artère brachiale. En outre, les pressions artérielles centrales semblent montrer une meilleure corrélation avec les résultats cardio-vasculaires que les pressions périphériques, notamment de l’artère brachiale. Ce résultat souligne l’importance non seulement de cibler une réduction de la PA brachiale, mais également de normaliser la structure et la fonction vasculaires, qui, lorsqu’elles sont altérées, affectent les organes cibles (cœur, rein) et contribuent à la morbidité et à la mortalité cardio-vasculaires.

Plus récemment, dans l’étude ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation) réalisée chez des patients atteints de diabète, le perindopril en association avec un diurétique métaboliquement neutre, l’indapamide, a entrainé une réduction de la mortalité cardio-vasculaire et totale (un paramètre composite des événements macro- et microvasculaires), ainsi que des événements coronaires et rénaux. Ces effets de l’association perindopril/indapamide n’ont pas été modifiés par les facteurs de confusion représentés par les valeurs initiales de la PA ou utilisation concomitante d’autres traitements.

Dans la mesure où la plupart des patients hypertendus nécessitent plusieurs médicaments pour atteindre leurs valeurs cibles de PA, les IEC, en raison de leur efficacité antihypertensive et des effets pléiotropes dont ils sont doués, doivent être considérés comme la pierre angulaire des associations thérapeutiques. À cet égard, le perindopril, tant en monothérapie qu’en association avec l’indapamide ou l’amlodipine, peut revendiquer le nombre le plus important d’études cliniques à grande échelle ayant démontré une réduction significative des événements cardio-vasculaires chez une large variété de patients hypertendus.
Pleiotropic effects of ACE inhibitors

by C. J. Pepine, USA

Clinical trials document that angiotensin-converting enzyme (ACE) inhibitors improve cardiovascular morbidity and mortality in patients with hypertension, heart failure, left ventricular dysfunction, acute myocardial infarction, and more recently in patients with stable coronary artery disease without left ventricular dysfunction, as well as those with dysglycemia and atrial fibrillation. Recent data also suggest improved arterial stiffness and reduced aortic aneurysm in Marfan syndrome. Pleiotropic effects of ACE inhibitors might be responsible for prevention of coronary disease–related adverse outcomes seen in meta-analyses in comparison with angiotensin receptor blockers. Also, reduced insulin resistance and improved insulin sensitivity have been associated with prevention of new-onset diabetes in patients treated by ACE inhibitors in comparison with diuretics and β-blockers. Accumulating evidence indicates that ACE inhibitors have direct vascular and myocardial protective effects that may explain their benefits. These effects, beyond those expected from blood pressure lowering, might also vary between individual ACE inhibitors, being dependent on tissue penetration and potency for tissue ACE and other characteristics. ACE inhibitors improve the balance between production of angiotensin II, a potent vasoconstrictor, and prevention of degradation of bradykinin, the latter being a potent stimulator of nitric oxide release. Angiotensin II has detrimental effects on vascular function and structure, while nitric oxide plays a crucial role in attenuation of endothelial dysfunction, an early manifestation of atherosclerosis. The effects of ACE inhibitors on smooth muscle cell growth and proliferation, fibrinolysis, and thrombogenesis, as well as endothelial apoptosis, may result in antiatherothrombotic benefits in excess of those expected from blood pressure lowering alone.

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Keywords: angiotensin-converting enzyme inhibitor; pleiotropic effect; cardiovascular morbidity and mortality; hypertension; coronary artery disease; heart failure; diabetes; atherosclerosis; angiotensin II; bradykinin; nitric oxide

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Pleiotropic effects of ACE inhibitors – Pepine
ACE expression was upregulated in atherosclerotic plaque and colocalized with low-density lipoprotein (LDL) cholesterol. This evidence supported the notion that ACE expression and angiotensin II (Ang II) were involved in plaque instability, which was responsible for progression and acute atherothrombotic events.

**Studies in patients without LV dysfunction or acute MI**

The forgoing findings provided the background for a series of trials attempting to modify acute coronary events with ACE inhibition. The QUinapril Ischemic Event Trial (QUIET) was the first attempt to test the hypothesis that prolonged ACE inhibition would reduce the morbidity and mortality associated with CAD. Unfortunately, this trial suffered from numerous design issues, being the initial trial to address this important question. Very important was clinical revascularization as a component of the primary outcome. During the course of the trial it became evident that percutaneous coronary intervention (PCI) was evolving as a practice option rather than a reliable indicator of disease progression. Coronary revascularization was highly prevalent in both treatment groups (38.6%). This resulted in a lack of power to detect differences in the more objective events (cardiovascular [CV] death, 1.5% and MI, 4.6%), which comprised the other components of the primary outcome cluster of events. The secondary outcome, death, MI, and resuscitated cardiac arrest, showed an interesting trend suggesting an approximately 13% relative risk reduction for ACE inhibition (Figure 1). The Heart Outcomes Prevention Evaluation (HOPE) used a higher-risk population (placebo CV mortality 8.1% vs 1.5% in QUIET), more extended follow-up (5 vs 2.25 years), a more appropriate cluster of events as the primary outcome (death, MI, or stroke), and a much more appropriate sample size (9297 vs 1750). In HOPE, ACE inhibition with ramipril 10 mg daily reduced MI risk by about 20%, stroke by 33%, and CV mortality by 25% in high-risk patients without clinical heart failure or a reduced ejection fraction (Figure 1). Subsequently, the EUROpean trial On reduction of cardiac events with Perindopril in stable coronary artery disease (EUROPA) confirmed that perindopril 8 mg daily in CAD patients without heart failure reduced CV mortality, nonfatal MI, and resuscitated cardiac arrest by 20% (Figure 1). Nonfatal MI alone was reduced 22%. In contrast, the Prevention of Events with Angiotensin-Converting Enzyme inhibition (PEACE) trial failed to show benefit with trandolapril 4 mg daily in CAD patients without heart failure or LV dysfunction (Figure 1). However, as in QUIET, the PEACE population was at lower risk for CV death and MI (than either HOPE or EUROPA) and had a relative low compliance rate with study medication. But perhaps also important, coronary revascularization was the major contributor (19.1%) to the cluster of events chosen for the primary outcome. This revascularization outcome issue was similar in QUIET, and again since revascularization was used more frequently in both treatment groups (19%) PEACE was underpowered.

An overview analysis of these 4 trials in a total of 31,555 patients (136,882 patient-years follow-up) with stable vascular disease without LV systolic dysfunction or heart failure has confirmed that ACE inhibition significantly reduces risk for all-cause mortality, CV mortality, nonfatal MI, stroke, need for PCI or coronary artery bypass surgery, and hospitalization for congestive heart failure, but not for hospitalization for angina. Occurrence of new-onset diabetes was also significantly reduced. They estimated that treating about 100 patients for about 4.5 years would prevent 1 death, 1 nonfatal MI, 1 CV death, or 1 coronary revascularization. Treating about 50 patients for this duration would prevent 1 MI (fatal and nonfatal) or 1 new case of diabetes.

The exact magnitude of the contribution of BP reduction from ACE inhibition to these improved outcomes remains controversial. In HOPE, mean systolic BP/diastolic BP reductions were 3/2 mm Hg and in EUROPA, 5/2 mm Hg, respectively. Clearly, BP reduction plays a role, but detailed analyses indicate that the improvement in outcomes exceeded that predicted from BP lowering alone. Furthermore, metaregression analyses, that include hypertension trials, confirm that outcomes in patients receiving ACE inhibitors are better than would be expected from BP lowering alone. A recent metaregression analysis of 140,000 subjects comparing ACE inhibitor and Ang II receptor blocker (ARB) trials concluded that ACE inhibition had a 9% greater effect on the reduction of MI and CV death, and benefits independent of BP reduction. Interestingly, with the ARBs, similar BP-independent ef-
effects were not observed and a suggestion of increased MI was noted. As a consequence of the above studies, guidelines for the management of MI, heart failure hypertension, and diabetes recommend that ACE inhibition be considered in patients at a very high risk for recurrent vascular events.

**Other areas**

**Insulin resistance (dysglycemia) and diabetes development**

Hypertension, heart failure, CAD, and CV risk factors like obesity, inactivity, etc., are major risk conditions for insulin resistance and development of type 2 diabetes, which is becoming epidemic. This knowledge has led to the concept of a continuum for hyperglycemia ranging from prediabetes to the development of new-onset diabetes. Furthermore, a recent meta-analysis suggested that the presence of diabetes in patients with CAD is associated with approximately a doubling in risk for death, MI, or stroke. Interest in prevention of diabetes among patients with CV disease has been stimulated by the understanding that certain drugs contribute to diabetes risk. In INVEST, a calcium antagonist–based strategy were compared with control BP in over 16,000 CAD patients without diabetes who were followed for adverse outcomes. During follow up, we observed approximately 400/year cases of new diabetes, and overall risk for newly diagnosed diabetes was reduced by 15% in the verapamil SR–based vs atenolol-based strategy (P<0.01). Characteristics associated with diabetes risk included place of residence (in the USA), LV hypertrophy, previous stroke/transient ischemic attack, Hispanic ethnicity, prior coronary revascularization, hypercholesterolemia, increased body mass index, and higher follow-up systolic BP (Figure 2, page 12). Addition of trandolapril to verapamil SR decreased diabetes risk and addition of hydrochlorothiazide to atenolol was associated with a dose-dependent increase in diabetes risk. We concluded that clinical findings associated with more severe vascular disease and Hispanic ethnicity identify a subgroup of patients at high risk for developing diabetes, whereas lower on-treatment BP and treatment with a calcium antagonist–ACE inhibition strategy attenuated this risk. Thus, the latter strategy should be preferred among patients at high risk for diabetes.

Recently, Elliott and Meyer, using a network-based meta-analysis of 22 BP-lowering trials that included 143,153 nondiabetic participants, confirmed that ACE-inhibitor use was associated with a 30% reduction in risk (P=0.0001) for new diabetes compared with diuretic use. The risk for developing diabetes was very similar comparing a diuretic and a β-blocker. The odds ratios for reduction in new diabetes did not differ significantly between an ACE inhibitor and an ARB. These findings have very important adverse outcome implications considering the long-term duration of hypertension treatment, as emphasized by others. Recently, glucose levels have also been associated with risk for developing AF.
ACE inhibition as a Cornerstone of Hypertension Treatment

![Graph](image)

Figure 2. Relation between follow-up systolic blood pressure (SBP) and diabetes development shows relative hazard for follow-up SBP (mean of measurements before death, diabetes development or censoring) with reference (hazard ratio=1.0) for 120 mm Hg. From the stepwise model, an SBP=150 mm Hg is associated with an 11.0% incidence of new diabetes. From reference 18: Modified after reference 18. Cooper-Deloff R, Cohen JD, Bakris GL, et al. Predictors of development of diabetes mellitus in patients with coronary artery disease taking antihypertensive medications (findings from the INternational VEdrapamir SR-Trandolapril SStudy [INVEST]). Am J Cardiol. 2006;98:890-894.

**What is the mechanism responsible for these pleiotropic effects of ACE inhibition?**

**Atrial fibrillation**
AF is another CV epidemic, affecting 5% of individuals aged >65 years, and is associated with increased risk of stroke and a doubling of mortality. Evidence in experimental models and patients suggests that RAAS inhibition may reduce the incidence of new-onset AF and also AF recurrence. A recent meta-analysis of 11 studies concluded that RAAS inhibition (ACE inhibition or ARB) was associated with reduced AF risk by $28\%$ (Figure 3). Another study suggests that combination of perindopril and low-dose amiodarone is more effective than amiodarone alone for prevention of AF recurrence in lone paroxysmal AF. Adding perindopril to amiodarone also inhibited left atrial enlargement in this group of patients. In these studies, the incidence of new AF was low, so a more definitive answer to the question whether patients without LV dysfunction benefit with reduced episodes of AF will require completion of several ongoing trials (second Canadian Trial on Atrial Fibrillation [CTAF-2]). Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events [ACTIVE-I], etc. At present it appears that ACE inhibitors and ARBs clearly prevent AF.

**Large artery stiffness, aortic aneurysm, and Marfan syndrome**
Weakening of the aorta wall leads to progressive dilation (eg, aeurysm formation), which is often not diagnosed, but as the diameter exceeds 5.5 cm, risk for rupture increases markedly. Treatment for aneurysms >5.5 cm is surgical, with or without endovascular repair, and better therapies are needed to prevent enlargement of aneurysms <5 cm. In rat models, ACE inhibition suppressed development of aortic aneurysms, and in aneurysm patients, ACE inhibition was associated with decreased stiffness and greater collagen turnover, both of which are favorable as increased stiffness is a risk factor for adverse events. In a recent case-control study, ACE inhibition, but not $\beta$-blockers, calcium antagonists, thiazides, or ARBs, was associated with reduced risk of abdominal aortic aneurysm rupture.

Although the number of patients using ARBs was small, their surprising lack of effect in reducing aneurysm formation has also been reported in animal studies. This finding suggests that ACE-inhibition–related protective effects on aneurysm formation and enlargement may be mediated by other angiotensin receptor subtypes, or production of other RAAS peptides, and/or reduced bradykinin degradation. Perindopril reduced both aortic stiffness and diameter in Marfan syndrome patients taking $\beta$-blockers, possibly through attenuation of transforming growth factor (TGF)-$\beta$ signaling. These are clearly very important findings, and large clinical trials are needed to assess the benefit of ACE inhibition in Marfan syndrome and other aortic aneurysm patients.

**Endothelial function**
In the clinical circumstances reviewed above, there is evidence that tissue ACE expression is increased, local Ang II is increased, and that signaling through both the angiotensin type-1 (AT$_1$) and type-2 (AT$_2$) receptor pathways contributes to the vascular disease processes. A unifying theme is that prolonged periods of oxidative stress result in dysfunction at the endothelial (EC) and smooth muscle cell (SMC) level, and also within the monocellular cells residing in the vessel wall and bone marrow–derived vascular progenitor cells (PCs). Oxidative stress arises from a number of conditions (oxidized LDL cholesterol, increased BP, smoking, hyperglycemia, etc), which produce reactive oxygen species that cannot be adequately quenched by our antioxidant systems. Excess oxidative stress shifts the balance in physiologic state that exists to maintain processes involved in vascular tone, cell growth, and proliferation, coagulation, platelet aggregation, inflammation, etc. These processes are, in part, mediated via local Ang II production acting via AT$_1$ receptors to activate NADH/NADPH oxidase, producing superoxide anion. At the EC and SMC level, superoxide anion reduces bioavailability of nitric oxide (NO) and also produces peroxynitrite, which is a potent oxidant. Ang II also releases endothelin and norepinephrine. These actions result in cellular dysfunction. Ang II stimulates SMC migration and replication and cardiomyocyte hypertrophy as well as plasminogen activator (PA) inhibitor (PAI)–1 synthesis to alter fibrinolytic balance (tissue [t]-PA/PAI-1 ratio). The overall vascular effect is to enhance tone (activate SMC contraction), promote inflammation (induce expression of monocyte chemotac-
tic protein [MCP]-1, vascular cell adhesion molecule [VCAM], tissue necrosis factor [TNF]-α, interleukin [IL]-6 and activate monocytes/macrophages, stimulate remodeling [induce platelet-derived growth factor (PDGF)], basic fibroblast growth factor [bFGF] insulin-like growth factor [IGF]-1, TGF-β expression to stimulate matrix glycoprotein/metalloproteinase production) and trigger thrombosis (activate platelets/increase aggregation/adhesion).  

ACE plays a key role in the above, via production of circulating and tissue Ang II acting at several specific receptors. Inhibition of ACE (eg, ACE inhibitors) decreases local Ang II production and blocks bradykinin degradation. The importance of this mechanism has been documented in studies showing that it permits ACE inhibition to lower BP in patients with low-renin hypertension. Others have directly confirmed that bradykinin contributes to short-term effects of ACE inhibitors on BP in both normotensive and hypertensive persons. Improved endothelial function in response to ACE inhibition is muted when a bradykinin B₂ receptor blocker is coadministered.  

In the PERindopril-Thrombosis, Inflammation, Endothelial dysfunction and Neurohormonal activation Trial (PERTINENT) substudy of EUROPA, abnormal endothelial function was documented by elevated von Willebrand factor (vWF) measurements in a subgroup of 1200 patients, and the level correlated with CV events. The occurrence of CV events was related to vWF level at entry. Furthermore, vWF levels significantly decreased after 1 year of perindopril treatment. Multivariable analysis confirmed that changes in vWF levels were related to this ACE inhibition treatment effect. Additionally, perindopril increased protein expression/activity of EC NO synthase and reduced apoptosis coincident with significant reduction in Ang II, an increase in bradykinin and reduction in TNF-α, and an increase nitrite/nitrate. All of these effects likely contributed to the clinical benefit documented in EUROPA.

**Vascular progenitor cells and vascular repair**  
New data suggest the regenerative potential of endothelial PCs and modulation of RAAS for remodeling/repairing defects of the vasculature. The concentration of PCs in the blood has an inverse relationship to the risk factor profile, and the presence and severity of CAD. Reduced levels of circulating endothelial PCs independently predict adverse cardiac events. The ability of bone marrow to generate enough numbers of functional PCs to provide adequate vascular repair of injury that is mediated by risk conditions is likely critical to the expression of CAD. Data linking endothelial dysfunction with low PC levels suggest that ongoing endothelial damage may lead to bone marrow depletion, resulting in insufficient repair or adverse remodeling of injured arteries, while a competent response may stabilize or fully repair the injury.

This EC-mediated function is lost early in the course of vascular injury due to a variety of inciting factors (risk conditions). ECs play an important regulatory role in the coronary microcirculation and where tissue-based components of the RAAS are synthesized NO and other EC-derived vasodilators (prostaglandin I₂ [PGL₂], endothelial-derived hyperpolarizing factor [EDHF], bradykinin, etc) offset constrictive effects of Ang II generated by tissue-based ACE and other endothelium-derived constrictive factors (endothelin, etc). When ECs are damaged, the microvessels and macrovessels rapidly lose their ability to dilate appropriately via endothelium-dependent pathways. Hence, even metabolic-induced arteriolar dilation may not provide sufficient increase in coronary flow when dysfunctional ECs do not provide mediators for shear-related vasodilation.

Treating CAD patients with ACE inhibition (ramipril, 5 mg/day) for only 4 weeks resulted in a 3-fold increase in circulating endothelial PC number and improved function (eg, migration, proliferation, adhesion, and in vitro vasculogenesis capacity). Type 2 diabetes treated with Ang II type 1 (AT₁) receptor blockade (olmesartan, 40 mg/day or placebo) for 12 weeks increased circulating CD34+ progenitor cells. These results were verified in a second trial treating type 2 diabetic patients with another AT₁ blocker (irbesartan, 300 mg/day) for 12 weeks. With AT₁ receptor blockade (irbesartan) endothelial PC number increased significantly after 4 weeks and continued at 12 weeks. In contrast, in patients treated with other antihypertensive agents to reduce BP to similar levels, similar effects on endothelial PCs were not observed. Exposure of cultured endothelial PC to Ang II significantly accelerates
rates of senescence and leads to impairment of proliferative activity. Ang II-induced endothelial PC senescence is inhibited by pretreatment with either AT1 receptor blockade (valsartan) or adding superoxide dismutase. Ang II significantly diminishes telomerase activity, which critically influences cellular senescence, although the effect was significantly reduced by pretreatment with either AT1 receptor blockade or superoxide dismutase.

All of these studies suggest that Ang II accelerates endothelial PC dysfunction through induction of oxidative stress, and that attenuation of the RAAS provides vascular benefit through improvement in vascular repair via PCs.

Glucose metabolism

The specific mechanisms responsible for ACE-inhibitor–related improvement in insulin resistance (dysglycemia) and reduced diabetes development are incompletely understood. Hyperglycemia decreases bioavailability of NO and PGI2 while increasing synthesis of vasoconstrictor prostanoids and endothelin. ACE inhibition acts to counter many of these effects in hyperglycemia to improve vascular function. Clearly improved vascular function, mostly at the microvascular level, is important, involving skeletal muscle, the kidney, and probably even the pancreas. Also, maintenance of intracellular potassium, particularly the ATP-sensitive potassium channel, is important, but is unlikely to be the only mechanism.

Atrial fibrillation

Potential mechanisms for ACE-inhibition and ARB prevention of AF include: (i) direct modulation of ionic channels; (ii) hemodynamic improvement; (iii) reduction of atrial stretching; and (iv) suppression of atrial fibrosis. Similarly, improved atrial endocardial function has been proposed by the mechanisms outlined above for endothelial function.

Atherosclerosis

Atherosclerosis and aortic aneurysms have in common ACE-rich macrophage infiltration into the vessel wall. When this process results in weakening and leads to progressive dilation, aneurysm formation occurs. Proteolysis, inflammation, and oxidant formation are important mechanisms in which local ACE and ACE-generated regulators are likely involved.32-36

Summary

The RAAS plays an important role in the development of CV disease and atherothrombotic complications. Modulation of RAAS with ACE inhibition and possibly ARBs alters pathological processes contributing to atherosclerosis and atherothrombosis. Evidence suggests that both the ACE-inhibitor and ARB classes of RAAS modulators have beneficial properties beyond those related to BP reduction, which may reduce the development of atherosclerosis and its complications.

REFERENCES

13. Verdecchia P, Angeli F, Reboldi G. New-onset diabetes, anti-
Are there differences between the RAAS inhibitors?

by B. I. Lévy, France

The renin-angiotensin-aldosterone system (RAAS) plays a major role in the systemic regulation of cardiovascular and renal homeostasis. Furthermore, there is now increasing evidence that RAAS may affect the normal and pathological vascular system through its action on fibrosis, angiogenesis, cellular proliferation, apoptosis, and inflammation. Recently, a significant role has been shown for endothelial cell apoptosis resulting from oxidative stress, the latter possibly related to the abnormal activation of membrane-bound reduced nicotinamide dinucleotide phosphate (NADPH) oxidase by angiotensin II (Ang II). Ang II–derived O2 is an important signaling component of the classic effects of Ang II. There has been substantial progress in the understanding of the relationship between Ang II, activation of the AT1 subtype receptor of angiotensin II (AT1), and NADPH oxidase production of O2.

It is now possible to block the RAAS at several levels, resulting in different biological and therapeutic effects. Three classes of drugs inhibiting the RAAS are currently available for the treatment of hypertension. This review discusses: (i) recent insights into the biology of the RAAS; (ii) the main therapeutic classes of RAAS inhibitors, as well as their biological and clinical effects; and (iii) the differences in clinical results obtained with these RAAS inhibitors.

The renin-angiotensin-aldosterone system

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The renin-angiotensin-aldosterone system

The renin-angiotensin aldosterone system (RAAS) hormonal cascade starts with the synthesis of renin by the juxtaglomerular cells that line the afferent arteriole of the renal glomerulus (Figure 1). Renin is synthesized as a preprohormone, and mature (active) renin is formed by a proteolytic process. Ma-

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**Selected abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
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<td>Ang II</td>
<td>angiotensin II</td>
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<td>ARB</td>
<td>angiotensin receptor blocker</td>
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<tr>
<td>AT1</td>
<td>angiotensin II type 1, 2, etc, receptors</td>
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<tr>
<td>AT2</td>
<td>angiotensin II type 1, 2, etc, receptors</td>
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<tr>
<td>CHF</td>
<td>congestive heart failure</td>
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<td>MI</td>
<td>myocardial infarction</td>
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<td>NO</td>
<td>nitric oxide</td>
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<td>RAAS</td>
<td>renin-angiotensin-aldosterone system</td>
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Figure 1. The renin-angiotensin-aldosterone system (RAAS) hormonal cascade.

Abbreviations: ACE, angiotensin-converting enzyme; Ang, angiotensin; AT1 R, AT2 R, etc., angiotensin II type 1, 2, etc., receptor; MAS, MAS oncogene; NEP, neutral endopeptidase; PEP, prolyl-endopeptidase; iPA, tissue plasminogen activator.

Are there differences between the RAAS inhibitors? – Lévy
cicular and cardiac hypertrophy, inflammatory responses, and oxidative stress angiogenesis, as well as being antiapoptotic.10 The AT2 receptor is believed to induce essentially opposite effects, including vasodilation and antiproliferation and antihypertrophic effects,11 and to play a significant role in blood pressure (BP) regulation. There is evidence, however, that signaling via the AT2 receptor induces proangiogenic effects in the retina and vessels12 and antian- giogenic effects in the skeletal muscle.13 The MAS oncogene is another RAAS receptor, which binds the Ang-(1-7) peptide.14 Ang-(1-7) may be generated directly from Ang II by the enzymatic activity of ACE2 (an exopeptidase that catalyses the conversion of angiotensin I to the nonapeptide angiotensin[1-9]), or from Ang I, via Ang-(1-9), a pathway that involves both ACE2 and ACE.15 ACE2 is present in many tissues with high concentrations in the heart, kidney, and gastrointestinal tract. Ang-(1-7) appears to have an inhibitory influence on many of the events induced by Ang II. Ang-(1-7) has depressor, vasodilator, apoptotic, and antiproliferative actions.16 Ang-(1-7) is suggested to inhibit angiogenesis, although further investigations are needed to confirm these effects in a wider range of patho-physiological conditions. In contrast, Ang-(1-7) may mimic some actions of Ang II such as the release of prostanoids, and also increase proliferation of some cells, such as epidermal stem cells after injury17 and hematopoietic progenitors in the bone marrow of myelosuppressed mice.18 The variety of physiological responses to the RAAS reflects that of the peptides and receptors and the different signaling pathways they induce.

It is generally thought that the physiologic role of tissue RAAS is complementary to the classic circulating RAAS and serves as a mechanism for the longer-term maintenance of balance or homeostasis at the tissue level between opposing effects mediated by this system (eg, growth promotion and inhibition in the heart and vasculature). Pathophysiological processes might hypothetically occur when components of the RAAS are overexpressed or inhibited, thus disturbing the intricate balance of this regulatory system. Ang II, via the AT1 receptor, also stimulates the production of aldosterone by the zona glomerulosa of the adrenal cortex. Aldosterone is a major regulator of sodium and potassium balance and thus plays a major role in regulating extracellular volume. It enhances the reabsorption of sodium and water in the distal tubules and collecting ducts and thus promotes potassium excretion. Ang II and the extracellular potassium levels are the major regulators of aldosterone.

**Inhibitors of the RAAS**

**Angiotensin-converting enzyme inhibitors** Early studies performed in the 1960s showed that peptides from the venom of a Brazilian viper inhibited kinase II, an enzyme that facilitates degradation of bradykinin, and which was later shown to be identical to ACE.19

The first of the orally active ACE inhibitors, captopril, included a sulphydryl-containing amino acid to serve as ligand for the zinc moiety. Numerous side effects of captopril, such as proteinuria, skin rashes, and altered taste, were attributed to the sulphydryl group, subsequent work led to the development of ACE inhibitors that replaced this group with a carbonyl group (eg, lisinopril, benazepril, quinapril, ramipril, perindopril, cilazapril, trandolapril) or phosphoryl group (fosinopril).20 The presence of the carbonyl group conferred greater lipophilicity, which actually improved binding to ACE as well as tissue penetration.21 ACE inhibitors competitively block the action of ACE and thus the conversion of Ang I to Ang II, thereby reducing circu- lating and local levels of Ang II. ACE inhibitors also decrease aldosterone secretion and sympathetic nerve activity. Short-term ACE-inhibitor therapy is associated with a decrease in Ang II and aldosterone and an increase in renin release and Ang I. There is evidence, however, that over the long term ACE inhibition may be associated with a return of Ang II and aldosterone to baseline levels (“ACE escape”)—perhaps, it is proposed, through activation of the so-called alternate pathways (Figure 1).22,23 Because ACE inhibitors all are competitive inhibitors of the enzyme, it is possible that increased levels of Ang I (provoked by the compensatory increase in plasma renin activity due to loss of negative feedback in-hibition) can tend to partially overcome the blockade.24 In general, short-term pharmacodynamic responses to decreases in Ang II through inhibition of ACE include dose-dependent reductions in cardiac preload and afterload, with lowering of systolic and diastolic blood pressure, but, in normotensive and hypertensive patients without cardiac dysfunc-tion, little or no change in cardiac output or capillary wedge pressure. Interestingly, unlike direct-acting arterial vasodilators, ACE inhibitor-induced reductions in total peripheral vascular resistance occur without significant change in heart rate. ACE inhibitors also decrease renal vascular resistance, increase renal blood flow, and promote sodium and water excretion. ACE inhibitors may also prevent the progression of microalbuminuria to proteinuria, reduce proteinuria in patients with established glomerular disease, and prevent or delay the pro-gression of renal insufficiency to end-stage renal disease. Efficacy in long-term trials has been demonstrated particularly in patients with nondiabetic

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**Figure 2. Metabolization of bradykinin to inactive protein by angiotensin-converting enzyme.**

**Abbreviations:** ACE, angiotensin-converting enzyme; BK1, 2 R, bradykinin 1 and 2 receptors.
nephropathies or in patients with insulin-dependent (type 1) diabetes. Because ACE is identical to kininase II, ACE inhibitors may also lead to elevation of bradykinin levels in some tissues; this effect is potentially associated with increased bradykinin-dependent release of NO and vasodilatory prostaglandins, including prostacyclin and prostaglandin E2. These actions may potentially contribute to the vasodilatory, antithrombotic, antiatherogenic, and antiproliferative effects of ACE inhibitors, although the importance of this pathway is debated. In 40% to 60% of patients with mild-to-moderate hypertension, ACE-inhibitor monotherapy produces a satisfactory reduction in blood pressure. In this population, ACE inhibitors contribute to the reversal of cardiac hypertrophy, and do so with significantly greater efficacy than β-blockers. In patients with congestive heart failure (CHF), ACE inhibitors relieve pulmonary congestion by a balanced reduction in cardiac preload and afterload. They appear to induce venous vasodilation, which increases peripheral venous capacitance and reduces right atrial pressure, pulmonary arterial pressure, capillary wedge pressure, and left ventricular filling volumes and pressures. ACE inhibitors also induce arterial vasodilation, which reduces peripheral vascular resistance (afterload) and increases cardiac output in this patient population. ACE inhibitors have also been shown to improve endothelial dysfunction in patients with heart failure, as well as in patients with coronary artery disease and type 2 diabetes. In early landmark trials in patients with CHF (such as CONSENSUS, SOLVD, and V-HeFT-II [Cooperative North Scandinavian ENalapril SUrvival Study; Studies Of Left Ventricular Dysfunction; Vasodilator-Heart Failure Trial III]), ACE inhibitors were shown not only to markedly improve symptoms and functional status, but also to dramatically reduce mortality. In subsequent studies in patients who have suffered a myocardial infarction (MI), such as SAVE, AIRE, and TRACE (Survival And left Ventricular Enlargement; Acute Infarction Ramipril Efficacy; TRAnslapril Cardiac Evaluation), ACE-inhibitor therapy has been shown to prevent or retard ventricular remodeling and progression to CHF, and thereby to reduce overall mortality and prolong survival. Furthermore, the results of HOPE (Heart Outcomes Prevention Evaluation) and other smaller studies have reported broad cardiovascular benefits of ACE-inhibitor therapy in “high-risk” patients (including both hypertensive and normotensive individuals), and it is possible that these benefits occur in part independently of their blood pressure-lowering effect. Several large-scale studies of various ACE inhibitors have shown a reduction in incidence of new-onset diabetes in association with ACE-inhibitor therapy. For example, this has been shown with captopril in hypertensive patients (CAPPP [Captopril Prevention Project]), with ramipril in patients at high risk for cardiovascular disease (HOPE), with atenolol in patients with left ventricular dysfunction (SOLVD), and with trandolapril in patients with stable coronary disease (PEACE, [Prevention of Events with Angiotensin-Converting Enzyme Inhibition]). The mechanism of this benefit has not been determined. ACE-inhibitor therapy is generally well tolerated by most patients, but is nonetheless associated with some significant side effects. Most frequent among these is a dry cough, which has been attributed to accumulation of substance P (which is normally degraded by kininase II). More serious side effects common to all ACE inhibitors include angioedema (which is potentiated by decreased catabolism of kinins) and fetal abnormalities and mortality.

**Angiotensin receptor blockers**

As mentioned earlier, the AT1 receptor mediates most of the known actions of Ang II that contribute to hypertension and volume dysregulation (vascular smooth muscle contraction, aldosterone secretion, renal sodium reabsorption, and pressor and tachycardiac responses) as well as to cardiovascular damage (cellular hypertrophy or proliferation, prothrombotic and proinflammatory effects, and superoxide formation). Thus, specific Ang II antagonism action at the AT1 receptor became a logical therapeutic target, one considered likely to be more specific than ACE inhibition. Development of orally active, nonpeptide, selective AT1 receptor blockers began in the 1990s with the synthesis of losartan. Since that time, several ARBs have been synthesized, including valsartan, irbesartan, candesartan, eprosartan, telmisartan, and olmesartan. In contrast to the ACE inhibitors, ARB therapy actually results in an increase in Ang II levels. As with ACE inhibition, AT1 receptor blockade inhibits the negative feedback loop, leading to increased renin secretion and thus increased Ang I synthesis. In the case of ARBs, the increase in Ang I leads to an increase in Ang II, which is able to bind freely to AT2 or other receptor subtypes. Earlier preclinical studies have suggested that, beyond AT1 receptor blockade, activation of the AT2 receptor may mediate additional beneficial actions on the vasculature, heart, and kidneys, in part via a bradykinin/NO/cGMP pathway, an effect that would further distinguish ARBs from ACE inhibitors. But as attractive as this hypothesis is, there are no clinical data to indicate that this pathway is a major mechanism of ARB action in humans. Furthermore, accumulating evidence now suggests that long-term AT2 stimulation may also exert a hypertrophic and antiangiogenic influence on cardiovascular tissues. Thus, the long-term consequences of ARB therapy may be less beneficial than previously supposed and could even be harmful in some circumstances. The potential consequences of such effects, if found to be clinically important, could include cardiac hypertrophy, vascular fibrosis, and decreased neovascularization in hypoxic tissues such as the myocardium. Like ACE inhibitors, ARBs reduce blood pressure by decreasing systemic vascular resistance; they do not affect heart rate and have minimal effect on cardiac output in the nonfailing heart. Reduced systemic vascular resistance results from a combination of inhibition of Ang II-mediated vasoconstriction, reduced sympathetic nervous system activity, and reduced extracellular volume (ie, by direct inhibition of proximal sodium reabsorption and by inhibition of Ang II synthesis).
of aldosterone release). ARB monotherapy produces a satisfactory reduction in blood pressure in 40% to 60% of patients with mild-to-moderate hypertension.\textsuperscript{29} ARB therapy has also been shown to reduce inflammation markers in patients with atherosclerosis,\textsuperscript{40,41} suggesting an anti-inflammatory effect, and to reverse endothelial dysfunction in patients with hypertension, indicating the possibility of significant antiatherogenic effects.

In patients with hypertension and left ventricular hypertrophy, ARB-based therapy, compared with β-blocker (atenolol)–based therapy with identical blood pressure control, has been shown to significantly reduce the composite risk of cardiovascular death, stroke, and MI and to decrease the rate of new-onset diabetes (LIFE [Losartan Intervention For Endpoint reduction in hypertension study]).\textsuperscript{42,43} Similarly, ARB-based therapeutic regimens, compared with conventional therapy, have been shown to reduce the progression of nephropathy in patients with diabetic nephropathy (IDNT, RENAAL [Irbesartan in Diabetic Nephropathy Trial; Reduction of Endpoints in Noninsulin-dependent diabetes mellitus with Angiotensin II Antagonist Losartan]).\textsuperscript{44,45} In patients with chronic heart failure, addition of an ARB, compared with placebo, to conventional treatment has been shown to significantly reduce the risk of cardiovascular mortality and hospitalization (CHARM, Val-HeFT [Candesartan in Heart failure Assessment in Reduction of Mortality and Morbidity with Valsartan–Heart Failure Trial]).\textsuperscript{46,47} In high-risk post-MI patients, ARB therapy has been shown to reduce the risks of all-cause mortality, recurrent MI, sudden cardiac death, revascularization, coronary artery bypass grafting, or all-cause hospital admission to a degree similar to that of ACE-inhibitor therapy (OPTIMAAL [Optimal Trial In Myocardial infarction with Angiotensin II Antagonist Losartan]).\textsuperscript{48}

Most adverse events reported with ARB therapy are related to expected potential effects of RAAS blockade—for example, hypotension, hyperkalemia, and worsening renal function—and are similar to those encountered in patients taking ACE inhibitors.

**Direct renin inhibitors**

Because renin is the initial and rate-limiting step in the RAAS cascade, it has long been considered the logical therapeutic target for blocking the system. Preclinical studies with antirenin antibodies and early synthetic renin inhibitors established the potential utility of RAAS inhibition. However, pharmacologic activity of the early renin inhibitors could only be achieved with intravenous infusion, and the development of an orally active direct renin inhibitor was fraught with numerous difficulties arising from issues of potency, low bioavailability, duration of action, and costs of synthesis. As a result, further development of these agents was halted in the mid-1990s. Concurrently, other strategies for inhibiting the RAAS progressed to clinical use. At present, the first nonpeptide orally active renin inhibitor has been developed and approved, with indications for the treatment of hypertension and cardiovascular and renal disorders. Renin inhibition induces a decrease in plasma renin activity, Ang I, Ang II, and aldosterone, alongside that in blood pressure.\textsuperscript{49} However blood-pressure-lowering activity has been found to be small. Because normal feedback inhibition is interrupted by angiotensin II, renin inhibition consistently elicits a rise in circulating active renin.

This escape process, which also occurs, at a lower degree, during treatment with ACE inhibitors and ARBs, explains why these three drug classes behave as incomplete blockers of the renin system. Whether renin inhibitors also improve insulin sensitivity, as ACE inhibitors and ARBs do, needs to be clarified. Sealey and Laragh recently published a review of 6 clinical trials of aliskiren involving more than 5000 patients.\textsuperscript{50} Because many antihypertensive drugs are already available in extended release form or in combination with other agents, these authors asked if there was anything unique about aliskiren that could justify its use. Although aliskiren suppresses plasma renin activity, it causes a much greater reactive rise in plasma renin concentration than any other antihypertensive class tested. Because aliskiren only blocks 90% to 95% of plasma renin, the pressor consequences of its greater reactive increase in plasma renin concentration appear to offset its net ability to lower blood pressure, especially at higher doses. We believe that this new therapeutic class will find its right place in combination with one or several other antihypertensive drugs. We are still lacking clinical data on these combinations; thus, we will not discuss here the use of renin inhibitors in the treatment of hypertension, but rather focus on the comparison between ACE inhibitors and ARBs.

**Differences in clinical results obtained with the different therapeutic classes**

Over the past 15 years, accumulating data have confirmed that ARBs indeed possess many of the same clinical benefits as ACE inhibitors, including blood pressure lowering, improvement in CHF symptoms, prevention of diabetic renal disease, reduction in stroke rates, and likely prevention of new-onset diabetes mellitus and atrial fibrillation. However, until 2008, we lacked clear, final, and definitive information to compare the clinical results obtained following treatment with ACE inhibitors and ARNs. However, despite these obvious similarities, it is now clear that ARBs and ACE inhibitors have significant differences, and experimental findings suggest that ACE inhibitors may provide better long-term benefits\textsuperscript{51,52} for at least two reasons:

- The increased stimulation of AT\(_2\) receptors that occurs in the presence of AT\(_1\) receptor blockade is believed to contribute to the benefits of ARBs, not just through control of BP, but also through antihypertrophic and antifibrotic effects. However, it is now clear that the effects of AT\(_2\) receptor stimulation are context-dependent. There are vessel type-dependent differences in the vascular responses to AT\(_2\) stimulation, and it is therefore difficult to pre-
dict the effects in human beings of long-term over-
stimulation of AT2 receptors by ARBs. This informa-
tion needs to be obtained by clinical trials in patients.

♦ Another factor, the effect on bradykinin, is likely to
favor ACE inhibition over ARB therapy. ACE inhi-
bition prevents the breakdown of bradykinin, a
peptide that has vasodilator and other favorable ef-
facts. Interestingly, a recent study using knockout
mice lacking the B2 receptor for bradykinin sug-
gests that these receptors play an essential role in
the host defense response to ischemic injury.24

Since 2006, several meta-analyses and one major
clinical trial directly comparing the effects of ARBs
and ACE inhibitors have been published, which pro-
vide more arguments in favor of ACE inhibitors:

♦ The Blood Pressure Lowering Treatment Trialist’s
Collaboration (BPLTT) published a meta-analysis of
26 large-scale trials totaling more than 146 000 in-
dividuals, comparing an ACE inhibitor or an ARB
with placebo or another drug class.25 In this meta-
analysis, treatment-relative risks for major cause-
specific outcomes (stroke, major coronary heart
diseases events and heart failure) were regressed
against follow-up blood pressure differences. The
findings showed comparable blood pressure–de-
pendent reductions in risk with ACE inhibitors and
ARBs. They also showed that ACE inhibitors elic-
et a blood pressure–independent reduction in rel-
ative risk of coronary disease events of 9%, while no
such effect was detected with the ARBs. This differ-
ence between ACE inhibitors and ARBs was statist-
ically significant (P=0.002). For both stroke and
heart failure, there was no evidence of any blood
pressure–independent effects with either the ACE
inhibitors or the ARBs. This publication provided
the first statistical evidence of an effect “beyond
blood pressure reduction” for ACE inhibitors and
not for ARBs.

♦ Actually, despite their clear theoretical and in-
tellectual interest, meta-analyses cannot provide
definitive evidence; some systematic reviews of ma-
jor ARB trials have concluded that ARBs do not pre-
vent MI or prolong survival, even when compared
with placebo, whereas others conclude that their
effects are “either neutral or may actually increase
the rate of MI despite similar levels of blood pressure
reduction.”26 The discordant results of meta-anal-
yses reflect their high degree of dependence on the
trials that have been included or excluded in them.
In an extensive review of the literature, Strauss and
Hall26 defended that ARBs could increase the risk of
MI. A careful analysis of the available major trials
dicates that whereas ACE inhibitors produce a
marked and consistent reduction in myocardial MI
and cardiovascular death, the same cannot be said of
ARBs. The major ARB trials in high-risk patients
have so far demonstrated an almost complete lack
of reduction in MI and mortality despite significant
reduction in blood pressure. Nine of 11 key clinical
ARB trials have even reported and excess of MI that
achieved statistical significance in two cases: VALUE
(ValSartan Antihypertensive Long-term Use Evalu-
at) and CHARM-Alternative. The marked ben-
efits of ACE inhibitors in terms of MI and mortality
in patients with heart failure seem disproportion-
ate to the drop in systolic pressure. The difference
in favor of ACE inhibitors has been attributed, by
Strauss and Hall, to overstimulation of the AT2, and/
or the AT4 receptors occurring during treatments
with ARBs. This latter receptor (AT4) could be re-
 sponsible for higher release of plasminogen activa-
tor inhibitor (PAI-1), a major inhibitor of fibrinol-
ysis. Finally, as already discussed above, the effect
on bradykinin is likely to favor ACE inhibitor over
ARB therapy.27

♦ Last year, Patel and coworkers28 published the
findings of a large clinical trial, in which a total of
11 140 patients with type 2 diabetes were random-
ized to treatment with a fixed combination of perin-
dopril and indapamide or matching placebo, in ad-
dition to current therapy. The primary end points
were composites of major macrovascular and mi-
crovascular events, defined as death from cardio-
vascular disease, nonfatal stroke, or nonfatal MI,
and new or worsening renal or diabetic eye disease.
After a mean of 4.3 years of follow-up, compared
with patients assigned placebo, those assigned ac-
tive therapy had a mean reduction of 5.6 mm Hg in
systolic blood pressure and 2.2 mm Hg in diastolic
blood pressure. The relative risk of major macro-
vascular or microvascular event was reduced by
9% (P=0.04). The relative risk of death from car-
diovascular disease was reduced by 18% (P=0.03),
and death from any cause was reduced by 14% (P=0.03).
There was no evidence that the effects of the
study treatment differed by initial blood pres-
sure level or concomitant use of other treatments
at baseline. The authors concluded that: “Routine
administration of a fixed combination of perind-
opril and indapamide to patients with type 2 diabetes
was well tolerated and reduced the risks of major
vascular events, including death.” This study under-
lines the importance of treating diabetic patients
whatever the level of blood pressure.

♦ Finally, as discussed above, the only definitive
clinical comparison between ACE inhibitors and
ARBs can be provided only by a large trial designed
to compare these two therapeutic classes. The re-
 sults of ONTARGET (Ongoing Telmisartan Alone
and in Combination with Ramipril Global End-
point Trial) have been recently published by Yusuf
et al.29 This large study (more than 25 000 patients)
confirmed beyond doubt that ARBs are no better
than ACE inhibitors at reducing fatal and nonfatal
cardiovascular events in patients who had vascular
disease or high-risk diabetes without failure. In this
trial, the authors showed that telmisartan (80 mg
once daily) preserved 94% of the benefit of 10 mg
of ramipril daily, as reported in the HOPE trial; in
a previous study with an almost identical design
(VAlSartan In Acute myocardial iNFarc-
tion), valsartan (160 mg twice daily) preserved
100% of the benefit of 50 mg of captopril three
times daily in patients with acute MI. There are of
course many methodological difficulties associated
with designing and interpreting large trials aim-
ing to evidence noninferiority of two treatments.
I conclude by citing the title used by John McMur-
ray30 in his editorial on the ONTARGET trial: “ACE
inhibitors in cardiovascular disease—unbeatable?”

Are there differences between the RAAS inhibitors? – Lány

ACE INHIBITION AS A CORNERSTONE OF HYPERTENSION TREATMENT
Conclusion

At present, there is strong evidence from experimental and clinical findings to suggest that:

- Most antihypertensive drugs improve cardiovascular risk in relation with the degree of reduction in blood pressure they achieve. However, inhibition of the RAAS has additional beneficial effects beyond the lowering of blood pressure.
- ACE inhibitors and ARBs have different biological
cal and therapeutic effects in hypertensive patients, but also in diabetic (hypertensive or normotensive) patients and in patients with heart failure. The available evidence suggests that ACE inhibitors could provide better results than ARBs.
- Finally, following John McMurray, we might propose that “Because ARBs are more costly than ACE inhibitors, their primary value is an alternative for patients who cannot tolerate ACE inhibitors because of cough.”

REFERENCES
10. Tamarat S, Silvestre JS, Duriez M, Levy BI. Angiotensin II ana
converting enzyme-related carboxypeptidase (ACE2) converts an-
20. Wong J, Patel RA, Kowey PB. The clinical use of angiotensin
22. Pitt B. “Escape” of aldosterone production in patients with left ventricular dysfunction treated with an angiotensin convert-

23. Biollaz J, Brunner HR, Gavras I, Waeber B, Gavras H. Anti-
hypertensive therapy with MK 421: angiotensin II-renin relations-
24. Atlas SA, Case DB, Yu ZY, Langh JL. Hormonal and metabolic effects of angiotensin converting enzyme inhibitors: possible dif-
26. Lewis EJ, Hunsicker LG, Bain RP, Rohe RD; Collaborative Study Group. The effect of angiotensin-converting-enzyme en-
30. SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with re-
31. SOLVD Investigators. Effect of enalapril on survival in pa-
tients with reduced left ventricular ejection fractions and con-
32. Group Italiano per lo Studio della Sopravvenza nell’infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-month mortality and ventric-
33. ISIS-4 (Fourth International Study of Infarct Survival) Col-
laborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrates, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocar-
35. Acute Infarction Ramiplir Effectiveness (AIRE) Study Investiga-
36. EUROPEAN trial On reduction of cardiac events with Perindo-
pril in stable coronary artery Disease [EUROPA] Investigators. Ef-
tensin converting-enzyme inhibition compared with conventional
al therapy on cardiovascular morbidity and mortality in hyper-
39. Vermes E, Ducharme A, Bourassa MG, Lessard M, White M, Tardif JC. Enalapril reduces the incidence of diabetes in patients with chronic heart failure: insight from the Studies Of Left Ven-
40. PEACE Trial Investigators. Angiotensin-converting-enzyme

Are there differences between the RAAS inhibitors? – Lévy
LES INHIBITEURS DU SYSTÈME RÉNINE-ANGIOTENSINE-ALDOSTÉRONE DIFFÉRENT-ILS ENTRE EUX ?

Le rôle du système tissulaire rénine-angiotensine-aldostérone (SRAA) est complexe car la rénine est synthétisée non seulement par et dans le rein mais aussi dans d’autres tissus comme le cerveau, les surrénales, les ovaires, le tissu adipeux vasculaire, le cœur et les vaisseaux sanguins. De la même façon, si le foie est la première source d’angiotensinogène systémique circulant, l’expression de l’ARNm de l’angiotensinogène a été détectée également dans le Rein, le cerveau, le cœur, les vaisseaux sanguins, les surrénales, les ovaires, le placenta et le tissu adipeux. Deux récepteurs principaux de l’angiotensine II (Ang II) ont été identifiés : le récepteur de type 1 de l’Ang II (AT1) active les voies de la croissance et assure la médiation des effets principaux de l’Ang II tels la vasoconstriction, l’augmentation de la contractilité cardiaque, la réabsorption rénale du sodium, la prolifération cellulaire, l’hypertrophie cardiaque et vasculaire, la réponse inflammatoire, le stress oxydatif, l’angiogène ; le récepteur AT2 a également des effets anti-apoptotiques ; le récepteur de type AT2 de l’Ang II a des effets vasomoteurs opposés (vasodilatation) et des possibles effets anticroissance et anti-hypertrophique. Cependant, l’activation des récepteurs AT2 est pro-angiogène au niveau de la rénine et entraîne une prolifération cardio-vasculaire. Les IEC (inhibiteurs de l’enzyme de conversion de l’angiotensine), les antagonistes des récepteurs de l’angiotensine (ARA) et les inhibiteurs directs de la rénine peuvent bloquer le SRAA à différents niveaux, avec de différences sur les plans clinique et expérimental. La plupart des anti-hypertenseurs améliorent le risque cardio-vasculaire proportionnellement au degré de réduction de la pression artérielle. Cependant, l’inhibition du SRAA se traduit par effets bénéfiques supplémentaires indépendants de la baisse de la pression artérielle. Les IEC et les ARA ont des effets thérapeutiques et biologiques différents chez les hypertendus, les diabétiques (hypertendus ou non) et les insuffisants cardiaques, les IEC s’étant montrés plus efficaces que les ARA. En pratique clinique, les recommandations actuelles préconisent le recours en première intention aux IEC pour bloquer le SRAA, les ARA restant une alternative pour les patients qui ne tolèrent pas les IEC.
Do ACE inhibitors differ, and in which way?

by R. Ferrari, Italy

The cardiovascular continuum is a sequence of related pathological predispositions and events running inexorably (if untreated) from risk factors to end-stage heart disease. Although its intimate mechanism is unknown and presumably multifactorial, key starting points include endothelial dysfunction and atherosclerosis, making inhibition of the renin-angiotensin-aldosterone system (RAAS) the prime treatment target. As a class, angiotensin-converting enzyme (ACE) inhibitors have an established preventive and therapeutic role across the continuum, enjoying the highest levels of evidence for efficacy and tolerability. But ACE-inhibitor profiles differ in critical pharmacological and clinical respects. Perindopril and ramipril markedly reduce cardiovascular risk in stable coronary artery disease (CAD), unlike quinapril or trandolapril. Major differences exist in tissue ACE affinity, bradykinin selectivity and potentiation, and effects on endothelial apoptosis. Perindopril (active form: perindoprilat) has a relative tissue affinity much greater than that of other ACE inhibitors, correlating with its antiatherosclerotic activity. Its effect on bradykinin potentiation is particularly marked: the bradykinin/angiotensin I selectivity ratio is much greater in vitro than with other ACE inhibitors, accounting for its greater efficacy in reducing cardiovascular events. In vivo, perindopril increases endothelial nitric oxide synthase expression and activity more than trandolapril, quinapril, ramipril, and enalapril at equihypotensive doses. Perindopril, and to a lesser degree ramipril, are the only ACE inhibitors to significantly reduce apoptotic rate. The burden of the experimental and clinical evidence supports that an ACE inhibitor such as perindopril or ramipril is a superior therapeutic option, in particular in low-dose combination therapies, than certain other ACE inhibitors in stable CAD.

Benefits of ACE inhibition throughout the cardiovascular continuum

ACE inhibitors are recommended as first-line therapy in the management of hypertension in patients aged <55 years and in patients with compelling indications such as HF, left ventricular (LV) dysfunction, MI, diabetes, or recurrent stroke.4 Patients with prolonged and uncontrolled hypertension have an increased risk of chronic renal disease due to the development of nephrosclerosis.
These structural changes within the kidney cause further increases in blood pressure (BP), forming a vicious cycle, and accelerating the pathophysiological continuum. The first sign of renal impairment in hypertensive patients is a reduced glomerular filtration rate. If poorly managed, this stage can rapidly progress to increasing levels of albuminuria and end-stage renal failure. Aggressive and sustained BP lowering in itself provides renal protection, and target BP goals are <130/80 mm Hg in hypertensive patients with renal disease. In type 2 diabetics who are either normotensive or well controlled with other antihypertensive agents, ACE inhibition with perindopril significantly reduces the progression of renal disease compared with placebo or a calcium channel blocker. This shows a direct renoprotective action of ACE inhibition, which is independent of its antihypertensive efficacy.

Type 2 diabetes mellitus is a major risk factor for the onset of cardiovascular disease. Moreover, over 70% of diabetics also suffer from hypertension, and the primary cause of death in diabetics is cardiovascular disease. For this reason, patients with both hypertension and diabetes need to be aggressively managed with BP targets <130/80 mm Hg. In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), 27% of the study population (n=5137) had diabetes at baseline, but no history of cardiovascular disease. In this subpopulation, amlodipine/perindopril reduced total cardiovascular events and procedures by 23% compared with β-blocker/diuretic (P<0.05). More recently, the Action in Diabetes and Vascular disease: PreterAx and Diamicron-N-MR Controlled Evaluation (ADVANCE) study evaluated the clinical benefits of background BP lowering with a fixed combination of perindopril and indapamide on top of standard management in a cohort of 11 140 diabetic patients. Perindopril/indapamide fixed combination reduced the incidence of the composite primary end point of macrovascular (nonfatal stroke, nonfatal MI, and cardiovascular death) and microvascular (new or worsening nephropathy and retinopathy) events by 9% versus placebo (P<0.05). Similar results were not reported from the International VErapamil SR Trandolapril study (INVEST), which tested a combination of trandolapril and verapamil in a similar population.


Although BP lowering in hypertensive patients is an effective primary prevention, the risks of stroke and major cardiovascular events are greater in patients with established cerebrovascular disease and there have been few clinical studies investigating the effects of BP lowering in this high-risk group. Perindopril is a useful treatment in this scenario as it maintains cerebral blood flow, even in normotensive patients. The Perindopril pRevention of Stroke Study (PROGRESS) was the first large-scale study to show that a perindopril-based regimen achieved a relative risk reduction (RRR) of stroke by 28%, major cardiovascular events by 27%, and nonfatal MI by 38%.

Coronary artery disease (CAD) is a consequence of endothelial dysfunction and atherosclerosis, i.e., the effects of the pathophysiological continuum on the cardiovascular continuum. The prevalence of CAD is higher in men than women, and rises sharply with age after the fourth decade. The Perindopril pR0tection aGainst REcurrent Stroke Study (PROGRESS) was the first proof of the efficacy of ACE inhibitors for the prophylaxis of cardiovascular events came from the
results of the Heart Outcomes Prevention Evaluation (HOPE) trial, which demonstrated that the ACE inhibitor ramipril significantly reduced the incidence of cardiovascular events in a wide range of high-risk patients, including those with CAD.15 The EUROpean trial on Reduction Of cardiac events with Perindopril among patients with stable coronary Artery disease (EUROPA)16 evaluated patients with a generally lower level of cardiovascular risk than in the HOPE study. Nevertheless, EUROPA corroborated and extended HOPE study findings: that is, in the EUROPA trial in >12 000 randomized patients, perindopril (added to standard background therapy with antiplatelet agents [92% of patients], β-blockers [62%], and/or lipid-lowering agents [58%]) significantly reduced relative risk of the composite primary end point of cardiovascular death, myocardial infarction (MI), or cardiac arrest by 20% versus placebo (P=0.0003).16

Before HOPE and EUROPA, another trial, the QUinapril Ischemic Event Trial (QUIET) tested the hypothesis that quinapril could be beneficial to patients subjected to elective angioplasty. Unfortunately, however, no benefits were shown (Figure 2).15-18 Subsequent to the HOPE and EUROPA trials, the findings of the Prevention of Events with Angiotensin-Converting Enzyme inhibition (PEACE) trial questioned the efficacy of ACE inhibition in certain types of patients with stable CAD.18 The PEACE trial examined the effects of trandolapril in patients aged >50 years with stable CAD and preserved LV function. After a median of 4.8 years, there was no difference in the incidence of the primary combined end point (death from cardiovascular causes, MI, and coronary revascularization) versus placebo. There has been much debate surrounding the differences in the results of EUROPA, HOPE, and PEACE.19 One hypothesis was that the negative result in PEACE was associated with the lower overall risk of the population. However, further analysis of EUROPA showed heterogeneous populations in terms of cardiovascular risk. Deckers et al investigated this point by classifying EUROPA patients according to baseline cardiovascular risk, ie, high (>3%), medium (1%-3%), or low (<1%) risk of reaching the primary end point at the end of the trial.20 Within each subgroup, perindopril treatment significantly reduced the risk of the primary end point by 17%, 32%, and 12%, respectively, compared with placebo. Importantly, the cardiovascular risk of the lowest tertile of EUROPA (n=3976) was lower than the average cardiovascular risk in the PEACE population.21 Moreover, the primary end point was also reduced by perindopril in EUROPA subgroups with preserved LV function (n=6878; RRR 16%, P=0.02)22 and with previous coronary revascularization (n=6709; RRR 17%, P<0.05).23 Notably, patients with previous coronary revascularization in HOPE had a similar 15% reduction in the primary end point, though this failed to reach statistical significance.24 Considering these results, we can be confident that the differences between the three studies are not linked to baseline risk of the populations.25 The other hypothesis is that ACE inhibitors are not equal with
The benefits of ACE inhibitors in the postinfarct setting are unequivocal.\textsuperscript{25,26} For instance, a meta-analysis of data from almost 100,000 patients with acute MI revealed that early ACE inhibition (ie, administered within 36 hours of MI) significantly reduced mortality during the first week and first month post infarct.\textsuperscript{22} Longer-term studies in post-MI patients with left ventricular (LV) dysfunction (EF <40%), such as the Acute Infarction Ramipril Efficacy (AIRE) trial,\textsuperscript{27} the TRAndolapril Cardiac Evaluation (TRACE),\textsuperscript{28} and the Survival And Ventricular Enlargement (SAVE) study,\textsuperscript{29} confirmed that these benefits are maintained over several years.

Nearly two thirds of EUROPA patients (n=7190) had a history of MI. In these patients, perindopril significantly reduced the primary end point versus placebo (RRR 22.4%, P<0.001).\textsuperscript{30} The main long-term complications following MI are further progression down the cardiovascular continuum starting with changes in ventricle size, shape, and function, a process referred to as cardiac remodeling, which can result in HF. Numerous studies have shown that ACE inhibition reduces morbidity and mortality in patients with residual LV dysfunction following MI through prevention of remodeling, and ACE inhibitors are therefore administered as prophylactic treatment 24 hours following MI.\textsuperscript{31} However up to 40% of MI patients admitted to hospital are elderly and have preserved LV function. Until recently, the benefits of ACE inhibitors for this patient subset were unclear. The Perindopril and Remodelling in Elderly with Acute Myocardial Infarction (PREAMI) trial has shown that LV remodeling occurs in elderly post-MI patients with preserved LV function and that these changes can be prevented by perindopril.\textsuperscript{26} Patients aged >65 years with recent MI and LV ejection fraction >40% (n=1252) were randomized to treatment with either perindopril or placebo on top of standard management. After 12 months, the composite primary end point of death, hospitalization for HF, and LV remodeling showed a RRR of 38% in favor of perindopril (P<0.001). The marked effects of perindopril on remodeling were the most beneficial component of the combined end point. Although HF represents one of the final stages of the cardiovascular continuum, successful management of patients here can still improve prognosis. ACE inhibitors are indicated in HF, and have beneficial effects on mortality, hospital admission rates, symptoms, and cardiac performance in patients with systolic HF.\textsuperscript{32}

**Mechanisms of action of ACE inhibition on the cardiovascular continuum**

One mechanism of the beneficial effects of ACE inhibition in the cardiovascular continuum is BP reduction, though this may not be the only one. For example, the degree of BP reduction was very similar in all trials on secondary prevention of CAD with quinapril, ramipril, perindopril, andtrandolapril, and, ironically, was slightly less in EUROPA and HOPE than in QUIET and PEACE, which do not show any benefit! Indeed, BP reduction alone could not be the sole explanation for the results of EUROPA, since the effect of perindopril was independent of BP at entry and was even recorded in patients in whom there was no reduction in BP upon perindopril treatment.\textsuperscript{33} Further evidence for the absence of an exclusive direct link between BP lowering and cardiac outcomes in CAD patients comes from ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine GITS), which tested the effect of a calcium channel blocker on clinical outcomes in the same type of population as in EUROPA.\textsuperscript{34} Nifedipine produced greater reductions in BP in ACTION (–6/3 mm Hg) than perindopril in EUROPA (–5/2 mm Hg),\textsuperscript{35} and yet it was not associated with a prognostic benefit. These observations imply that BP reduction is not the only explanation for the clinical efficacy of ACE inhibition in stable CAD. Another possible mechanism for the action of ACE inhibition on coronary atherosclerosis is a beneficial effect on the endothelium. In this context, we should note that the primary end point of the EUROPA trial (ie, cardiovascular death, nonfatal MI, or resuscitated cardiac arrest) is a composite of acute coronary syndromes (ACSs). The most common cause of ACS is progression and subsequent disruption of atherosclerotic plaque, which is directly related to damage of the endothelium. This implies that, if the endothelium was somehow protected by ACE inhibition, atherosclerosis would not progress or would progress to a lesser extent, and thus ACS would be prevented. The endothelium is the lining of the vessel, which is made up of a continuous layer of cells, rather like tiles on a floor. The average human endothelium weighs around 1.5 kg, with a surface area of more than 800 m²! It is capable of producing more than 250 biologically active substances that help regulate vascular structure and function. ACE is primarily a tissue enzyme (80% to 90%) and indeed it is present, among many other tissues, in the endothelium and smooth muscle. ACE promotes the formation of angiotensin II from angiotensin I in the RAAS, as well as the degradation of bradykinin, leading to the regulation of BP.\textsuperscript{36} Chronic overexpression of tissue ACE results in the overproduction of angiotensin II, a potent constrictor and growth factor, which among several other actions causes vasoconstriction, inflammation, vascular remodeling, thrombosis, apoptosis, and eventually plaque rupture. The concomitant decrease in bradykinin reduces the vasodilatory, antioxidative, proteolytic, and antiapoptotic effects of this kinin, ie, protective effects against angiotensin II. Experiments in genetically modified mice with no tissue ACE found that they developed hypertension as a result of inactivation of the RAAS.\textsuperscript{37} This shows just how vital tissue ACE is to BP regulation, even in the presence of plasma ACE. Another important, and often forgotten, feature of the endothelium is that, like almost every cell of the body it undergoes a life/death cycle, which includes the process of programmed cell suicide or apoptosis, matched by a consequent regeneration.
If there is an imbalance between the endothelial life/death cycle, and apoptosis outweighs regeneration, then there is a loss of continuity of the layer of the vessel, thus favoring the occurrence and progression of atherosclerosis. Furthermore, if the imbalance occurs at the level of endothelium already covering an existing atherosclerotic plaque, then thrombus formation is likely to occur, leading to an ACS.

Tissue ACE is known to be upregulated in ACS patients, which implies an alteration in the balance between angiotensin II and bradykinin. The increase in angiotensin II and reduction in bradykinin has a net negative effect on endothelial function, including the rate of its life/death cycle, which is another central feature of atherosclerosis. All this points toward the endothelium as another possible target, in addition to hypertension, for the prevention of ACS via ACE inhibition.

**ACE inhibition and endothelial function**

The beneficial effect of ACE inhibition on endothelial function can be assessed via biological end points of endothelial function, the most widely used being the activity and expression of endothelial nitric oxide synthase (eNOS) and the rate of endothelial apoptosis. These parameters, however, are difficult to measure in humans. Instead, in the clinical setting, endothelial function can be evaluated by measurement of levels of the procoagulant von Willebrand factor (vWF), which is a marker of endothelial damage, or by evaluation of endothelium-dependent dilations or of ischemia-induced flow-mediated dilatation (FMD). In order to assess the effect of perindopril on patients with stable CAD, an attempt was made to determine endothelial function via all of these routes in EUROPA.2,3,14,29

The PERTINENT substudy (PERindopril–Thrombosis, Inflammation, Endothelial dysfunction, and Neurohormonal activation Trial)2 assessed both clinical and biological markers of endothelial function. Blood samples were collected from EUROPA patients (n=1200) at baseline and after 1 year of perindopril or placebo for evaluation of vWF. Elevated vWF at baseline (ie, higher than the median level of 142%/unit) was significantly related to the occurrence of cardiovascular events over the 4 years of the EUROPA study (P<0.01).2 This constitutes direct evidence of endothelial damage in the EUROPA population, and of the serious implications of its presence. ACE inhibition with perindopril improved endothelial function after just 1 year in the PERTINENT population, as shown by the significant reduction in vWF versus placebo (P<0.001).2

Table I. Angiotensin-converting enzyme (ACE) inhibitors reduce tissue and circulating levels of angiotensin II, and increase levels of bradykinin correspondingly.

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<tr>
<th>Reduced angiotensin II leads to reduced</th>
<th>Increased bradykinin leads to increased</th>
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<tr>
<td>Endothelial dysfunction</td>
<td>Antioxidant activity</td>
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<td>Extracellular matrix degradation</td>
<td>Antiremodeling activity</td>
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<td>Monocyte adhesion</td>
<td>eNOS expression</td>
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<td>Oxygen free radical production</td>
<td>Monocyte antiadhesion</td>
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<td>PAI-1 and thrombogenesis</td>
<td>Preservation of endothelial function</td>
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<td>SMC growth, proliferation, and migration</td>
<td>t-PA and fibrinolysis</td>
</tr>
<tr>
<td>Vasoconstriction</td>
<td>Vasodilation</td>
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Abbreviations: eNOS, endothelial nitric oxide synthase; PAI-1, plasminogen activator inhibitor I; SMC, smooth muscle cell; t-PA, tissue plasminogen activator.


In smaller subgroup of PERTINENT, isolated human endothelial cells were incubated with serum from EUROPA patients with stable CAD (n=43 perindopril; n=44 placebo) and with serum from healthy age-matched controls (n=45).2 These experiments were designed to mimic the effects of circulating blood on endothelial function by measuring eNOS protein expression and activity and the rate of apoptosis. Incubation with serum from the stable CAD patients at baseline caused significantly greater downregulation of eNOS protein expression and activity, by 26% and 30%, respectively, than incubation with serum from the healthy controls (P<0.01).2 This is most likely directly related to the upregulation of ACE in stable CAD, which increases the degradation of bradykinin, leading to reduced eNOS expression and activity in stable CAD. When these patients are treated with perindopril for 1 year, which increases bradykinin levels, eNOS protein expression and activity were upregulated by 19% and 27% versus placebo (P<0.05).2 In addition, there was a significant difference between the rates of apoptosis upon incubation with serum from CAD patients at baseline versus serum from healthy controls (1.3±0.6% for controls versus 7.8±2.9% for CAD patients, P<0.01).2 In agreement with the increased rate of apoptosis, incubation with the serum of CAD patients also resulted in an increase in the Bax/Bcl-2 ratio (from 0.3±0.2 for controls versus 0.9±0.9 for CAD patients, P<0.01).3

In parallel to PERTINENT, another EUROPA sub-study, PERFECT (PERindopril–Function of the Endothelium in Coronary artery disease Trial),23 assessed change in ischemia-induced FMD over 3 years in patients (n=333) receiving perindopril or placebo. Perindopril produced a greater reduction in FMD (2.6% to 3.3% over 3 years) than placebo (2.8% to 3.0%), and the 6-monthly change in FMD was significant for perindopril (0.14%, P<0.05), but not for placebo (0.02%, P=0.74).23 Thus, it is possible to postulate a series of events, which could be summarized in simple terms as follows:

- CAD itself causes an upregulation of tissue ACE, particularly that in the vascular tissue.
- As a consequence, these autocrine changes alter the balance of angiotensin II/bradykinin with an increase in angiotensin II, which is proapoptotic, and a decrease in bradykinin, which is antiapoptotic.
- The cycle between endothelial life and death is altered, with an excess of apoptosis, leading to a loss of endothelial continuity.
- Which facilitates the origin and progression of the atherosclerotic process.

Effective ACE inhibition with perindopril slows down and/or prevents this series of events.
All ACE inhibitors are not the same

The properties and effects of ACE inhibitors are often attributed solely to a class effect. However, and particularly in CAD, all ACE inhibitors are not necessarily the same: several key pharmacological, efficacy, and tolerability differences exist between compounds in this class. Regarding basic pharmacology, some ACE inhibitors are prodrugs that require initial metabolism for activation, whereas others are not. Substantial differences exist between ACE inhibitors in terms of absorption, plasma levels, intermediary metabolism, half-lives, elimination characteristics, durations of action, and trough/peak plasma concentration relationships.

Major differences have been reported among ACE inhibitors in terms of affinity for tissue ACE, bradykinin selectivity and potentiation, and effects on endothelial cell apoptosis. For example, perindopril is a prodrug ester that is converted, in the liver and plasma, to perindoprilat, a potent, lipophilic ACE inhibitor with high tissue ACE affinity and a long duration of action. Perindoprilat has wide-ranging pharmacodynamic properties that include the following: vasodilatation; restriction of cardiovascular remodeling; antiatherogenic, anti-ischemic, and antithrombotic activity; enhanced endothelial function; and improved fibrinolytic balance (Table I).

Perindoprilat in vitro has demonstrated greater relative tissue affinity than other ACE inhibitors (Figure 3), and this affinity is correlated with antatherosclerotic activity. Moreover, perindoprilat has a particularly marked effect on bradykinin potentiation. In in vitro double-displacement binding experiments, various ACE inhibitors displayed different affinity for bradykinin than angiotensin I binding sites on ACE, thus suggesting that ACE inhibitors are, primarily, inhibitors of bradykinin degradation and, secondarily, inhibitors of angiotensin II formation. Importantly, in vitro, perindoprilat demonstrated a markedly greater bradykinin/angiotensin I selectivity ratio than other ACE inhibitors (Figure 4), and in a different experimental model, restoration of bradykinin levels has been reported at perindopril dosages much lower than those needed to decrease angiotensin II levels. These findings of bradykinin potentiation with perindoprilat are supported by clinical data from the PERTINENT trial; showing that marked bradykinin/angiotensin I binding-site selectivity may, to some extent, explain the substantial efficacy of perindopril in reducing cardiovascular events, which has been widely observed in clinical trials.

In an in vivo model, perindopril increased eNOS protein expression and activity in rat aortic endothelial cells to a greater extent than trandolapril, quinapril, ramipril, and enalapril administered at equihypotensive dosages. Regarding eNOS protein expression, perindoprilat was significantly more effective than enalapril (P<0.001), ramipril (P<0.05) and quinapril (P<0.01); and regarding eNOS activity, perindoprilat was significantly more effective than enalapril (P<0.01), ramipril (P<0.05) and trandolapril (P<0.05). The favorable effects of perindopril on eNOS were attributed to increased bradykinin bioavailability. In a similar in vivo rat model, in which endotoxic shock induced by bacterial lipopolysaccharide was shown to significantly increase the rate of apoptosis in aortic endothelial cells, perindopril and ramipril were the only ACE inhibitors tested to significantly reduce the apoptotic rate (Figure 5, page 30), with the effects of perindopril being superior to those of ramipril. A cautious explanation for this favorable perindopril effect was greater bradykinin/angiotensin I binding-site selectivity for perindopril relative to the other ACE inhibitors. This is important because bradykinin has a strong antiapoptotic action, whereas angiotensin is proapoptotic.

Regarding clinical differences among ACE inhibitors, the disparate results from EUROPA and HOPE on the one hand, and PEACE and QUIET on the other, highlight the fact that an ACE inhibitor such as perindopril or ramipril is likely to be a better therapeutic option than certain other ACE inhibitors in the setting of stable CAD.
Conclusions

Among cardiovascular medications, ACE inhibitors have the greatest level of evidence for cardiovascular prevention across the entire spectrum of cardiovascular disease (Figure 1). Compared with other agents targeting the RAAS, ACE inhibitors remain the drug of choice. It is important to emphasize that not all ACE inhibitors are the same in terms of their pharmacological efficacy and tolerability profiles. Perindopril and ramipril, for example, have demonstrated markedly reduced cardiovascular risk in patients with stable CAD, whereas quinapril andtrandolapril have had no such effects.

Importantly, a current major trend in cardiovascular disease and other areas of medicine is a move toward increased use of combination therapies. Such therapies are associated with simplification of treatment regimens, greater convenience for patients, improved patient adherence to medication schedules and, potentially, with improved clinical efficacy and tolerability. The data presented in this manuscript underline that, in the arena of cardiovascular therapeutics, any combination therapy designed to provide secondary prevention should contain an ACE inhibitor as one of the constituents.

Perindopril has the largest body of evidence of any ACE inhibitor, with data from the ASCOT-BPLA (Blood Pressure Lowering Arm), ADVANCE, and PROGRESS studies confirming the major cardiovascular risk-reducing benefits obtained with perindopril-containing combination schedules.

REFERENCES

16. Fox KM; European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among


**LES IEC DIFFÉRENT-ILS ENTRE EUX ET COMMENT ?**

Arterial compliance, central aortic blood pressure, and ACE inhibition

by G. M. London, France

Recent prospective epidemiological studies suggest that systolic blood pressure (SBP) may be a better predictor of cardiovascular mortality and end-organ damage than diastolic blood pressure (DBP). SBP is the resultant of: (i) left ventricular ejection parameters (left ventricular ejection time and stroke volume); (ii) aortic stiffness; and (iii) wave reflection intensity and the timing of incident and reflected pressure waves. Under physiological conditions, the interaction of arterial stiffness and wave reflection determines the magnitude of SBP and of the amplification of pulse pressure from the aorta toward the peripheral arteries. Left ventricular function is mainly influenced by the pressure in the aorta. However, a preferential decrease in aortic pressure does not always translate into measurable changes in peripheral (brachial) BP. Recently published interventional studies [PREterax in regression of Arterial Stiffness (PREAR) and Conduit Artery Functional Endpoint/Anglo-Scandinavian Cardiac Outcomes Trial (CAFE/ASCOT)] have documented that antihypertensive treatment with the angiotensin-converting enzyme (ACE) inhibitor perindopril in combination with a diuretic (indapamide) or a calcium blocker (amlodipine) was associated with a greater decrease in SBP and pulse pressure in the aorta and central arteries than in the brachial artery. These findings have focused attention on the role of drug treatments able to selectively reduce arterial stiffness and wave reflections, which, by preferentially reducing central and aortic pressures, have a more pronounced beneficial effect on end-organ protection and patient outcomes.

Keywords: arterial stiffness; wave reflection; aortic pressure; ACE inhibition; perindopril

Hypertension is a well-established risk factor for cardiovascular disease. Traditionally, the severity of hypertension was evaluated by blood pressure (BP) measurements recorded in peripheral arteries, usually the brachial artery. As the first randomized trials were focused on middle-aged populations in whom diastolic blood pressure (DBP) was more strongly associated with the clinical impact, the severity of hypertension was classified on the basis of DBP. Nevertheless, many cross-sectional studies have shown that end-organ damage in hypertensive people was more strongly associated with systolic blood pressure (SBP) and recent prospective epidemiological studies have focused the attention on SBP as a better guide than DBP to evaluate cardiovascular mortality.

Blood pressure measured conventionally over the brachial artery was assumed to adequately reflect pressures in all parts of arterial system. However, this neglected an essential fact, namely, that peripheral (brachial) blood pressure differs from blood pressure recorded in the aorta and central arteries such as common the carotid artery (Figure 1). While mean BP and diastolic pressure are almost constant along the arterial tree, due to the stiffness of large arteries and the timing and magnitude of wave reflections, SBP and pulse pressure are amplified from the aorta to peripheral arteries, so that brachial artery SBP only indirectly reflects SBP in the aorta and central arteries. Several recent studies have shown that the effects of antihypertensive drugs are not the same in peripheral and central arteries, a fact that could account for the differing effects of various drugs in terms of improvement in end-organ damage, such as regression of left ventricular hypertrophy. Moreover, it has been shown that aortic and central artery pressure (or their determinants) are stronger predictors of end-organ damage and cardiovascular outcome than conventionally measured brachial pressure.

General principles and determinants of arterial pressure

BP is the resultant of the mechanical energy imparted to the blood by ventricular ejection and of the resistance of the systemic arterial system. Because ventricular contraction is intermittent, BP is recorded as a pressure oscillation around a mean value during cardiac cycles, ie, in the form of an arterial pulse pressure curve. Using Fourier analysis of oscillatory phenomena, the pulse pressure curve can be decomposed into two distinct components: a steady component, namely, mean blood pressure (MBP), determined exclusively by cardiac output (CO) and total peripheral resistance (TPR), and an oscillation around this mean—the pulse pressure, whose boundaries during a cardiac cycle are the SBP and DBP.

Mean blood pressure

The driving force of systemic blood flow from the aorta through tissues back to the right atrium is the difference between the MBP and right atrial pressure (RAP). By analogy with Ohm’s law, system-
ic blood flow can be calculated as MBP-RAP/TPR, where TPR is total peripheral resistance. Systemic blood flow is equal to cardiac output (CO), and since RAP is small, the usual expression of the formula becomes: MBP = CO × TPR. Essential and chronic hypertension is most frequently characterized by normal CO and increased TPR, whose magnitude depends on the number of arterioles and on their radius. Reduced number of arterioles (rarefaction) as well as reduced arteriolar radius are classically observed in essential hypertension and secondary hypertension. MBP is maintained by a hierarchy of control systems. The keystone of long-term BP control is the kidney–blood volume–pressure regulatory system known as the pressure–natriuresis relationship.

**Central aortic pressure vs conventional brachial artery pressure: role of arterial stiffness and wave reflection**

SBP results from the interaction of three main factors: left ventricular ejection parameters (left ventricular ejection time and stroke volume); the damping function of large arteries, ie, arterial stiffness (compliance or distensibility); the propagative and reflective properties of the arterial tree (intensity of wave reflections and timing of incident and reflected pressure waves). Besides their role as conduits, arteries dampen the pressure oscillations resulting from intermittent left ventricular ejection and transform the arterial pulsatile flow and pressure into an almost steady flow in peripheral tissues and organs. During systole, roughly 40% to 50% of stroke volume is forwarded directly to peripheral vessels, arteries dampen the pressure waves. The incident wave propagates along the arterial tree at a PWV of 5 to 15 m/s, and as the wave moves away from the heart, part of the energy is reflected back at various sites of the arterial tree (dotted line) and backward-reflected (solid line) pressure waves.

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**Figure 1. Pressure waves recorded along the arterial tree and relationship to age.**


**Figure 2. Schematic representation of peripheral and aortic interactions between forward- (dotted line) and backward-reflected (solid line) pressure waves.**

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**Figure 2. Schematic representation of peripheral and aortic interactions between forward- (dotted line) and backward-reflected (solid line) pressure waves.**

Selected abbreviations and acronyms

<table>
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<tr>
<td>ACE</td>
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<tr>
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<td>Anglo-Scandinavian Cardiac Outcomes Trial</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
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<tr>
<td>CAFE</td>
<td>Conduit Artery Functional Endpoint (trial)</td>
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<td>CO</td>
<td>cardiac output</td>
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<td>MBP</td>
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<td>PWV</td>
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<td>RAP</td>
<td>right atrial pressure</td>
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<td>REASON</td>
<td>pREterax in regression of Arterial Stiffness in a cOntrolled double-blND study</td>
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<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
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<td>TPR</td>
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Arterial compliance, central aortic blood pressure, and ACE inhibition – London

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Arterial compliance, central aortic blood pressure, and ACE inhibition – London
Arterial compliance, central aortic blood pressure, and ACE inhibition – MEDICOGRAFIA, VOL 31, No. 1, 2009

Figure 3. Diagrammatic representation of pressure-volume relationships.

Evidence from clinical and epidemiological studies based on conventional brachial artery pressure measurements has shown that this measurement remains an invaluable tool in epidemiology and clinical practice. Why then measure aortic and central blood pressure and/or the different factors influencing pressure wave amplitude and shape? During systole, the left ventricle directly faces the aorta and central arteries whose geometrical and structural properties determine the actual resistance to ventricular ejection (characteristic impedance). Brachial pressure is measured at a site distant from the heart and only reflects the left ventricular pressure load. Because central artery BP—and not brachial BP—is directly “facing” the left ventricle, it more realistically reflects cardiac load. Aortic systolic pressure is more strongly associated with left ventricular mass and function, and aortic systolic and pulse pressure are much stronger predictors of clinical outcomes than conventional brachial pressure. Moreover, analysis of aortic pulse wave morphology in parallel with the study of aortic stiffness (PWV) permits a detailed analysis of the mechanisms responsible for abnormal systolic or pulse pressure amplitude. Indeed, high aortic systolic pressure could be the resultant of different alterations: (i) stiffening and higher incident/forward pressure wave; (ii) high wave reflection coefficient; (iii) different timing between duration of ventricular ejection (left ventricular ejection time/heart rate) and transit time of wave reflections (depending on the proximity of reflecting sites/arterial length and PWV), or combination of all of the above.

The understanding of these mechanisms also allows a better approach to drug effects and drug indications. Short-term and longitudinal studies have shown that different antihypertensive classes have more important BP-lowering effects on aortic or central artery systolic and pulse pressures, despite similar effects on brachial pressure. These pressure differences could account for differences in observed clinical outcomes and regression of end-organ damage. Indeed, experimental and human studies have documented that despite similar reduction in peripheral (brachial) blood pressure, several antihypertensive drugs are more ef-
effective at regressing left ventricular hypertrophy, carotid intima thickness, and remodeling of resistive arteries. These observations are at the origin of a debate about how much of these beneficial effects are due to blood pressure reduction or to drug-specific effects “beyond blood pressure reduction.” But the problem of all these debates is that they consider only brachial blood pressure and not the fact that brachial and aortic pressures can be different and differently affected by drugs.

While almost all drugs that reduce BP improve arterial stiffness, not all drugs have a similar effect on the intensity and timing of wave reflections. Reduction of wave reflections can be achieved by arterial- and arteriolar-dilating agents. Nitrates are particularly effective and can virtually abolish wave reflections in the ascending aorta, with a reduction in aortic peak systolic pressure, without this leading to any apparent change in peripheral brachial blood pressure. This left ventricular afterload–reducing effect (which, again, goes undetected by the measurement of brachial pressure) is in great part responsible for the high efficacy of nitrates in the treatment of acute pulmonary edema and angina pectoris.

Angiotensin-converting enzyme (ACE) inhibitors have a beneficial effect on aortic stiffness and can reduce the intensity of wave reflections, resulting in a greater fall in aortic pressure than expected from brachial pressure changes. This was demonstrated by the recently published REASON trial (PRETerax in regression of Arterial Stiffness in a cOntrolled double-blinded study), which showed that the fixed perindopril/indapamide combination induced a more pronounced reduction in systolic and pulse pressure in the central (carotid) artery than in the peripheral brachial artery, in comparison with atenolol (Figure 4a). While PWV decreased in parallel with BP to the same extent with perindopril/indapamide and atenolol, the more pronounced effect of perindopril/indapamide on central BP was related to a significant attenuation of wave reflections with perindopril/indapamide. This more pronounced effect of perindopril/indapamide on central BP was associated with a significantly greater reduction in left ventricular hypertrophy than with atenolol despite similar changes in brachial BP (Figure 4b). Moreover, the differences in left ventricular mass were linked to changes in central and not peripheral pulse pressure. Therapeutic regimens that preferentially decrease aortic and central artery BP should be associated with better organ protection and better cardiovascular outcomes. This was recently demonstrated by a large-scale clinical trial, CAFE (Conduit Artery Functional Endpoint), a large ASCOT substudy (Anglo-Scandinavian Cardiac Outcomes Trial). CAFE compared the central aortic versus brachial blood pressure–lowering effects of two drug combinations, amlodipine ± perindopril and atenolol ± ibidiazide. Despite a similar reduction in brachial systolic BP between treatment groups, there was a more efficient reduction in central aortic pressure with the amlodipine regimen. By means of Cox proportional hazards models, it was shown that central pulse pressure was significantly associated with a post-hoc-defined composite outcome of cardiovascular events. This strongly suggested that central aortic pulse pressure may be a determinant of clinical outcome, and that differences in central pressure with different drug regimens may explain the differences in clinical outcomes with different drug regimens. Moreover, understanding the different factors influencing the amplitude and shape of pressure waves permits a more subtle analysis of the different drug effects. In the REASON and CAFE trials, it was shown that the differences in effect could not be attributed to changes in aortic stiffness, since pulse wave velocity was similar with both treatments. The difference was due to the higher percentage of systolic pressure attributable to wave reflection (augmentation index) in the atenolol group. The principal mechanisms for this effect was the different timing between incident and reflected waves, with a longer duration of ventricular ejection time with atenolol, responsible for a higher overlap with reflected waves. The possibility that the drug treatments had a different impact on the systemic reflection coefficient was not investigated in the CAFE substudy, and cannot be ruled out. Results of the above trials, and especially of the CAFE trial, support those of recent meta-analyses that suggest that some β-blockers may not be the optimal recommendation for treatment of essential uncomplicated hypertension.
Conclusion

The European Society of Hypertension guidelines state that central (aortic) blood pressure, which is usually lower than pressure measured in the arm, may be more predictive of outcome in certain populations and differently affected by antihypertensive drugs.

REFERENCES

8. Kelly MP, Gibbs HH, O’Meara M, et al. Nitroglycerine has more favorable effects on left ventricular afterload than is apparent from measurement of pressure in a peripheral artery. Eur Heart J. 1980;11:136-144.

Recent large-scale trials have shown that central arterial hemodynamics may provide treatment targets. Effects of antihypertensive drugs on central/aortic pressure may not be evidenced by pressure measurements in peripheral arteries. This may explain why drugs eliciting similar reductions in brachial pressure have different impacts on end-organ damage reduction and cardiovascular outcomes.
COMPLIANCE ARTÉRIELLE, PRESSION AORTIQUE CENTRALE ET INHIBITION DE L’ENZYME DE CONVERSION DE L’ANGIOTENSINE

Des études épidémiologiques prospectives récentes indiquent que la pression artérielle systolique (PAS) serait un meilleur facteur prédictif de mortalité cardio-vasculaire et des lésions des organes cibles que la pression diastolique (PAD). La PAS résulte : 1) des paramètres d’éjection ventriculaire gauche (temps d’éjection ventriculaire gauche et volume systolique) ; 2) de la rigidité aortique ; et 3) de l’intensité de l’onde réfléchie et de la chronologie des ondes de pression réfléchies et incidentes. Dans les conditions physiologiques, l’interaction de la rigidité artérielle et de la réflexion de l’onde détermine l’amplitude de la PAS et de l’amplification de la pression pulsée de l’aorte jusqu’aux artères périphériques. La fonction ventriculaire gauche est influencée principalement par la pression aortique. Cependant, une diminution préférentielle de la pression aortique ne se traduit pas toujours par des modifications mesurables de la PA périphérique (brachiale). Des études interventionnelles récemment publiées, l’étude REASON (pREterax in regression of Arterial Stiffness in a cOntrolled double-bliNd study) et l’étude CAFE/ASCOT (Conduit Artery Functional Endpoint/Anglo-Scandinavian Cardiac Outcomes Trial) ont démontré qu’un traitement antihypertenseur avec un inhibiteur de l’enzyme de conversion de l’angiotensine (le perindopril) associé à un diurétique (l’indapamide) ou à un inhibiteur calcique (l’amlodipine) conduisait à une diminution plus importante de la PAS et de la pression pulsée dans l’aorte et les artères centrales que dans l’artère brachiale. Ces résultats soulignent le rôle des traitements capables de réduire de façon sélective la rigidité artérielle et la réflexion de l’onde. En réduisant préférentiellement les pressions centrale et aortique, ces médicaments présentent un effet bénéfique plus prononcé sur la protection des organes cibles et sur l’évolution clinique des patients.
Combination strategy based on perindopril for the treatment of hypertension: what are the options?

by P. Rossignol and F. Zannad, France

Angiotensin-converting enzyme (ACE) inhibitors are recommended for the treatment of hypertension, both uncomplicated (as one of the first-line antihypertensive agents) and in the presence of subclinical organ damage and concomitant cardiovascular diseases. Among the ACE inhibitors, robust evidence concerning perindopril has been provided by several large, well-designed and conducted trials (PROGRESS*, EUROPA, PREAMI, ASCOT-BPLA, ADVANCE). Perindopril is a true once-daily ACE inhibitor with demonstrated effectiveness in monotherapy in the control of blood pressure. However, taking into consideration the fact that any monotherapy achieves normalization in only a fraction of patients, a combination therapy is needed in order to achieve optimal blood pressure control. Combinations of perindopril with indapamide, a thiazide-like diuretic, or amlodipine, a long-acting calcium channel blocker, are of particular interest due to their additive mechanisms of action, complementary pharmacological effects in hypertension, safety profile, and data from large outcome trials, which are discussed in the following review.

Blood pressure studies

The combination of a renin-angiotensin system (RAS) inhibitor with a diuretic is potentially advantageous: the RAS inhibitor offsets the diuretic-induced increase in plasma renin activity, whereas the diuretic-induced salt loss potentiates the effect of the RAS inhibitor. This latter effect may be further magnified if the dietary salt intake is reduced. The benefits and the tolerance of the perindopril/indapamide combination compared with other treatments have been investigated in several clinical settings.

The pREterax in regression of Arterial Stiffness in a controlled double-blind (REASON) study was a 12-month, multicenter, controlled, randomized, double-blind, two-parallel-group trial,1 which enrolled 562 patients with essential hypertension, without cardiovascular complications or diabetes. This study aimed at determining whether a perindopril (2 mg/day)/indapamide (0.625 mg/day) combination was able to decrease systolic blood pressure (SBP) and pulse pressure (PP) more than the β-blocker atenolol (50 mg/day), for the same diastolic blood pressure (DBP) reduction. The study drug dosage could be doubled if deemed necessary depending on blood pressure levels. The study further aimed to elucidate whether the perindopril/indapamide combination’s blood pressure–lowering effect was mediated by a decrease in large artery stiffness and attenuation of wave reflections. After 1-year follow-up, office measurements of brachial SBP, DBP, and PP decreased significantly in the two

**Selected Abbreviations**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
</tr>
<tr>
<td>AER</td>
<td>albumin excretion rate</td>
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<tr>
<td>LVH</td>
<td>left ventricular hypertrophy</td>
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<tr>
<td>PP</td>
<td>pulse pressure</td>
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<tr>
<td>RAS</td>
<td>renin-angiotensin system</td>
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<tr>
<td>RRR</td>
<td>relative risk reduction</td>
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* For full names of studies, see Trials Acronyms Box page 39.
treatment groups. The magnitude of the decrease in DBP was the same in each treatment group, but the perindopril/indapamide combination achieved a significantly greater reduction in office brachial SBP and PP than atenolol (SBP -6.02 [95% confidence interval (CI), -8.9 to -3.14]; PP -5.57 [-7.7 to -3.44, P=0.001]). A subsequent ambulatory blood pressure measurement ancillary study confirmed these results.2 Of note, the safety pattern was comparable (96 emergent adverse events in 60 patients given atenolol and 94 events in 66 patients receiving the perindopril/indapamide combination, leading to 20 and 19 dropouts, respectively). The most frequently reported adverse events (≤5%) were headache, dizziness, asthenia, and cough. Interestingly, in the REASON study, pulse wave velocity decreased significantly in both treatment groups, and almost identically, whereas decreases in carotid and aortic SBP and PP were substantially higher with perindopril/indapamide as compared with atenolol (P<0.001).3 This hemodynamic profile reflected changes of wave reflections originating from distal arterial and arteriolar territory, where perindopril/indapamide, but not atenolol, is known to improve vessel wall structure.4 This greater reduction in arterial stiffening with the perindopril/indapamide combination, compared with atenolol, may have major implications, since arterial stiffness is an independent predictor of cardiovascular events in several clinical settings, including hypertension.5 Interestingly, a REASON substudy revealed that left ventricular mass decreased significantly more with the perindopril/indapamide combination than with atenolol, the effects being more pronounced on central than on brachial measurements.6

The STRAtgies of Treatment in Hypertension: Evaluation (STRATHE) study was assessed to compare the efficacy and tolerability of 3 different therapeutic approaches in the treatment of hypertension. A Hypertensive patients (n=533) were randomized to a 9-month treatment aimed at lowering blood pressure below 140/90 mm Hg. The study was discontinued in patients allocated the amlodipine/perindopril regimen, leading to a 9-month treatment aimed at lowering blood pressure below 140/90 mm Hg. The study was discontinued in patients with normal blood pressure at month 6. In the combination group (n=180), perindopril (2 mg) and indapamide (0.625 mg) were administered first, with the possibility of increasing the dosage in two steps up to 4 mg and 1.25 mg, respectively. In the “sequential monotherapy” group (n=176), the treatment was initiated with atenolol (50 mg), and then by losartan (50 mg), and finally, if needed, to be coadministered with hydrochlorothiazide 12.5 mg. The percentage of patients having achieved the target blood pressure was significantly greater in the combination group (62%) than in the sequential monotherapy (49%, P=0.02) and stepped-care group (47%, P=0.005). The percentage of patients having normalized their blood pressure without experiencing drug-related adverse events was also significantly higher in the combination group (56%) than in the sequential monotherapy (42%, P=0.002) and the stepped-care group (42%, P=0.004).6

Outcome studies

◆ Perindopril/amlodipine combination and prevention of cardiovascular events

The Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA) study sought to compare the effect of the amlodipine/perindopril combination versus atenolol/thiazide on nonfatal myocardial infarction and fatal coronary heart disease.7 This was a multicenter, prospective, randomized controlled trial in 19 257 patients aged 40 to 79 years, with hypertension and at least three other cardiovascular risk factors. Patients were assigned either to amlodipine 5 to 10 mg, adding perindopril 4 to 8 mg as needed, or atenolol 50 to 100 mg, adding bendroflumethiazide 1.25 to 2.5 mg and potassium as needed, depending on the blood pressure levels. At every follow-up visit, the antihypertensive therapy was titrated to achieve target blood pressures (<140/90 mm Hg for patients without diabetes and <130/80 mm Hg for patients with diabetes). After a median follow-up of 5.5 years, the study was prematurely stopped because of a significantly higher mortality in the atenolol-based group. By the end of the trial, most patients (78%) were taking at least two antihypertensive agents. Compared with patients allocated the β-blocker-diuretic-based regimen, blood pressure values were lower throughout the trial in those allocated the amlodipine/perindopril-based regimen, with an average difference of 2.7/1.9 mm Hg. Fewer patients on the amlodipine/perindopril regimen experienced a primary end point compared with the atenolol/bendroflumethiazide-based regimen, although this did not reach statistical significance (429 vs 474; hazard ratio 0.9 [0.79-1.02]; P=0.1), presumably because the study was underpowered for this end point, in the early discontinuation setting. However, all other prespecified secondary end points (except fatal and nonfatal heart failure, with a non-significant 16% reduction) were significantly reduced in patients allocated the amlodipine/perindopril combination group (56%) than in the sequential monotherapy (49%, P=0.02) and stepped-care group (47%, P=0.005).
Combination therapy based on perindopril for the treatment of hypertension – Rossignol and Zannad

...Combination therapy based on perindopril for the treatment of hypertension – Rossignol and Zannad...
those in the general population, HYVET provides unique evidence that hypertension treatment based on indapamide, (mostly) with or without perindopril, in the very elderly, with a target blood pressure of 150/80 mm Hg, is beneficial, with a number-needed-to-treat of 40 to prevent 1 death during a 2-year period.13

Clinical efficacy in diabetes

The Action in Diabetes and Vascular disease: PerterAx and Diamicron-MR Controlled Evaluation (ADVANCE) study was a large-scale trial designed to investigate the benefits of blood pressure lowering and intensive glucose control in patients with type 2 diabetes.14 It was a 2×2 factorial, randomized, controlled trial evaluating the effects on macrovascular and microvascular disease achieved by decreasing the blood pressure using a fixed combination of perindopril (2 to 4 mg) and indapamide (0.625 to 1.25 mg) versus placebo, and by an intensive glargine MR-based glucose control regimen, targeting an HbA1c of 6.5% or less vs standard guidelines-based therapy for glucose control. The primary end points were composites of major cardiovascular and microvascular events, defined as death from cardiovascular disease, nonfatal stroke or nonfatal myocardial infarction, and new or worsening renal or diabetic eye disease. A total of 11 140 patients with type 2 diabetes were randomized. The results of ADVANCE15 are discussed in detail elsewhere in this issue. Importantly, they show that after a mean of 4.3 years of follow-up, the relative risk of a major macrovascular or microvascular event in the active treatment group was reduced by 9% (P=0.04), suggesting that for every 66 patients commencing long-term treatment with perindopril and indapamide, 1 patient would avoid at least 1 major vascular event in 5 years as a direct consequence of this treatment.15

The PREterax in albuMinuria rEGression (PREMIER) study was conducted to compare the efficacy of a perindopril 2 mg/indapamide 0.625 mg combination (up titrated to 8 mg/2.5 mg if needed) versus an enalapril target of below 140/80 mm Hg) versus 10 mg enalapril (up titrated to 40 mg if needed) for 52 weeks, on urinary albumin excretion rate (AER) in patients aged between 40 and 75 years with type 2 diabetes with hypertension and albuminuria.16 This was a 12-month, randomized, controlled, double-blind, 2-parallel-group study. Results from 457 patients (intention-to-treat analysis) were available. The main outcome measures were overnight AER and supine BP. Although both treatments reduced BP, perindopril/indapamide treatment resulted in a statistically significantly higher fall in both BP (−3 mm Hg [−5.6; −0.4], P=0.012 for SBP; −1.5 [−3; −0.1], P=0.019 for DBP) and AER (−42% versus −27% with enalapril). Importantly, the greater AER reduction remained significant even after adjustment for mean BP. Adverse events were similar in both groups.16

Effects on cardiac structure and function

The Perindopril/Indapamide in a double blind Controlled study versus Enalapril in Left ventricular hypertrophy (PICXEL) was a 1-year multicenter, randomized, double-blind study aimed at comparing the efficacy of a first-line combination with perindopril/indapamide (n=284) versus monotherapy with enalapril (n=272) (both uptitrated from 2 mg/0.625 mg to 8 mg/2.5 mg, and 10 to 40 mg, respectively) to achieve predefined BP targets depending on BP levels at baseline) in reducing left ventricular hypertrophy (LVH) in hypertensive patients. The perindopril/indapamide combination achieved a significantly greater degree of LVH reduction than enalapril monotherapy, with a between-group difference of 9.3 g/m2 [5.7; 13], P<0.0001, and a higher blood pressure decrease (between-group difference of 4.9 [2.7; 7.1], P<0.0001, and 2 [0.6; 3.4], P= 0.003 for SBP and DBP, respectively. Adverse events related to treatment occurred in 17.3% of patients in the perindopril/indapamide group vs 15.7 % in the enalapril group (P=0.57), the most common side effect being cough (4.1 % vs 4.4 %, P=0.83).17

Conclusion

In conclusion, the aforementioned data support the widespread use, both in primary and secondary prevention setting, of a combination therapy based on perindopril with either indapamide or amlodipine. Such combinations have been found to be effective and safe.

For patients requiring three-drug therapy to achieve blood pressure control, a combination of perindopril, indapamide, and amlodipine could be considered, although, to date, no specific comparative study has addressed this question.

REFERENCES

8. Williams B, Lacy PS, Thom SM, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clin-
Combination therapy based on perindopril for the treatment of hypertension – Rossignol and Zannad

**QUELLE ASSOCIATION THÉRAPEUTIQUE COMPORTANT LE PERINDOPRIL FAUT-IL ENVISAGER DANS LE TRAITEMENT DE L'HYPERTENSION ARTÉRIELLE ?**


* Les noms complets des études sont indiqués dans l’encadré au bas de la page 39.
Initial discussions on a trial that eventually became the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) study took place almost 20 years ago. In the late 1980s, despite the advent of the angiotensin-converting enzyme (ACE) inhibitors and the calcium channel blockers (CCB), there were no plans to conduct outcome trials with these drugs in hypertensive populations. Many expressed concern that their increasing use as part of treatment strategies for hypertension lacked a firm evidence base from morbidity/mortality trials. Outcome trials with older drugs, particularly diuretics and β-blockers and their combination, had provided good evidence for the prevention of stroke, but less convincing evidence for protection against coronary heart disease (CHD) events. Several hypotheses had been put forward to explain the latter, which included adverse metabolic effects associated with both diuretics and β-blockers. It thus seemed reasonable that, with newer classes of drugs apparently immune from adverse metabolic sequelae, the shortfall in CHD prevention seen in the earlier trials could be overcome with trials based on ACE inhibitors and CCBs. However, at the time, prospects for such outcome studies were bleak.

Simultaneously in Europe and in the USA, discussions were taking place on the design of studies addressing the question of “was new better than old?” and several trial designs were considered. In the USA, support from the National Heart, Lung, and Blood Institute (NHLBI) led to the design and launch of the Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial (ALLHAT) study. In Europe, despite substantial enthusiasm for such a study, funding sources were not appa-
ent. However, by the mid 1990s, reports began to emerge from Curt Furberg and his colleagues about potential hazards of CCBs and a possible increase in CHD events in studies particularly with short-acting dihydropyridines. Although most of these studies had significant design flaws, the damage had been done and many clinicians were anxious about possible harm associated with CCBs. It was this issue that is likely to have persuaded Pfizer (who was already contributing to the ALLHAT study) to offer funding for a major European outcome trial incorporating amlopipine as the CCB, in a strategy of a new antihypertensive regimen compared with an older diuretic/β-blocker–based regimen on cardiovascular (CV) outcomes.

The ASCOT Working Group, and subsequently the Steering Committee, considered several possible designs and ultimately came up with a simple and ultimately to be proven in hypertension). In the UK, physicians were divided by their choices (never ultimately to be proven in hypertension).

The Working Group was, however, in 1996, offered bendroflumethiazide-K at doses of 1.25 mg or 2.5 mg by Leo Laboratories and these doses were used in the trial.

Other trial design issues

Blood pressure (BP) targets were derived from contemporary guidelines, and were set at <140/90 mm Hg in those without diabetes and <130/80 mm Hg in those with diabetes. Obviously, in order to achieve BP targets in a large hypertensive population, additional drugs would be required. The α-blocker doxazosin was widely used in combination therapy and selected as a common add-on to each limb of the trial. Other drugs included moxonidine and spironolactone, but were left to the choice of the trial physician. The design recommended avoiding an ACE inhibitor or CCB as add-on drugs in the β-blocker/diuretic limb, and vice versa.

Because pooled analyses of the earlier placebo-controlled trials of drug intervention in hypertensive patients had suggested a shortfall in prevention of CHD events, the Working Group proposed that the primary end point in ASCOT should be CHD events. Initial power calculations indicated that to observe a reasonable benefit (circa 15%) on CHD outcome in favor of the newer regimen of the CCB and ACE inhibitor, we would require 1150 CHD events. We predicted that following 18000 patients for 5 years would achieve this objective.

From the outset we were impressed by the emerging benefits of statins in the prevention of CHD events and because of the relative lack of benefit on CHD in the early hypertension trials, we planned in ASCOT to test an additional hypothesis, by way of a factorial designed trial of lipid-lowering, that lowering cholesterol with a statin, atorvastatin,
would confer additional benefits compared with placebo on CHD events in this hypertensive population (Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm [ASCOT-LLA]).

**Trial design and methods**

The detailed ASCOT protocol has been published previously¹ and further information is available at www.ascotstudy.org. In summary, patients were recruited between February 1998 and May 2000, largely from family practices in the UK, Ireland, and the Nordic countries. Hypertensive patients, on or off antihypertensive treatment, with no prior history of myocardial infarction (MI) or clinical CHD, but with three or more risk factors for cardiovascular disease (CVD), were eligible for the Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm (ASCOT-BPLA). These risk factors included male sex, age ≥55 years, a history of smoking, left ventricular hypertrophy or other specified ECG abnormalities, a history of early CHD in a first-degree relative, microalbuminuria or proteinuria, non–insulin-dependent diabetes, peripheral vascular disease, previous stroke or transient ischemic attack, or ratio of plasma total cholesterol—to–high-density lipoprotein (HDL) cholesterol of 6 or higher. Exclusion criteria included prior MI, currently treated angina, cerebrovascular event within the previous 3 months, fasting serum triglycerides greater than 4.5 mmol/L, heart failure, uncontrolled arrhythmias, or any clinically important hematological or biochemical abnormalities.

Following a 4-week run-in period, during which eligibility and consent were confirmed, patients were randomized to one of the two BP strategies in ASCOT-BPLA, either amlodipine ± perindopril or atenolol ± bendroflumethiazide, and those with a fasting total cholesterol of ≤6.5 mmol/L (250 mg/dL) who were currently untreated with a statin or fibrate were randomized, using a factorial design, to either 10 mg atorvastatin daily or matching placebo in ASCOT-LLA. Overall 19,342 patients were assigned either amlodipine ± perindopril treatment or atenolol ± thiazide treatment and, of these, 10,305 were assigned atorvastatin or placebo. The management of those randomized to ASCOT-BPLA is detailed elsewhere.¹ In summary, at each follow-up visit, antihypertensive drug therapy was titrated according to common risk factors were age ≤55 years (in 84% of patients) and male sex (in 77%). At baseline, approximately 80% of subjects were receiving treatment with prior antihypertensive drugs; however, BPs were poorly controlled and were similar in the two treatment groups (164 mm Hg systolic and 95 mm Hg diastolic pressure).

Following randomization, information was recorded about adverse events and any new CV event or procedure including the cause for any hospital admission. Central review of end points by the End point Committee was carried out blinded to treatment allocation using the criteria for classifying diagnoses that have been reported at www.ascotstudy.org. The primary end point of both ASCOT-LLA and ASCOT-BPLA was the composite of nonfatal (including silent) MI and fatal CHD. Secondary end points included nonfatal or fatal stroke and a number of additional composite CV end points. Prespecified tertiary objectives included an evaluation of any synergy between the BP-lowering and lipid-lowering regimens.

**Statistical methods**

Time to first events in the atorvastatin and placebo groups were compared on an intention-to-treat basis until closeout of ASCOT-LLA (median follow-up time 3.3 years) and subsequently at the end of the ASCOT-BPLA (median follow-up time 5.5 years) using the log-rank and Cox proportional hazard models. In order to check the proportional hazard assumption, we assessed the proportionality by considering the interaction of the treatment indicators and time. The P-values for time-intervention were for all end points larger than 0.30. Wald's test for interaction between atorvastatin and the two BP treatment strategies was performed using the full Cox model. All significance tests were two-tailed and conducted at the 0.05 level.

**Results**

- **Baseline population characteristics**
  ASCOT recruited 19,342 patients between February 1998 and May 2000. They were randomized to one of the two antihypertensive treatment regimens. The characteristics of the hypertensive patients at baseline in the two randomized groups were well matched.¹² Subjects were mainly white (95%) and male (77%) with a mean age of 63 years. The most common risk factors were age ≥55 years (in 84% of patients) and male sex (in 77%). At baseline, approximately 80% of subjects were receiving treatment with prior antihypertensive drugs; however, BPs were poorly controlled and were similar in the two treatment groups (164 mm Hg systolic and 95 mm Hg diastolic pressure).

- **Blood pressure reduction**
  BPs were substantially reduced in both treatment arms, although notably in the first 6 months of the trial, BP lowering was more effective on the amlodipine ± perindopril strategy compared with the atenolol ± thiazide strategy (Figure 1, page 46). By the end of the trial, BPs had fallen to 137.7/79.2 mm Hg in the atenolol ± thiazide strategy treatment group and to 136.1/77.4 mm Hg in the amlodipine ± perindopril treatment group. The majority of patients (77.8%) by the end of the trial were taking at least two antihypertensive drugs, and for 50% and 55% of the total patient-years of follow-up, the prespecified combinations, with or without other drugs, were taken in the atenolol ± thiazide and amlodipine ± perindopril treatment groups respectively (Table I, page 46).¹²

- **Premature termination of ASCOT-BPLA**
  The study was stopped prematurely after 5.5 years median follow-up and accumulated a total of 106,153 patient-years of observation. The Data Safety Monitoring Board (DSMB) recommended to the Steering Committee that the trial be stopped early on the...
grounds that there were significant reductions in all-cause mortality and stroke events in those assigned amloidipine ± perindopril and it was deemed unethical to continue the trial, despite the fact that a significant reduction in the primary CHD end point had not been achieved. A major consequence of the early stopping of the trial was that this occurred when only 903 primary events had been reported, whereas the trial was appropriately powered on the basis of attaining 1150 primary end points. At the final BPLA visits, complete information was obtained on more than 98% of the subjects randomized.

In the amloidipine ± perindopril treatment group, there was a nonsignificant 10% reduction in the primary end point of nonfatal MI and fatal CHD when compared with the atenolol thiazide treatment group, and there were significant reductions in several of the secondary end points in the trial among those allocated to the amloidipine ± perindopril treatment group, including all-cause mortality, total coronary events, total CV events and procedures, CV mortality, and fatal and nonfatal stroke (Figure 2).15 One of the most striking findings among the predefined tertiary end points was a >30% lower incidence of the development of new onset-diabetes mellitus in those assigned amloidipine ± perindopril (Figure 2).15 Assignment to amloidipine ± perindopril compared with atenolol ± thiazide was also associated with a highly significant reduction in the onset of renal impairment.

**Post-hoc analysis**

Two factors dictated the conduct of a post-hoc analysis, which included the primary end point to which the number of coronary revascularization procedures was added. As ASCOT progressed, the management of acute coronary syndromes (ACS) in clinical practice changed and increasing numbers of revascularization procedures were being undertaken for patients presenting with ACS, thereby reducing the potential number of primary end points. In addition, because the trial was stopped early and there was an associated loss of power in detecting a significant difference in the primary end point, it was deemed reasonable to repeat the coronary end point analysis using a combined primary end point plus coronary vasculization procedures. This analysis included observations on 1284 coronary events and confirmed a significant 14% risk reduction in favor of amloidipine ± perindopril. In subgroup analyses, there was no evidence for heterogeneity, inasmuch as the risk reductions in all predefined subgroups did not differ significantly from that of the whole trial population. Approximately 25% of the subjects stopped therapy due to adverse events, but there were no significant differences overall between the two groups. Stopping therapy due to serious adverse events occurred in 1.7% in those assigned amloidipine ± perindopril and 2.6% in those assigned atenolol ± thiazide.

**Discussion**

**Premature termination and study power: the post-hoc analysis**

The early stopping of outcome trials invariably causes problems,16 not least because failure to reach the anticipated number of primary end points reduces the power of the study. In ASCOT, the Steering Committee was persuaded by the Drug Safety Monitoring Board (DSMB) that the trial should be stopped when all-cause mortality and stroke outcome were significantly reduced in those assigned amloidipine ± perindopril. By the time the trial was stopped, there had been almost 750 strokes and over 1550 deaths. It was felt that in continuing the trial, there would be a persistent excess of strokes and deaths in those assigned atenolol ± thiazide and that this was both unacceptable and unethical. The trial was stopped at a time when 903 primary events had been recorded—a number significantly lower than the 1150 planned, thereby reducing the power to detect potential differences between the two treatment groups in their impact on CHD outcome. As mentioned earlier, the failure to reach the anticipated number of primary events was compounded by the fact that as the trial continued ac-


**Table I. Mean proportion of time on antihypertensive treatment by treatment**


<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean difference (%)</th>
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<tbody>
<tr>
<td><strong>Randomized to amloidipine ± perindopril</strong></td>
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<tr>
<td>Amlodipine (+/− others)</td>
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<tr>
<td>Perindopril (+/− others)</td>
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<td>Amlodipine + perindopril (+/− others)</td>
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<tr>
<td><strong>Randomized to atenolol ± thiazide</strong></td>
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<tr>
<td>Atenolol (+/− others)</td>
<td>79.4</td>
</tr>
<tr>
<td>Bendroflumethiazide (+/− others)</td>
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</tr>
<tr>
<td>Atenolol + bendroflumethiazide (+/− others)</td>
<td>54.9</td>
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</table>
tual event rates for CHD were declining, partly due to changing cardiological practice and an increasing tendency for early intervention to prevent MI in those presenting with ACS, and increasing use of statins following the earlier closure of LLA.17

Our post-hoc analysis, in which the primary CHD events and the number of coronary revascularization procedures were combined, restored the power of the study and clearly demonstrated a significant benefit in favor of amlodipine ± perindopril. The robustness of this conclusion is also supported by the fact that a secondary composite coronary end point was also significantly reduced by amlodipine ± perindopril.

How much of the BP reduction in ASCOT was due to a true drug effect?

Hypertensive patients recruited into ASCOT were poorly controlled at baseline. While selection of patients for the trial does not necessarily indicate that they are typical of those hypertensives routinely followed in clinical practice, their BP levels, reflecting inadequate treatment, are commonplace in the “real” world. After randomization and following the instigation of a defined algorithm, irrespective of treatment arm, there were substantial falls in BP, by on average 27/17 mm Hg. In the absence of a placebo control, it is not possible to ascertain how much of the BP fall was attributable to a true drug effect, but by extrapolation from earlier placebo-controlled trials of BP reduction where the placebo response averaged out about 10-15 mm Hg systolic and 5-10 mm Hg diastolic, a genuine treatment effect in ASCOT would be of the order of 15 mm Hg systolic and 10 mm Hg diastolic pressures.

From observational data10,15 and the pooled analyses of the intervention trials12,20 on outcome in relation to the magnitude of the BP reduction, we predicted that this would be associated with a reduction in CHD incidence of about 30% and a stroke incidence of about 45%. These risk reductions are broadly similar to those observed in the trial in subjects not randomized to atorvastatin.13 Of particular note is the rapidity with which benefit is conferred both for CHD and for stroke outcome14 and adds support for the urgency for BP control in the hypertensive population. In order to achieve BP targets, the majority of patients needed to take two or more drugs (77.8%) and for 55% and 50% of the total patient-years of follow-up, the prespecified combinations (with or without other drugs) were taken in the amlodipine

Table 2 – Effect of amlodipine ± perindopril and atenolol ± thiazide on the incidence of new-onset diabetes. (HR = hazard ratio).

Figure 2 – Effect of amlodipine ± perindopril and atenolol ± thiazide on primary, secondary, tertiary, and post-hoc end points.

Figure 3. Effect of amlodipine ± perindopril and atenolol ± thiazide on the incidence of new-onset diabetes. (HR = hazard ratio).

ACE inhibition as a cornerstone of hypertension treatment

Effects (compared with other drugs) particularly on BPLA could be all attributed to BP,27 (an opinion the overall hypothesis of ASCOT).25 CAFE clearly differentiated the aldopril strategy on CV outcome in ASCOT-BPLA.26

Despite opinions that outcome differences in ASCOT could be attributed to differences in BP between the two treatment groups, as the average difference throughout the trial was 2.7/1.9 mm Hg in favor of amlodipine ± aldopril treatment. This issue was discussed at length in a second manuscript accompanying the original report of the BPLA findings.22

Various statistical models have been used in an attempt to separate out BP-lowering benefits, but all are potentially flawed. Serial mean (median) matching and multiple regression analyses all have their problems as they involve breaking the randomization of comparator groups and thus the true robustness of randomized-controlled comparison is lost.23 Not withstanding these cautions, post-hoc analyses demonstrated no temporal relationship between BP differences (maximal in the first year of the trial and CV outcomes (no differences in the first year of the trial).23 These observations contrast with the reported finding from the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial.24

In multiple regression analyses, adjustments for BP had virtually no impact on the differences in CHD outcome, but explained about 30% of the difference in stroke outcome between the two treatment groups. Including other variables in the regression analysis demonstrated that differences in HDL cholesterol (largely due to atenolol) explained about 30% of the differences in CHD outcome. While this type of analysis may underestimate the contribution of changes in in-trial variables, such as BP and cholesterol, there is a strong indication that an alternative explanation is required to fully account for the observed benefits of the amlodipine ± perindopril strategy on CV outcome in ASCOT-BPLA.

Further insight into these differences is provided by the Conduit Artery Functional Endpoint (CAFE) substudy of ASCOT.25 CAFE clearly differentiated the hemodynamic response to atenolol ± thiazide from that of amlodipine ± perindopril regimen. In the former, despite equivalent brachial artery pressures, when compared with the amlodipine ± perindopril, central pressures remained higher by, on average, 4 mm Hg systolic pressure. Together with reports from other studies showing reductions in cerebral blood flow with β-blockers compared with vasodilator drugs,26 on occasions when peripheral artery pressures were equivalent, these studies highlight the hemodynamic disadvantages of β-blocker-based regimens, which could contribute to their adverse effects (compared with other drugs) particularly on stroke outcome.

ACE-inhibitor therapy: CHD benefits beyond those attributable to BP reduction

Despite opinions that outcome differences in ASCOT-BPLA could be all attributed to BP,27 (an opinion the ASCOT authors reject!),28 apart from the analyses reported above, two other issues are important. The first is that, in recently reported pooled analyses from the Blood Pressure Lowering Treatment Trialists Collaboration (BPLTTC)29 and from Staessen and colleagues,30 trial regimens based on ACE inhibitors confer benefits on CHD outcome that are greater than those predicted from the magnitude of the BP lowering—an observation influenced by outcome trials with ACE inhibitors in high CV risk patients. Moreover, in outcome trials based on CCBs, there is an excess benefit on stroke compared with that predicted from the magnitude of BP lowering. It is therefore, perhaps, not altogether surprising that in ASCOT we have observed and reported on excess benefit on both CHD and stroke outcome with both the CCB and ACE inhibitor, that appears to go beyond the lowering of BP.

ASCOT-BPLA: benefits associated with amlodipine ± perindopril enhanced by atorvastatin

The second important issue is the potential influence of atorvastatin on the CV benefits of the amlodipine ± perindopril regimen. We had specified that we would investigate any potential interaction between blood pressure and lipid-lowering regimens in ASCOT.14 LLA was also stopped prematurely, after 3.3 years follow-up, on account of major CV benefits of atorvastatin, including a highly significant reduction in the primary end point of nonfatal myocardial infarction and fatal CHD.17 Overall, the primary end point was reduced by 36% compared with placebo. However, when the LLA population was divided by blood pressure treatment groups, atorvastatin reduced CHD events by 53% in those assigned amlodipine ± perindopril (P<0.001) but nonsignificantly by 16%, in those assigned atenolol ± thiazide.30 Tests for heterogeneity, indicative of possible synergy, were of borderline significance (P=0.02). It thus seems that atorvastatin enhances the benefits associated with the amlodipine ± perindopril regimen on CHD end points. If these observations were confirmed in other trials, the implications for future therapeutics strategies in hypertension would be profound.

Dramatic decrease in new-onset diabetes

A recent overview of treatment in patients with diabetes concluded that proportional benefits of BP lowering on CV outcomes were similar in those with and without diabetes and were not influenced by assignment to any particular drug group.21 In those with diabetes, there is more substantial evidence for the benefits devised by achieving lower target pressures. ASCOT randomized over 5000 patients with type 2 diabetes and the risk reductions associated with the amlodipine ± perindopril arm for the composite CV end point were similar to those observed in the nondiabetic.15

One of the more dramatic observations in the trial was the development, over the course of the 5.5 years follow-up, of new-onset diabetes in 1366 cases with more than 30% fewer cases (34% after correction for baseline variables) in those assigned amlodipine ± perindopril (P<0.001 versus atenolol ± thiazide).32 The differential effect of the two anti hypertensive treatments is illustrated in these observations.
pertensive regimens is likely to be a composite of adverse effects produced by atenolol + thiazide plus the protective effect of perindopril, with amlodipine probably playing a neutral role.

**ASCOT rewrites the guidelines**

Clearly, the longer-term risks associated with new-onset diabetes give cause for concern, and the weight of evidence implicating both β-blockers and diuretics in its causation is now substantial. Of all the hypertensive trials reported over the last decade, the results of ASCOT have probably had the greatest impact on guidelines for the prevention of CV disease. ASCOT-LLA was stopped early because of substantial benefits of atorvastatin in the primary prevention of CHD in a hypertensive population at modest risk, but with normal or only modestly raised cholesterol levels. The more recent recommendations, including reductions in the thresholds for intervention with lipid-lowering therapy, have been strongly influenced by the ASCOT results. The ASCOT-BPLA results have also resulted in changes to the latest UK guidelines reported by the National Institute for Clinical Excellence (NICE) and the British Hypertension Society (BHS).

These guidelines advocate selection of first-line drugs based on the age of the hypertensive patient, advocating, in younger subjects (<55 years), treatment with a drug that blocks the renin system (ACE inhibitor or angiotensin receptor blocker [ARB]) in case of ACE-inhibitor intolerance, whereas in older subjects (and blacks), low renin status is more common, and a CCB or a thiazide-like diuretic is recommended. These recommendations have been confirmed following analyses of the ASCOT database which show highly significant effects of age on BP-lowering efficacy of antihypertensive drugs.

**REFERENCES**


ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm) : ARGUMENTS EN FAVEUR DE L’UTILISATION DE L’ASSOCIATION PERINDOPRIL-AMLODIPINE

L’étude ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm), réalisée chez 19 257 patients hypertendus à risque modéré de développer des événements cardio-vasculaires, a été arrêtée prématurément à cause de la réduction du nombre de critères atteints, comme la mortalité toutes causes (11 %; \( p = 0,025 \)) et la mortalité cardio-vasculaire (24 %; \( p = 0,001 \)) dans le groupe amloidine ± perindopril comparé au groupe aténolol ± thiazide. Étant donné l’arrêt précoce de l’étude et la prescription croissante des statines tout au long de l’étude, la réduction du risque relatif de 10 % du critère primaire (infarctus du myocarde non fatal et maladie coronaire [MC] fatale) dans le bras amloidine ± perindopril n’a pas atteint la signicativité statistique en raison du nombre insuffisant d’événements (903 critères atteints contre 1 150 prévus). Néanmoins, ce traitement était associé à une diminution de 13 % des événements coronaires (\( p = 0,007 \)), de 22 % des AVC totaux (\( p = 0,003 \)), de 16 % de tous les événements et interventions cardio-vasculaires (\( p < 0,0001 \)) et de 30 % d’apparition de nouveaux diabètes (\( p < 0,0001 \)). La différence moyenne de pression artérielle en cours d’étude était de 2,7/1,9 mmHg en faveur de l’association amloidine ± perindopril. Les analyses après ajustements multiples ont montré que l’ajustement pour la pression artérielle expliquait environ 30 % de la différence de survenue des AVC entre les deux groupes de traitement alors qu’il n’a eu quasiment aucun impact sur la MC. Les résultats de l’essai ASCOT-BPLA fournissent ainsi l’argumentaire pour la prescription de l’association amloidine-perindopril dans le traitement de l’hypertension artérielle.
Treating diabetic hypertensive patients: new insights from the ADVANCE trial

by G. Grassi and G. Mancia, Italy

Therapeutic interventions aimed at reducing elevated blood pressure in diabetic hypertensive patients encompass a number of limitations and are frequently faced with at least partial clinical lack of success. Several reasons may explain this discouraging scenario, among which two stand out: first, the difficulties to achieve optimal blood pressure control; and second, no more than 10% to 15% treated hypertensive diabetics in current clinical practice display blood pressure values less than 130/80 mm Hg, as recommended by current guidelines. Another reason that may explain the abovementioned findings is that the drugs used to lower elevated blood pressure in diabetic patients are not always capable of exerting cardioprotective and nephroprotective effects and thus of improving the elevated risk profile of these subjects. A challenging strategy in the therapeutic approach to diabetic hypertension is that adopted by the Action in Diabetes and Vascular disease: PreterAx and DiamicroN-MR Controlled Evaluation (ADVANCE) trial. In this trial, the largest ever performed in diabetes, use of the perindopril/indapamide combination allowed effective blood pressure control and significantly reduced the risk of the major macrovascular and microvascular complications that these high-risk patients frequently display. The favorable effects of this angiotensin-converting enzyme inhibitor/diuretic combination, together with its excellent tolerability profile, make it the first-choice treatment in the management of the diabetic patient.

Keywords: hypertension; diabetes; antihypertensive treatment; cardiovascular risk; clinical trial; ACE inhibitor; diuretic; perindopril; combination treatment

Evidence from several studies has clearly demonstrated that the risk associated with elevated blood pressure in patients with diabetes is reversible if blood pressure is reduced, regardless of the therapeutic strategy employed. The Systolic Hypertension in the Elderly Program (SHEP) enrolled patients, aged 60 years and older, with isolated systolic hypertension, including 4149 patients without diabetes mellitus and represents an important risk factor for cardiovascular events, including macro- and microvascular complications, such as nephropathy. Evidence provided by large-scale clinical trials has shown, however, that the risk is not irreversible and that blood pressure reduction by antihypertensive treatment can provide effective cardiovascular protection in patients classified, according to the 2007 European Society of Hypertension/European Society of Cardiology (ESH/ESC) Guidelines on Hypertension, as being at “very high-risk.”

This paper focuses on three major issues. First, it examines the benefits of blood pressure reduction in providing cardiovascular protection in hypertensive patients with diabetes mellitus. Second, it examines the differences in obtaining optimal blood pressure control in these patients and the therapeutic strategies to achieve this goal. Finally, we discuss the main features and the results obtained so far in the Action in Diabetes and Vascular disease: PreterAx and DiamicroN-MR Controlled Evaluation (ADVANCE) trial, the largest trial ever performed in a population of diabetic hypertensives.

Benefits of blood pressure reduction in diabetic hypertensives

Selected abbreviations and acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>ABCD</td>
<td>Appropriate Blood Pressure Control in Diabetes</td>
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<tr>
<td>ADVANCE</td>
<td>Action in Diabetes and Vascular disease: PreterAx and DiamicroN-MR Controlled Evaluation</td>
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<tr>
<td>ASCOT</td>
<td>Anglo-Scandinavian Cardiac Outcomes Trial</td>
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<tr>
<td>IDNT</td>
<td>Irbesartan Diabetic Nephropathy Trial</td>
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<tr>
<td>LIFE</td>
<td>Losartan Intervention For Endpoint reduction in hypertension</td>
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<tr>
<td>PAMELA</td>
<td>Pressioni Arteriose Monitorate E Loro Associazioni</td>
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<tr>
<td>RENAL</td>
<td>Reduction of Endpoints in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan</td>
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<tr>
<td>SHEP</td>
<td>Systolic Hypertension in the Elderly Program</td>
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<td>STRATEH</td>
<td>STRategies of Treatment in Hypertension Evaluation</td>
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<tr>
<td>UKPDS</td>
<td>United Kingdom Prospective Diabetic Study</td>
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Evidence suggests that it is advantageous to initiate antihypertensive therapy in patients with diabetes who have blood pressure levels in the high–normal range with the goal of reducing SBP to less than 130 mm Hg. The Appropriate Blood pressure Control in Diabetes (ABCD) trial evaluated the effect of moderate or intensive antihypertensive therapy on diabetic vascular complications in normotensive patients with type 2 diabetes. A total of 480 patients were randomly assigned to receive 5 years’ treatment with “intensive therapy” with either enalapril or nisoldipine, or moderate therapy, with placebo and then either enalapril or nisoldipine in those who subsequently became hypertensive during the study. Respective mean blood pressure for the last 4 years of the study was 128/75 and 137/81 mm Hg, in the intensive and moderate therapy groups. Cerebrovascular events occurred in a significantly smaller proportion of patients in the intensive therapy group than the moderate therapy group. As a result of the ABCD trial, and in the face of similar evidence from other studies, guidelines for the management of hypertension and diabetes currently recommend a target blood pressure of less than 130/80 mm Hg in patients with diabetes, renal disease, or high cardiovascular risk. In addition, antihypertensive therapy should be initiated in high-risk patients with blood pressure in the high–normal range of less than 140/90 mm Hg.

Evidence from the United Kingdom Prospective Diabetic Study (UKPDS) trial indicated that blood pressure reduction contributed to the relative reduction in cardiovascular events to a greater extent than glycemic control. A comparison of “tight” blood pressure control and “tight” glucose control in patients with type 2 diabetes has shown that blood pressure control was associated with significantly greater risk reductions in stroke, diabetic end points, diabetes-related mortality, and microvascular complications. Two possible mechanisms may explain the advantages of rigorous blood pressure control in patients with diabetes. First, patients with diabetes lose the ability to autoregulate blood pressure early on, and so there is a passive increase in blood pressure at the level of microcirculation, transmitting the traumatic effect of pressure from the arterial compartment into arterioles and capillaries of the target organs. A second possible mechanism suggests that even in the “uncomplicated phase,” patients with diabetes may lose the ability to lower blood pressure during sleep, even in the early stages of the disease. Data from a study...
using 24-hour intra-arterial blood pressure monitoring demonstrated that mean arterial pressure and heart rate both decrease significantly at night, compared with daytime values, in normotensive and hypertensive patients with and without diabetes.23 The results of another study,24 however, suggested that the nighttime decrease in arterial pressure and heart rate in hypertensive patients with diabetes may be only approximately 50% of the reduction observed in hypertensive patients without diabetes. In the absence of a decrease in blood pressure during sleep, patients with diabetes would therefore have a 24-hour blood pressure load that is greater than patients without diabetes for any given daytime blood pressure.

Blood pressure control in diabetes: current evidence and future strategies

It is becoming increasingly clear that it is difficult to control blood pressure to the degree that scientific evidence and guidelines indicate is necessary to provide adequate protection. An analysis performed several years ago by our group on 22 sets of blood pressure values from 13 hypertension trials showed that whereas diastolic blood pressure was often reduced to less than 85 mm Hg, SBP remained greater than 130 mm Hg, and even greater than 140 mm Hg in several studies.25 Moreover, in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT),26 only approximately 30% of patients with diabetes achieved blood pressure targets (defined as a blood pressure level of <130/80 mm Hg), compared with 60% of patients without diabetes (defined as a blood pressure level of <140/90 mm Hg).

In clinical practice, it appears that even fewer patients are being treated to target. A cross-sectional survey of diabetic patients determined that only 17.4% of respondents with concomitant hypertension had blood pressure controlled to less than 140/90 mm Hg, and this rate was not significantly different between the subgroups of patients with macroalbuminuria or microalbuminuria.27 In the ForLife study,28 only 3% of 2491 patients with diabetes and hypertension achieved blood pressure control to less than 130/80 mm Hg, in agreement with the ESH/ESC Guidelines.4 Whereas a further 14.9% achieved a blood pressure level between 130/80 and 140/90 mm Hg, 85.1% of the study population had blood pressure greater than 140/90 mm Hg.29 These data suggest that the rate of optimal blood pressure control is very low and that the target of 130/80 mm Hg is ambitious.

Improving blood pressure control in diabetic hypertensives

It is widely acknowledged that combination therapy is necessary to achieve adequate blood pressure control in patients with diabetes and hypertension. On average more than two antihypertensive agents were required to achieve adequate blood pressure control in the UKPDS study, and more than three were required in the Reduction of Endpoint in Non-Insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) and IDNT studies.20,21-23 In the HOT, Losartan Intervention For Endpoint reduction in hypertension (LIFE), and International Nifedipine GITS Study Intervention as a Goal in Hypertension Treatment (INSIGHT) studies, a greater proportion of hypertensive patients with diabetes required combination therapy compared with those without diabetes.13,30,31 Furthermore, despite the greater use of combination treatment, SBP values during treatment remained higher in patients with diabetes compared with those without. Current guidelines recommend that high-risk patients start with combination treatment.3,17-18 Three different 9-month treatment strategies were compared in the STRATegies of Treatment in Hypertension Evaluation (STRATHE) study.19 These included: (i) combination treatment (perindopril 2 mg plus indapamide 0.625 mg) with an increase in dosage according to patient response; (ii) sequential monotherapy strategy with atenolol initially, changing to losartan (if no response), then to amlopidine; and (iii) the classic step-by-step strategy with valsartan monotherapy, with an increase in the dose (if no response), and then combining valsartan plus hydrochlorothiazide. The combination treatment strategy was accompanied by a significantly greater rate of blood pressure reduction to less than 140/90 mm Hg (Figure 2).22 This difference was clear from the beginning of treatment and was mainly the result of a better decrease in SBP in the group treated by perindopril/indapamide.

Finally, evidence has been provided that not only office (or sphygmomanometric), but also 24-hour blood pressure have a major impact on cardiovascular morbidity and mortality. The Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study24 investigated home, office, and 24-hour ambulatory blood pressure measurements, and fatal events and their causality in a cohort of over 2000 patients followed for more than 12 years. Patients in whom blood pressure was normal when recorded by each of the three methods had a favorable outcome, but...
outcome, including both cardiovascular-related deaths and all-cause fatalities, worsened progressively as the number of methods that recorded an elevated blood pressure increased. This increased mortality occurred regardless of whether blood pressure elevations were detected on the basis of office versus ambulatory or office versus home blood pressure methods. Although it is acknowledged that epidemiology precedes treatment, it does provide information that can be used for treatment. Therefore, ideally, blood pressure control should be assessed not only by measuring office blood pressure, but also home and 24-hour ambulatory blood pressure. The practicality of implementing this in clinical practice (particularly in diabetic hypertensives), however, warrants further discussion.

ADVANCE trial: objectives and design

The difficulties in achieving blood pressure control in diabetic hypertensives as well the lack of information related to the benefits of blood pressure and blood pressure–lowering interventions on major vascular disease represent the background for ADVANCE, the largest multicenter, multinational, randomized prospective trial ever carried out in patients with type 2 diabetes. This trial had three major goals, which included a blood pressure–as well as a blood glucose–lowering arm. First, ADVANCE was planned with the aim of determining the effects of blood pressure reduction on macro- and microvascular disease. Specifically, the trial evaluated the effects of a fixed combination of an ACE inhibitor (perindopril) and a diuretic (indapamide) given on top of all other cardiovascular therapy on vascular events. Finally, ADVANCE was also aimed, in its blood glucose-lowering arm, at assessing whether more intensive blood glucose control (glycated hemoglobin levels <6.5%) could prevent microvascular as well as macrovascular disease and death.

The study population included patients aged 55 years or more and with type 2 diabetes. More than 70% of the enrolled patients were hypertensives and already under antihypertensive drug. Following a 6-week run-in phase, during which patients were assessed for their eligibility and likely compliance with treatment, patients were assigned to a randomized treatment. For the blood pressure–lowering arm of ADVANCE, participants were randomly assigned, on a double-blind basis, to perindopril–indapamide fixed-dose combination (initially 2.0/0.625 mg, increasing to 4.0/1.25 mg a day after 3 months) or matching placebo in addition to standard antihypertensive therapy, as required. For the glucose control arm of the study, participants were randomly assigned to an open comparison of a gliclazide-MR–based intensive glucose control regimen, targeting HbA1c levels of 6.5% or less, compared with a standard guidelines–based glucose regimen. Results of this glucose-lowering arm have been recently published, providing evidence on the benefits (~10% of the primary end point represented by combined macrovascular and microvascular events) of an intensive glucose-lowering intervention. The primary outcome of ADVANCE, which was the same for the two arms of the study, was a composite macrovascular end point (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death) and a composite microvascular end point (new or worsening nephropathy or microvascular eye disease), analyzed together or separately.

All suspected primary outcomes and all deaths were reviewed by an End Point Adjudication Committee that was blind to randomized treatments for both the blood pressure and the glucose control.
arms. The trial was an independent, investigator-led study, which was carried out in more than 200 clinical centers located in Europe, North America, Asia, and Australia. Coordination was performed at the University of Sidney, with participation of five coordinating centers located in the five aforementioned geographic areas of the world.

ADVANCE trial: main results

The results of the blood pressure-lowering treatment arm have been published in 2007 in Lancet. A total of 11 140 diabetic patients were randomized to active treatment or placebo. More than 2/3 of them, as already mentioned, were hypertensives and their entry mean blood pressure values were, despite treatment, well above the target recommended by current guidelines (145/81 mm Hg).

The results of the trial can be summarized as follows. First, administration of a fixed combination of indapamide and perindopril was associated with a greater reduction in systolic and diastolic blood pressure (5.6/2.2 mm Hg) than was placebo. This blood pressure difference was accompanied by a significant reduction in the combined incidence of macrovascular and microvascular complications (Figure 3). It was further accompanied by reductions of 14% in coronary events, 21% in renal events, and 14% in all-cause death (Figure 4). This leaves no doubt as to the protective effects of blood pressure-lowering strategies in diabetics. It also illustrates the value of strategies than can lower blood pressure more effectively than is commonly achieved in clinical practice. This because in ADVANCE blood pressure values achieved were 140/73 mm Hg in the placebo group and 136/73 mm Hg in the actively treated group, indicating that the beneficial effects are evident at blood pressure values below 140/90 mm Hg. This is also because the benefits are apparent not only in the hypertensive patients, but also in those who did not have a history of hypertension and/or who displayed initial blood pressure values below 140/90 mm Hg.

Three other aspects of the study are also worthy of mention. First, the patients recruited were well treated for the diabetic condition and for the frequent coexistence of cardiovascular risk factors, and more so during treatment than at baseline. As a result, average values were as follows: glycated hemoglobin 6.9%, total serum cholesterol 176 mg/dL, low-density lipoprotein (LDL) cholesterol 100 mg/dL, and triglycerides 66 mg/dL. This indicates that the benefit of the fixed combination of perindopril-indapamide administration occurred on top of what was an optimal cardiovascular preventive treatment. Second, reduction in renal events in the perindopril-indapamide group includes a 21% lower incidence of new-onset microalbuminuria. This suggests that the treatment employed in the study had a primary preventive effect on the appearance of diabetic nephropathy, a benefit presumably shown for ACE-inhibitor administration at blood pressure values higher than those explored in ADVANCE. Microalbuminuria and nephropathy considerably increase the already elevated cardiovascular risk of diabetes, in addition to shortening the life of the kidneys. Finally, the results of the ADVANCE are likely to considerably modify the idea that antihypertensive treatment of diabetes is difficult, frequently unsuccessful, and subject to great caution because of the high incidence of hypertension and other side effects.

Conclusions

The ADVANCE results provide evidence that the fixed combination treatment used in the trial and administered on top of all other drugs (antihypertensive drugs, statins, aspirin, and blood glucose-lowering agents) had a favorable impact on the elevated cardiovascular risk profile of the diabetic patient. This makes this therapeutic strategy mandatory in diabetic patients because, according to the ADVANCE trial results it is: (i) practical and affordable in clinical practice around the world; (ii) safe, well tolerated, and requires little monitoring; and (iii) effective in the majority of patients, independently of age, gender, baseline blood pressure, and level of cardiovascular risk.

In commenting on the ADVANCE trial results, an obvious question should be addressed, namely whether the study data imply that the fixed combination of perindopril-indapamide should become a routine therapeutic approach for patients with diabetes mellitus, even when blood pressure is not elevated. An analysis of the ADVANCE data suggest that this is the case, also considering the fact that the recent European Guidelines for the management of hypertension speak in favor of initiating antihypertensive treatment in diabetic patients even when blood pressure is still in the high-normal range.

REFERENCES

4. ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial); a randomized controlled trial. Lancet. 2007;370:829-840.
8. First International Study of Infarct Survival Collaborative Group. Randomised trial of intravenous atenolol among 10 027

**Le traitement du patient diabétique hypertendu : réflexions sur l'étude ADVANCE**

Les traitements visant à abaisser la pression artérielle des patients diabétiques hypertendus sont confrontés à un certain nombre de limites et ne se révèlent souvent qu’un succès clinique partiel. Ce scénario décevant peut s’expliquer de plusieurs façons, deux d’entre elles se distinguant : tout d’abord, la difficulté d’obtention d’un contrôle optimal de la pression artérielle ; et d’autre part, le fait que plus de 10 % à 15 % des diabétiques hypertendus traités en pratique clinique actuelle ne présentent des valeurs de pression artérielle inférieures à 130/80 mmHg, comme les directives le préconisent. Une autre raison pouvant expliquer cet état de fait est que les médicaments utilisés pour abaisser la pression artérielle élevée des diabétiques ne sont pas toujours capables d’exercer des effets cardioprotection et néphroprotection et donc d’améliorer le risque élevé de ces patients. L’étude ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation) a adopté une stratégie novatrice dans son approche thérapeutique de l’hypertension chez les diabétiques. Dans cette étude, la plus grande jamais réalisée sur le diabète, l’utilisation de l’association perindopril/indapamide a permis un contrôle efficace de la pression artérielle et a réduit de façon significative le risque des complications macrovasculaires et microvasculaires majeures présentées fréquemment par ces patients à haut risque. Les efforts positifs de cette association d’un inhibiteur de l’enzyme de conversion de l’angiotensine et d’un diurétique, assortis d’une excellente tolérance, en font le traitement de premier choix dans la prise en charge du patient diabétique.
What determines your choice between free and fixed combinations in the management of your hypertensive patients?

1 A. de la Sierra, Spain

The established view on antihypertensive therapy (and also the treatment plan used in most published clinical trials) is that treatment should commence with a single drug, with the possibility of combining two drugs being reserved for patients who do not achieve target blood pressure. However, recent guidelines suggest antihypertensive treatment may be initiated with a combination of two drugs at low doses. Also, when considering combination therapy, whether at the beginning of treatment or as add-on therapy, doctors frequently ask themselves if it’s better to use two agents separately (a free combination) or as a single tablet (fixed-dose combination). What are the advantages and disadvantages of fixed-dose combinations? There are obviously some disadvantages but, fortunately, most remain theoretical. Firstly, a combination of two agents may increase the number of adverse reactions. If this occurs when using a fixed-dose combination, it may be more difficult to identify the causal agent of the adverse effect. Moreover, if this usually implies down titration or interruption of the drug responsible, it is usually difficult to proceed without modifying the entire treatment. However, recently developed antihypertensive drugs are almost free of side effects and the sum of two drugs with side effects does not usually result in an increase. In fact, some reports suggest that combining low-dose diuretics or calcium channel blockers (CCBs) with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) reduces the deleterious metabolic effects of diuretics and the pedal edema associated with CCBs, in comparison with when these agents are used in monotherapy. Secondly, most fixed-dose combinations are not available at low doses and doctors are concerned about an excessive blood pressure drop if a fixed-dose combination is used as initial therapy. Therefore, combinations containing low doses of both antihypertensives, such as the perindopril/indapamide combination, are preferable when used as initial therapy. In contrast, the greatest advantages associated with antihypertensive treatment based on fixed-dose combinations are the improvement in compliance and the achievement of earlier blood pressure control in a higher proportion of patients with a single tablet. The latter is extremely important in high-risk hypertensives, as was clearly demonstrated in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, where the benefits observed in the group receiving amlopidine were associated with a greater and more rapid blood pressure reduction. Two recent trials have clearly shown the benefits of antihypertensive treatment based on fixed-dose combinations, either as add-on antihypertensive treatment or as initial treatment. The Action in Diabetes and Vascular disease: PreterAx and Dia- microN-MR Controlled Evaluation (ADVANCE) trial used the fixed-dose combination of perindopril and indapamide in more than 11 000 type 2 diabetic patients, hypertensives, or normotensives. Even when used on top of other drugs blocking the renin-angiotensin system, such as an ACE inhibitor or an ARB, treatment with perindopril and indapamide significantly reduced the rate of combined microvascular and macrovascular events (9%) and total (14%) and cardiovascular (18%) mortality. The other trial in favor of fixed-dose combination, whose findings are not yet published, is the Avoiding Cardiovascular events through COMBination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial. This trial used two fixed combinations of an ACE inhibitor with either a CCB or a thiazide diuretic in high-risk hypertensives (60% diabetics). Beginning treatment with such fixed-dose combinations was associated with a high percentage of patients whose blood pressure was controlled (80%) and with an unexpectedly low proportion of add-on antihypertensive treatments required. As mentioned above, fixed-dose combinations are also associated with better compliance than free combinations. This is essentially related to the simpler therapeutic scheme and the lower number of pills. This better compliance is important for all types of patients, including younger patients, because they will need antihypertensive therapy for a longer period of time in order to adequately prevent lifelong complications, as well
as for high-risk patients with multiple comorbidities and on polypharmacy, who usually require several treatments for these comorbidities. All efforts to simplify the therapeutic scheme are therefore welcome. In conclusion, a greater proportion of hypertensive patients are candidates for treatment with a combination of two antihypertensives to achieve better blood pressure control and more efficacious cardiovascular protection. Fixed-dose combinations represent an alternative to free combinations. They are associated with documented better protection in high-risk patients and their use also improves treatment adherence. Based on these arguments they are the treatment of choice for most hypertensive patients.

REFERENCES

O ne of the most fascinating moments in the history of medicine was the discovery of substances in the human blood able to induce major changes in function in multiple tissues when Robert Adolph Armand Tiberstedt, a physician from the Karolinska Institute, and his young collaborator Ron Bergman discovered renin in 1898.1 They were far from imagining that their extraordinary contribution to the understanding of a new system would continue to this day to yield surprising insights. Pharmacotherapy targeting the renin-angiotensin system (RAS) is one of the most successful strategies for the treatment and control of a number of diseases such as: hypertension, stroke, heart failure, proteinuria, and ischemic heart disease, particularly in type 2 diabetic patients.2 Renin was discovered in 1898 by Tiberstedt.3 The first ACE inhibitor to be developed, in 1975, was captopril, which was shown to increase survival in patients with heart failure thanks to its antihypertensive efficacy. This was followed by a spate of basic science and clinical studies that evidenced new effects of angiotensin-converting enzyme inhibition relative to the kinin-kallikrein system, mitotic activation, and its role as indirect modulator of the thrombotic system, principally via angiotensin (Ang) IV.4 Nevertheless, despite the success of drugs that block RAS activity, the prevalence of cardiovascular disease (CVD) has been increasing steadily over the past several decades. This has led many researchers to conclude that new approaches and drug targets must be discovered in order to develop more effective therapeutics for both better control and eventual cure of CVD. In this regard, the discovery of ACE2 and the pronin receptor (PRR) are extremely relevant because they provide novel targets for CVD therapeutics.5 Robust evidence has confirmed that the ACE inhibitors have a major role in the treatment of CVD. Their therapeutic efficacy and safety is so far superior to that of other drug classes, and for the first time it was possible to demonstrate that a drug was able to increase both quality and quantity of life in patients with heart failure.6 Paradoxically, their principal side effect, cough, which occurs in around 10% to 20% of patients, and which is related to the capability of ACE inhibitors to block the breakdown of bradykinin, may be useful as bradykinin is a powerful vasodilator. The discovery of specific angiotensin II type 1 (AT1) receptors showed that this receptor played a crucial in vascular injury and mitotic effects via Ang II.7 However, despite the numerous large trials that have attempted to prove the superiority of other treatment strategies, the ACE inhibitors remain unparalleled to date, and their use in combination to elicit double renin-angiotensin-aldosterone system blockade has now also been approved.8 ACE inhibition increases the levels of Ang (1-7). Over the last 5 years, several studies have demonstrated the crucial role of Ang (1-7) as a vasodilator and antithrombotic peptide in cardiovascular drug therapy. In addition, new pathophysiological mechanisms have been discovered in connection with the currently available RAS blocking agents (ACE inhibitors and angiotensin receptor blockers [ARBs]), which heighten the potential therapeutic impact of Ang (1-7) in clinical practice.9 Another relevant point to keep in mind is the role of sodium in hypertension. More than 50% of hypertensive...
patients are salt-sensitive, and this disorder increases with the patients’ age. Indapamide is a diuretic that possesses all the properties of hydrochlorothiazide and the same potency, but is free of effects on carbohydrate metabolism. Based on findings from the most recent large clinical trial (PROGRESS, \(^{10}\) ADVANCE, \(^{12}\) HYVET, \(^{13}\) ASCOT-BPLA, \(^{14}\) CONSENSUS) and the outcomes of ONTARGET, STITCH, and others, there is now strong evidence that a fixed-dose combination of ACE inhibitor and indapamide is beneficial in the treatment of hypertension. Finally, although there is class effect of ACE inhibitors, important differences have been evidenced that may be relevant for combined therapy. Perindopril elicits a rapid increase in bradykinin levels, and yet the rate of cough was found to be lower in the PERTINENT study, which suggests that other mediators of cough exist apart from bradykinin. Further studies are needed to clarify this point. The benefits of fixed-dose combination therapy, based primarily on RAS blockade and ACE inhibition plus indapamide, amlodipine, and others at appropriate dose are now well established. \(^{15}\) Compliance and adherence to treatment are paramount to achieve vascular and target-organ protection. In addition, the individual pathological and comorbidity profile of each hypertensive patient should also be taken into consideration, including genetic and sociocultural aspects, when selecting a first-line antihypertensive drug therapy.

REFERENCES


TRIAL ACRONYMS

ADVANCE Action in Diabetes and Vascular disease: PreterAx and Diamicron-MR Controlled Evaluation

ASCOT-BPLA Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm

CAFÉ Conduit Artery Function Evaluation trial

HYVET Hypertension in the Very Elderly Trial

ONTARGET ONGoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial

PERTINENT PERindopril-Thrombosis, InflammatioN, Endothelial dysfunction and Neurohormonal activation Trial

PROGRESS Perindopril rPOsition aGainst REcurrent Stroke Study

STITCH Simplified Treatment Intervention to Control Hypertension
R. R. Azar, Lebanon

Recent hypertension guidelines recommend starting a combination of two antihypertensive agents in the treatment of patients with blood pressure 20/10 mm Hg above of its target. This is based on the knowledge that monotherapy alone is not sufficient to control blood pressure in this category of patients. In addition, even in patients with mild hypertension, combination therapy with two agents at low dose allows a superior reduction in blood pressure and a lower rate of side effects when compared with a single agent at high dose. This has led the pharmaceutical industry to develop multiple fixed combinations of antihypertensive agents that can be used in the treatment of mild-to-moderate hypertension. Fixed antihypertensive combinations have many advantages over free combinations. The compliance rate is higher in patients receiving fixed-dose combinations. This is an important issue because antihypertensive drugs are a lifelong treatment. The National Council on Patient Information and Education estimated that the compliance rate is just over 30% for chronic conditions like hypertension. Polyprescription is among the most important causes of non-compliance. Persistence on therapy decreases as the number of pills taken per day increases. Sturkenboom et al. compared compliance rates between fixed-dose and free combination therapies of angiotensin-converting enzyme (ACE) inhibitors and diuretics in 755 hypertensive patients. Persistence with treatment was 12% lower (at 1 and 2 years) in patients on two pills versus patients on a one pill combination. Similarly, Bangalor et al. performed a meta-analysis of nine studies of 20,242 patients with various chronic conditions who were on fixed versus free drug combinations. Fixed-dose combinations resulted in a 24% greater patient compliance compared with free drug combinations. Another advantage of fixed combinations is the overall reduction in cost of treatment because the patient is buying a single medication rather than two separate drugs.

Finally, fixed combinations contain two drugs that work well together. The combination is usually “ideal,” allowing enhancement of each drug’s antihypertensive effect and attenuation of each other’s side effects (i.e., the hypokalemia caused by thiazide diuretics can be prevented by concurrent use of an ACE inhibitor). Fixed combinations, however, may have disadvantages over free combinations. The physician does not have the freedom of choosing and titrating the dose of an individual component because they usually come with fixed doses. For example, the dose of one of the two components may not be high enough to obtain a specific effect (i.e., more potent diuresis or an effect beyond blood pressure lowering). In addition, most of the fixed combinations available contain a diuretic and/or a β-blocker. Recent studies comparing “new” drugs (calcium channel blockers + ACE inhibitors or angiotensin receptor blockers (ARBs) versus “old” drugs (diuretics + β-blockers) have shown the superiority of “new” antihypertensive combinations in reducing the morbidity of hypertension. Fixed combinations containing an ACE inhibitor (or ARB) and a calcium channel blocker are less available in some parts of the world, and may be more expensive than a free combination of generic drugs. Finally, if a side effect occurs, substitution of the responsible drug is easier in free compared to fixed combinations. In conclusion, to the question “What determines your choice between fixed and free fixed combinations in the management of your hypertensive patients?” my answer is the availability of the two drugs I want to use in a single pill at the appropriate dosage (the dose proven in clinical trials to reduce morbidity and mortality of hypertension). Compliance with treatment is the most important issue in a lifelong therapy. I have no doubt that compliance is much better with fixed combination, especially in patients on polypharmacy who have multiple risk factors or multiple co-morbidities.

REFERENCES

In the management of hypertension, low-dose monotherapy is recommended as initial therapy. If blood pressure is not controlled, the initial drug may be given at full dose or a new drug of a different class may be substituted especially if there is no response to the first agent. Although this “sequential monotherapy” approach may allow individualized therapy, it is not a popular choice for the practicing clinicians and patients. It is time-consuming and laborious, and many patients are frustrated that their blood pressures remain uncontrolled with this empirical trial-and-error approach. Furthermore, achievement of target blood pressure goals usually does not exceed 20% to 30% of all hypertensive patients with monotherapy. Major clinical trials have shown that target blood pressures can be achieved with a combination of two or more drugs. The concept of combination therapy is not new. Antihypertensive drugs of different classes can be combined if they have different and complementary mechanisms of action. Often the combined antihypertensive effect is greater than that of either component alone. Recent guidelines now recommend the use of combination therapy as an alternative to monotherapy in the initial therapy for hypertension. The advantages of using this approach are:

- Blood pressure goals and targets can be achieved more effectively and earlier and in more patients, which is of critical importance especially in high-risk patients.
- Adverse reactions or side effects may be fewer because of the smaller doses of individual medications than with single agents at higher dose. Combination therapy can be given either as a free or fixed combination. The advantages of free combination are flexibility in dosing and timing. Each drug can be titrated and adjusted according to the patients’ blood pressure responses. However, multiple drugs have the potential of becoming very complex and expensive for the patients. In practice, most drugs used in combination therapy are often given together at standard doses. Fixed combination is therefore much preferred. It is convenient and easy to prescribe by busy clinicians and convenient for the patients. The cost of fixed-dose combinations is usually less than that of the constituents prescribed separately. In my practice, I usually start low-dose monotherapy in patients with mild hypertension, especially in the elderly, many of whom respond well to monotherapy. However, most of my patients often require two or more antihypertensive medications especially the diabetic, renal, and high-risk patients. However, many patients are not keen to start with more than one drug as they are wary of the side effects associated with multiple-drug therapy, especially diabetic and high-risk patients who are already taking many other medications. One approach is to titrate each individual component and once the appropriate dose of each is reached, an appropriate fixed-dose combination that contains the same doses of each component can then be given. Another approach is to substitute the initial monotherapy with a fixed-dose combination when the former fails to control the blood pressures to target. The latter approach often achieves blood pressure control earlier and causes less frustration to patients, with minimal changes in medications and pills. Reducing the number of pills necessary to control hypertension is an important factor in improving blood pressure control and compliance. When patients see fewer pills to control their blood pressure, psychologically, they perceive their hypertension as less severe and well under control. They will be happy with the treatment and less likely to try another complementary approach, which often results in noncompliance with the antihypertensive therapy. It is also not uncommon that patients do not take all the medications as prescribed. They may intentionally reduce the dosage or omit some tablets, often claiming side effects as a reason, while in fact, for cultural reasons, they feel that too many “Western” medicines are harmful to one’s body. Fixed-dose combination therapy with fewer pills will thus contribute to a better rate of patient adherence to therapy and a better outcome. Only a small number of my patients are not on fixed-dose combination, in the following cases:

- When fixed-combination dosages are not appropriate.
- When fixed combination of the two drugs are not available at our hospital, and
- When patients cannot tolerate combined dosages taken at the same time.

There are many fixed-dose combinations available on the market. The β-blocker atenolol and dihydropyridine calcium antagonist nifedipine fixed-dose combination is popular among many general practitioners in Singapore as it is relatively inexpensive, effective, and relatively free of side effects. The concern with this combination is whether it is effective with once-a-day dosing. The combination of a thiazide diuretic and a β-blocker is also a time-honored combination, which has been used successfully in many trials. But this combination is not very commonly used in practice as most clinicians are concerned about the dysmetabolic side effects when they are administered together, especially to diabetic and dyslipidemic patients. Angiotensin-converting enzyme (ACE) inhibitor and thiazide-like diuretic (perindopril/indapamide), and thiazide diuretic and angiotensin receptor antagonist (ARB) fixed combinations (hydrochlorothiazide and losartan/sartan/candesartan/ telmisartan) are the most commonly used fixed combinations. The combination of a diuretic and ACE inhibitor or ARB is well tolerated and highly effective. Both classes of drugs have reduced morbidity and mor-
tality in long-term outcome trials in hypertensive patients. More recently, the Action in Diabetes and Vascular disease: PreterAx and Dia-micronN MR Controlled Evaluation (ADVANCE) trial showed that the combination of perindopril/indapamide reduces mortality in type 2 diabetic patients, irrespective of their blood pressure. The combination is useful in elderly and blacks with low-renin hypertension, and in patients with heart failure, left ventricular dysfunction, diabetic nephropathy, and left ventricular hypertrophy. In conclusion, fixed-dose combinations often contain the appropriate drugs at the effective dosage, with minimal side effects. They are easy and convenient to use and simplify the treatment regimen. They improve cost-effectiveness and compliance. For all these reasons, they preferred by many clinicians and patients.

5. T. Ecder, Turkey

The primary goal of treatment of hypertensive patients is to achieve maximum reduction in the long-term total risk of cardiovascular morbidity and mortality. This starts with the lifestyle modifications and with the addition of different antihypertensive agents. According to current guidelines, blood pressure should be reduced to at least below 140/90 mm Hg and to lower values, if tolerated, in all hypertensive patients. Target blood pressure should be less than 130/80 mm Hg in diabetics and in high- or very-high-risk patients, such as those with associated stroke, myocardial infarction, renal dysfunction, or proteinuria. Many hypertensive patients need the combination of two or more drugs to reach blood pressure goals. In patients with stage 2 hypertension, therapy should be started with a combination. Moreover, combination treatment should be considered as first choice particularly when there is a high cardiovascular risk, such as subclinical organ damage, diabetes, or renal or cardiac disease. Starting treatment with a two-drug combination allows blood pressure targets to be reached earlier than with monotherapy, which is of critical importance in high-risk patients. The 2007 European Society of Hypertension and European Society of Cardiology (ESH/ESC) Guidelines for the Management of Arterial Hypertension recommend starting therapy with a two-drug combination at low doses in patients with marked blood pressure elevation, in patients with high/very high cardiovascular risk, and in conditions with a lower blood pressure target. If the target blood pressure level is not reached, increasing the previous combination to full dose or adding a third drug at low dose is recommended. The advantages of combination therapy are that the antihypertensive efficacy can be maximized by the additive effects. Moreover, the two drugs can be given at low doses, which are more likely to be free of side effects compared with full-dose monotherapy. The combination therapy can be given either as a free or fixed combination. Free combination of different drugs allows upward and downward dose titration of each agent. However, it has the disadvantage of using a higher number of pills. This is an important drawback, especially in high-risk patients who need to use several other medications, such as statins, antiplatelet agents, and additional antihypertensive agents. Combinations of two drugs in a single tablet, usually at low doses, are now widely available, particularly those of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) with a diuretic or with a calcium channel blocker. Although the fixed combination limits the flexibility of upward and downward dose titration, it has several advantages. Fixed combinations reduce the number of tablets to be taken by the patients, which increases compliance with treatment and improves the rate of hypertension control. The results of the ADVANCE (Action in Diabetes and Vascular disease: PreterAx and Dia-micronN-MR Controlled Evaluation) trial suggest that the use of a fixed combination has the advantage of reducing the risks of major vascular events and death in patients with type 2 diabetes mellitus. The ADVANCE trial was designed to assess the effects on vascular disease of a fixed combination of the ACE inhibitor perindopril, and the diuretic indapamide, in a diverse population of patients with type 2 diabetes and a broad range of blood pressure values. This study showed that the addition of a fixed combination of perindopril and indapamide on the background therapy of patients with type 2 diabetes significantly reduced the risks of death and major macrovascular or microvascular complications, irrespective of initial blood pressure level. The fixed combination regimen used in ADVANCE was also well tolerated. In conclusion, fixed combinations have the advantage of ensuring early and effective blood pressure control in hypertensive patients with cardiovascular disease. These are generally well tolerated and can be given once daily, providing better compliance with treatment.
Treatment of hypertension may be initiated either with monotherapy or combination therapy. According to the European Society of Hypertension/European Society of Cardiology (ESH/ESC) 2007 Guidelines, treatment with combination therapy is recommended in patients at higher cardiovascular risk: particularly those with high blood pressure values or multiple risk factors, subclinical organ damage, diabetes mellitus, or renal or cardiovascular disease. Both forms of combination therapy—free and fixed drugs combinations—have their advantages and disadvantages. Simplification of therapy using fixed-dose combination preparations significantly increases patient motivation to comply with the therapy, as well as their satisfaction. Usage of fixed doses of two antihypertensive drugs increases the probability of achieving target blood pressure in more patients and earlier, thus decreasing the number of follow-up visits, titrations of doses, and modifications of preparations used. Furthermore, it is also cost-effective. However, fixed-dose combinations have their disadvantages as well. It is more difficult to find the most appropriate dose, although some of the combinations are available in a wide range of dosages now. If patients present with side effects, it is more difficult to determine which substance is the one responsible for them. In my opinion, fixed-drug combinations should be preferred in patients suspected to be poor compliers, as reduction in the daily number of pills increases compliance. It should also be the therapeutic approach of choice when the patient does not require any particular proportions of doses of the drugs used. An example of such a situation may be moderate hypertension (stage 2) when only one pill per day may help achieve normal blood pressure values. The STRAtegies of Treatment in Hypertension: Evaluation (STRATHE) study, which compared the antihypertensive effectiveness of three approaches to treatment initiation: (i) fixed-dose combination (perindopril/indapamide); (ii) sequential monotherapy (atenolol switched to losartan and further to amlopidine); and (iii) stepped-care approach (valsartan uptitrated, and hydrochlorothiazide added) in 533 patients with hypertension of at least moderate severity. Initiation of treatment with fixed-dose combination was found to be the most effective. Another example of a situation in which I prefer fixed-dose combinations is mild-to-moderate hypertension with concomitant diabetes. The goal for blood pressure values is lower than standard and often more than one drug is needed to achieve it. Therefore, fixed-dose combination treatment, adding one pill only to the number already taken by the patient may help maintain compliance high and allows for early target blood pressure achievement. The Action in Diabetes and Vascular disease: PreterAx and Diamicron-MR Controlled Evaluation (ADVANCE) study has also shown that the fixed-drug combination of an angiotensin-converting enzyme (ACE) inhibitor and a diuretic could reduce the risk of macro- and microvascular complications in diabetic patients, irrespective of initial blood pressure values. This study included 11,140 type 2 diabetic patients with cardiovascular disease or at least one risk factor, and the observation lasted for 4.3 years. In my clinical practice free-drug combinations are a preferable option for antihypertensive treatment when maximal doses of drugs are required, for example as with the ACE inhibitors in hypertension concomitant with heart failure. Also, patients with a history of multiple side effects are more likely to develop side effects during a future treatment, and should be preferably given free combination, which allows easy withdrawal of the drug responsible for the unwanted effect. I would also recommend this approach in the event that high dosages of drugs (exceeding doses used in fixed-dose combinations) are expected to be necessary to reach target blood pressure values. In summary, clinical situations when free combinations are to be preferred include: severe hypertension; when high doses or three-drug combination treatment are needed; patients with a history of multiple side effects; heart failure concomitant with hypertension; left ventricular hypertrophy in a patient with hypertension (higher dose of ACE inhibitor preferred); or hypertension in a post–myocardial infarction patient when a β-blocker not used in fixed drug combinations is required.

REFERENCES
here is now universal agreement among authoritative guidelines, that the great majority of patients with hypertension will need combination treatment to achieve recommended targets. Indeed, the most recent European guidelines state that concentration on choice of initial drug is outdated due to the need for combination treatment in most cases. This is because the combination of drugs with different primary actions increases efficacy, while permitting the use of lower doses that decrease side effects and improve tolerability. These guidelines also stress the advantage of fixed combinations in improving adherence and thus, contributing to improving the efficacy of treatment. The increasing complexity of chronic illness in an aging population, and increasing awareness of the need to address total cardiovascular risk, have multiplied the number of drugs the patient has to take everyday and sometimes 2 or 3 times a day. It is not uncommon for a patient with previous myocardial infarction to have hypertension, and diabetes requiring 2 blood pressure–lowering drugs, 2 oral hypoglycemic agents and a β-blocker, an angiotensin-converting enzyme (ACE) inhibitor, a statin, and aspirin for the coronary disease—a total of 8 drugs. Elderly patients may be taking 10, 12, or more drugs each day. Any measures that simplify the therapeutic regimen will be welcomed by patients and it makes great sense to reduce the number of tablets a patient has to swallow, by combining some of the drugs into a fixed-dose combination. Many physicians have an ingrained resistance to the use of fixed combinations, preferring to titrate each individual drug to optimal dose, before introducing the next drug. However, the weight of opinion, exemplified by the guidelines quoted earlier, is slowly moving toward the use of fixed combinations.

Factors favoring the choice of fixed combinations
Most physicians will be tempted to use a fixed-dose combination (see Box below) for patients at high cardiovascular risk, who have multiple risk factors and comorbidities and a relatively high current level of the pressure, the target blood pressure the physician is aiming to achieve, and the magnitude of the gap between these two pressures. Yet another factor will be the blood pressure–lowering drugs that the patient may already be taking and the doses of these drugs, since if there is a fixed dose combination available for these same drugs, at the same doses, the switch to a fixed dose combination becomes simple. Finally, of course, the availability of a fixed-dose combination that combines the two drugs that the physician wishes to prescribe in a dosage that suits the purpose. Another consideration may well be the availability of this fixed-dose combination in multiple strengths, so that the physician can start with a low dose form and increase the dose progressively.

Factors that will influence the choice of free or fixed combinations of blood pressure–lowering drugs
Two of the main factors will be the number and complexity of comorbidities and risk factors that accompany the patient’s hypertension, and the number of drugs the patient is already taking (see Box below). The patient’s total cardiovascular risk will plainly be a major influence. Factors relating to the blood pressure will include the

Factors favoring the use of fixed-dose combinations
◆ High total cardiovascular risk
◆ Presence of comorbidities (especially diabetes, coronary, cerebrovascular, and renal disease)
◆ Multiple cardiovascular risk factors
◆ High levels of blood pressure—especially systolic
◆ Low target blood pressure
◆ Availability of suitable fixed-dose formulation
◆ Patient already stabilized on separate components of a fixed-dose combination
◆ Evidence of efficacy from randomized clinical trials

Factors influencing the choice of fixed or free combinations
◆ Number of comorbidities present
◆ Number of risk factors needing drug therapy
◆ Total cardiovascular risk
◆ Level of blood pressure—especially systolic blood pressure
◆ Target blood pressure
◆ Availability of suitable fixed-dose formulations

Free or fixed antihypertensive drug combinations?
Free or fixed antihypertensive drug combinations?

**FACTORS FAVORING THE USE OF FREE COMBINATIONS**

- Traditional preference for dose titration of individual drugs
- Lack of formulation combining the two preferred drugs
- Lack of formulation combining the desired drugs in the preferred dosage

**REFERENCES**


For years, hypertension experts have argued that monotherapy seldom gets blood pressure (BP) down to target and that combination therapy is a better treatment option. Numerous regular and low-dose fixed combinations are available nowadays. We can choose between thiazide- or nonthiazide-based preparations. But many clinicians are still reluctant to start off with a combination therapy, keeping this approach as a preferential option for severe and/or resistant hypertension. With recent consensus reports endorsing the need for more intensive BP control below traditionally accepted levels in much larger patient populations, there is a far greater need for initial combination therapy. According to the European Society of Hypertension/European Society of Cardiology (ESH/ESC) recommendations, such a therapeutic strategy may be valuable in all patients, regardless of the severity of hypertension, but preference should be given to fixed low-dose combinations as initial therapy. According to US experts, the use of first-line combination therapy should be considered in patients with systolic blood pressure (SBP) ≥160 mm Hg and/or diastolic blood pressure (DBP) ≥100 mm Hg. Until recently, advocates of initial fixed-dose combination therapy had no data to make their case. The results from recent clinical trials have changed the situation. The Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA) and Avoiding Cardiovascular Events through COMbination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial provided very important data through comparison of efficacy and tolerability of different combinations of antihypertensive agents. As a consequence, the traditionally popular combination of a thiazide diuretic and a β-blocker is under revision at least in patients with the metabolic syndrome or at high risk of incident diabetes. The ACCOMPLISH data strongly supported combination antihypertensive therapy as a comprehensive strategy and confirmed the high value of the angiotensin-converting enzyme (ACE) inhibitor/calcium channel blocker (CCB) combination. After the VALsartan antihypertensive Long-term Use Evaluation (VALUE) trial, we know that if BP in high-risk hypertensives is not controlled well within the first 6 months, we get higher morbidity and mortality. So time to target BP is probably an important consideration in high-risk hypertensive patients. The data from the Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation (ADVANCE) trial significantly broadened our experience with fixed-dose antihypertensive therapy by demonstrating its efficacy, safety, and good tolerability in type 2 diabetic patients irrespective of initial BP level or the use of other antihypertensive drugs. The STRATEGies of Treatment in Hypertension: Evaluation (STRATEGE) trial clearly demonstrated that a therapeutic strategy based on fixed low-dose perindopril/indapamide combination was more effective in achieving target BP than “step-by-step” or sequential monotherapy approaches. Thus, in view of all currently available data, it is time to put the old “start low, go slow” strategy to rest. What determines the choice between free and fixed combinations in the management of hypertensive patients? First of all, the advantages and disadvantages of both regimes. For fixed-dose combinations these are summarized in Table I. The advantages presented in Table I are in favor of the used of fixed-dose combinations, while the situations listed as disadvantages support the use of free combinations. The choice of free or fixed combinations should take into account both the individual patient’s clinical profile (eg, other cardiovascular risk factors, concomitant diseases limiting the use of particular classes of antihypertensive drugs or requiring a special titration regimen), and the potential of the combination to prevent or reverse target-organ disease. Low-dose fixed combination could be the initial treatment for mild BP elevation with a low or moderate total cardiovascular risk. It is a good initial choice in uncomplicated hypertensives and in the elderly, where antihypertensive therapy should normally be initiated gradually. Switching from ineffective monotherapy is another option for low-dose fixed combinations. But low-dose combinations, even if more effective in lowering BP than monotherapies, do not allow BP normalization in every patient at the initial dose and it is occasionally necessary to use a combination containing the same components, but at higher doses. A combination of two drugs at regular doses should be preferred as first-step treatment in the presence of grade 2 or 3 initial BP or when total cardiovascular risk is high or very high. In high-risk hypertensives, target BP should be achieved more promptly, which favors initial regular-dose combination therapy and quicker adjustment of doses. If we are looking to achieve SBP/DBP reduction of more than 30 mm Hg, we should start in most cases with a free full-dose combination. But the fixed combination of a regular-dose combination (eg, ACE inhibitor/diuretic) with an addi-
tional drug (eg, CCB) is also an option. We can also start with a free combination of two agents and then substitute it with a fixed-dose preparation. This approach is usually tried in inpatients or outpatients with exacerbated arterial hypertension. Treatments with lower and higher doses of the same agents are becoming more and more popular. This means that we can resort to “step-by-step” strategy with regard to combination therapy. Moreover a “step-down” scheme in patients with well controlled BP may also be used. The treatment of hypertension is being increased increasingly complex, but in everyday practice, a simpler, easier approach is generally sufficient. The Simplified Treatment Intervention to Control Hypertension (STITCH) trial has clearly demonstrated the advantages of a simplified approach to antihypertensive treatment with fixed-dose combinations. Initial combination therapy is very effective, and there is now substantial evidence to broaden the use of combination therapy as initial treatment. At this point, continued hesitation about the use of combinations, whether free or fixed-dose, does more harm than good.

REFERENCES

LARGE INTERVENTION TRIALS HAVE CLEARLY DEMONSTRATED THAT MONOTHERAPY IS ABLE TO ADEQUATELY CONTROL BLOOD PRESSURE LEVELS ONLY IN ABOUT 30% OF HYPERTENSIVE PATIENTS, THEREBY SUGGESTING THAT COMBINATION THERAPY IS NEEDED IN THE MAJORITY OF PATIENTS. ACCORDINGLY, THE EUROPEAN SOCIETY OF HYPERTENSION/EUROPEAN SOCIETY OF CARDIOLOGY (ESH/ESC) GUIDELINES FOR THE MANAGEMENT OF ARTERIAL HYPERTENSION, PUBLISHED IN 2007, STATED THAT INITIAL TREATMENT CAN MAKE USE OF MONOTHERAPY OR COMBINATION OF TWO DRUGS AT LOW DOSES WITH A SUBSEQUENT INCREASE IN DRUG DOSES OR NUMBER, IF NEEDED. THE AVAILABILITY OF FIXED COMBINATIONS OF ANTIHYPERTENSIVE DRUGS HAS CERTAINLY IMPROVED ANTIHYPERTENSIVE THERAPY BY REDUCING THE DAILY NUMBER OF PILLS, WHICH IS INVERSELY CORRELATED WITH THE PATIENT’S ADHERENCE TO THE TREATMENT. THIS INFLUENCE ON COMPLIANCE IS FURTHER CORROBORATED BY THE OBSERVATION THAT DESPITE THE LIMITATIONS IN TERMS OF FLEXIBILITY OF UPWARD AND DOWNWARD TITRATION ATTACHED TO THE FIXED DOSES OF THE COMBINATION COMPONENTS, THE USE OF FIXED COMBINATIONS IN THE TREATMENT OF HYPERTENSION IS LARGER THAN IN ANY OTHER THERAPEUTIC FIELD. THIS BEING SAID, IF FIXED COMBINATIONS REPRESENT THE FIRST CHOICE, WHY ARE MANY PHYSICIANS STILL USING FREE COMBINATIONS? IN MY OPINION, THE MAIN DETERMINANT OF THIS CHOICE IS THE CLINICAL CHARACTERISTICS OF THE PATIENTS. FIRST OF ALL, WE HAVE TO CONSIDER THE SEVERITY OF HYPERTENSION. IN A PATIENT WITH GRADE 1 HYPERTENSION, THE PROBABILITY THAT ONE DRUG ALONE WILL ACHIEVE SATISFACTORY BLOOD PRESSURE CONTROL IS QUITE HIGH, AND IT IS THEREFORE JUSTIFIED TO START WITH ONE DRUG AND, SUBSEQUENTLY, IF THE BLOOD PRESSURE RESPONSE IS NOT SATISFACTORY, TO ADD A NEW DRUG AS A FREE COMBINATION, SO THAT THE INITIAL PRESCRIPTION CAN BE MAINTAINED. THE OBVIOUS ADVERSEITY OF INITIATING TREATMENT WITH TWO DRUGS IS THAT OF POTENTIALLY EXPOSING SOME PATIENTS TO AN UNNECESSARY AGENT. ON THE CONTRARY, IN A PATIENT WITH STAGE 2 OR 3 HYPERTENSION, IT MAKES SENSE TO START WITH A COMBINED PREPARATION. SINCE IT HAS BEEN DEMONSTRATED THAT EARLY CONTROL OF BLOOD PRESSURE IS ASSOCIATED WITH BETTER IMPROVEMENT IN CARDIOVASCULAR PROGNOSIS, FURTHERMORE, USE OF COMBINATION THERAPY HAS BEEN FOUND TO BE EVEN MORE FREQUENTLY NEEDED IN DIABETIC, RENAL, AND HIGH-RISK PATIENTS, AND IN GEN-

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eral whenever lower blood pressure targets are pursued. All fixed combinations of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor antagonists (ARBs) and diuretics utilize thiazides, and it is well known that the latter are contraindicated in patients with severe renal impairment. This explains why it is necessary to prescribe free combinations with loop diuretics in those patients. Similarly, combinations of thiazide diuretics and a β-blocker are also largely used, but evidence is now available that these drugs have unfavorable metabolic effects, which may be even more pronounced when they are administered together. On the contrary, β-blockers with vasodilating properties, such as carvedilol and nebivolol, which have less or no dysmetabolic action as well as a lower incidence of new-onset diabetes compared with classic β-blockers, are not available in fixed combinations. Furthermore, the combination of a thiazide and a potassium-sparing diuretic has been widely used for years in order to prevent the loss of potassium associated with thiazide administration, possibly preventing glucose intolerance and decreasing the incidence of diabetes associated with thiazide-induced hypokalemia. Thus, in patients with metabolic syndrome and when there is a high risk of incident diabetes, it is mandatory to use a free combination of vasodilating β-blockers and diuretics.

**REFERENCES**


**Free or fixed antihypertensive drug combinations?**

**Controversial Question**

P. Ramachandran, India

The benefit and safety of an aggressive strategy to reduce blood pressure to a target of below 140 mm Hg systolic and 90 mm Hg diastolic has been clearly demonstrated.1 Hypertension-induced stroke appears to be largely preventable, and a significant reduction is seen in hypertension-attributable coronary artery disease.2 However, reaching and maintaining this target is a challenge in the majority of patients. Clinical practice has been to begin monotherapy with an antihypertensive agent and follow a stepped up, sequential drug strategy till the blood pressure target is reached. However, in many cases, stepping up the dose leads to only modest increases in blood pressure response at the cost of more frequent or severe side effects,3 and most patients need more than one drug either as multiple “free” individual drugs, or as a fixed-dose combination (FDC). Compliance with treatment is a sine qua non for the successful long-term management of hypertension. FDCs have a major advantage because they simplify the medication regimen and improve compliance. In a recent meta-analysis involving 20 242 patients, FDCs significantly decreased the risk of noncompliance by 24% compared with free-drug combination regimens.4 Although there is no randomized trial evidence to guide in the selection of a specific formulation, the FDC of amlodipine 5 mg and perindopril 4 mg mirrors the application of these agents in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) study. This study, the only one to date comparing treatment regimens, demonstrated substantial and significant cardiovascular risk reduction, and long-term acceptability with the free combination of amlodipine and perindopril compared with atenolol and diuretic.5 Consistent with present guidelines, and provided there is no contraindication or compelling need to use other agents, the FDC of amlodipine and perindopril can be used for the initial treatment of patients with stage 2 hypertension. In uncontrolled patients, it can replace monotherapy with a calcium channel blocker or an angiotensin-converting enzyme inhibitor, or a 2-drug combination regimen. In patients under blood pressure control, it can substitute another 2-drug combination if there are serious side effects, or if compliance is poor with a free 2-drug regimen.


Coversyl: at the core of cardiovascular disease prevention and treatment

by O. A. Aseeva, France

Angiotensin-converting enzyme (ACE) inhibitors were initially developed for the treatment of hypertension, for which they remain a cornerstone of therapy. According to recent guidelines, among the available classes of antihypertensive agents, ACE inhibitors have the broadest spectrum of use, and are particularly recommended in hypertensive patients with concomitant subclinical organ damage (left ventricular hypertrophy [LVH], microalbuminuria), clinical events (previous myocardial infarction, stroke, heart failure, atrial fibrillation), or conditions (diabetes mellitus, metabolic syndrome). Meta-regression findings published in 2003 by the Blood Pressure Lowering Treatment Trialists’ Collaboration (BPLTTC) have shown a 28% reduction in stroke, 20% reduction in coronary heart disease, and 22% reduction in major cardiovascular events with ACE inhibitors in comparison with placebo. More recently, ACE inhibitors were shown to be associated with a blood pressure (BP)-independent reduction in risk of coronary heart disease, an effect not necessarily shared by other newer antihypertensive classes such as angiotensin receptor blockers (ARBs) or calcium channel blockers (CCBs).

Finally, the ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial--Blood Pressure Lowering Arm) was the first trial to show a superior effect of more recently introduced antihypertensive therapies such as ACE inhibition with perindopril (Coversyl)*, in terms of reduction of total and cardiovascular mortality, in comparison with the traditional approach based on a β-blocker and a thiazide diuretic. In ASCOT-BPLA, the amlodipine/ACE inhibitors were initially developed for the treatment of hypertension, for which they remain a cornerstone of therapy. According to recent guidelines, among the available classes of antihypertensive agents, ACE inhibitors have the broadest spectrum of use, and are particularly recommended in hypertensive patients with concomitant subclinical organ damage (left ventricular hypertrophy [LVH], microalbuminuria), clinical events (previous myocardial infarction, stroke, heart failure, atrial fibrillation), or conditions (diabetes mellitus, metabolic syndrome). Meta-regression findings published in 2003 by the Blood Pressure Lowering Treatment Trialists’ Collaboration (BPLTTC) have shown a 28% reduction in stroke, 20% reduction in coronary heart disease, and 22% reduction in major cardiovascular events with ACE inhibitors in comparison with placebo. More recently, ACE inhibitors were shown to be associated with a blood pressure (BP)-independent reduction in risk of coronary heart disease, an effect not necessarily shared by other newer antihypertensive classes such as angiotensin receptor blockers (ARBs) or calcium channel blockers (CCBs).

* Coversyl® (perindopril) is also available under the trade names: Aceon, Acrel, Armix, Bioprexanil, Coverene, Coverex, Coversum, Prestarium, Prexum, Vectoryl.

Keywords: Coversyl (perindopril); ACE inhibition; cardiovascular disease continuum; hypertension; diabetes; coronary artery disease

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Coversyl: at the core of cardiovascular disease prevention and treatment – Aseeva

Table I. Summary of evidence with Coversyl from the morbidity-mortality trials. 

<table>
<thead>
<tr>
<th>Year</th>
<th>Trial</th>
<th>Patients (number)</th>
<th>Intervention</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>PROGRESS</td>
<td>Post stroke/TIA (6105)</td>
<td>Perindopril/indapamide vs placebo</td>
<td>Recurrent stroke: -28%</td>
</tr>
<tr>
<td>2003</td>
<td>EUROPA</td>
<td>Stable CAD (12218)</td>
<td>Perindopril high dose vs placebo</td>
<td>CV death/MI/cardiac arrest: -20%</td>
</tr>
<tr>
<td>2005</td>
<td>ASCOT-BPLA</td>
<td>HT at risk of CV events (19 257)</td>
<td>Amlodipine-perindopril vs atenolol/thiazide diuretic</td>
<td>CV mortality: -24%</td>
</tr>
<tr>
<td>2006</td>
<td>PREAMI</td>
<td>Post-MI (1252)</td>
<td>Perindopril high dose vs placebo</td>
<td>CV events and procedures: -16%</td>
</tr>
<tr>
<td>2006</td>
<td>PEP-CHF</td>
<td>Diastolic HF (850)</td>
<td>Perindopril vs placebo</td>
<td>Death/HF/cardiac remodeling: -22%</td>
</tr>
<tr>
<td>2007</td>
<td>ADVANCE</td>
<td>Type 2 diabetes (11140)</td>
<td>Perindopril+indapamide vs placebo</td>
<td>Death/HF hospitalization: -31%</td>
</tr>
</tbody>
</table>

Coversyl in patients with risk factors for cardiovascular disease

*Hypertensive patients*

The antihypertensive efficacy of Coversyl has been demonstrated in monotherapy in a large population of 10 425 hypertensive patients, including the elderly, blacks, and patients nonresponsive to previous antihypertensive therapy. In the subgroup of 970 patients who were not responding to previous therapy with ACE inhibitors, Coversyl achieved a clinically and statistically significant decrease in BP with a mean decrease in BP from baseline to week 12 of 13.3 mm Hg for systolic blood pressure (SBP) and 6.9 mm Hg for diastolic blood pressure (DBP). Overall, 34.7% of patients nonresponsive to previous therapy with ACE inhibitors other than Coversyl achieved BP control on Coversyl at the end of the 12-week study. This remarkable efficacy of Coversyl in comparison with other antihypertensives, including other ACE inhibitors, appears to result, at least in part, from its long duration of action and specific effects on arterial function and structure. Coversyl compares favorably with other ACE inhibitors owing to its true 24-hour BP control with once-daily dosage, the trough-to-peak ratio of Coversyl being 75% to 100%. In contrast to other antihypertensive agents, including vasodilating β-blockers and ARBs, Coversyl has been shown to improve endothelial function to a larger extent than expected from BP reduction alone. The effects of long-term treatment with Coversyl on arterial structure and function have been extensively studied both in monotherapy and in combination with the diuretic indapamide (perindopril+indapamide = Preterax†). In a 12-month comparative study versus atenolol, despite similar BP reduction in both treatment groups, only Coversyl restored impaired media-to-lumen ratio of subcutaneous arteries to normal values. In comparison with a thiazide diuretic, only Coversyl significantly increased common carotid artery distensibility after 6 months, whereas both treatments produced similar BP-lowering effects. REASON (pResterax in regression of Arterial Stiffness in a controlled double-blind study of 12 months) versus atenolol showed a significantly greater reduction in total mortality by 11%, major cardiovascular events and procedures by 16%, and new-onset diabetes by 31%, in comparison with the atenolol/thiazide regimen. The ASCOT-BPLA investigators based their choice of Coversyl on its long duration of antihypertensive action.

Today, Coversyl, which is the focus of this review, is one of the best studied antihypertensive agents, with evidence ranging from experimental research to large morbidity/mortality trials involving the entire extent of the cardiovascular disease continuum, from treatment of patients with risk factors for cardiovascular disease, such as hypertension and diabetes mellitus, to established coronary artery disease and heart failure (Table I).1-10

Abbreviations: TIA, transient ischemic attack; CAD, coronary artery disease; HT, hypertension; MI, myocardial infarction; HF, heart failure. Trial acronyms: see box on same page. Based on data from references 5-9.

**STUDY ACRONYMS**

| ADVANCE | Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation |
| ASCOT-BPLA | Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure–Lowering Arm |
| BPLTTC | Blood Pressure Lowering Treatment Trialists’ Collaboration |
| CAFE | Conduit Artery Function Evaluation |
| DAPHNET | Diabetes Artery Perindopril Hypertension Normalization Excess stiffness |
| EUROPA | European trial on Reduction Of diabetic events with Perindopril in stable coronary artery disease |
| PEP-CHF | Perindopril in Elderly People in Chronic Heart Failure |
| PERSPECTIVE | PERindopril’s Prospective Effect on Coronary aThrombosis by IntraVascular ultrasound Evaluation |
| PERTINENT | PERindopril—Thrombosis, InflammationN, Endothelial dysfunction and Neurohormonal activation Trial |
| PICXEL | Perindopril/indapamide in a double blind Controlled study versus Enalapril in Left ventricular hypertrophy |
| PREAMI | Perindopril and Remodeling in Elderly with Acute Myocardial Infarction |
| PREMIER | PRIeretax in albuMinuria Rgession |
| PROGRESS | Perindopril pRotection aGainst REcurrent Stroke Study |
| REASON | PRIesterax in regression of Arterial Stiffness in a controlled double-blind study |
| ONTARGET | ONGoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial |
| PReFESS | PRevention Regimen For Effectively avoiding Second Stroke |

† Preterax (perindopril+indapamide) is also available under the trade names: Bionoliprel, Biprel, Bipreterax, Coversyl Plus, Predonium, Prelectal, Noliprel, Norplex.
study) was a multicenter, multinational, controlled, randomized, double-blind study conducted in 406 patients to compare effects of Coversyl/indapamide combination versus atenolol on brachial and central BP parameters. At 12 months, for the same diastolic BP reduction, the Coversyl/indapamide combination produced a greater reduction in systolic BP and pulse pressure in comparison with atenolol. This difference was significantly more pronounced at the carotid artery level than at the brachial artery level. In hypertensive heart disease, Coversyl decreases LVH and induces structural repair of coronary arteries. In the PICXEL study (Perindopril/Indapamide in a double blind Controlled study versus Enalapril in Left ventricular hypertrophy), 556 hypertensive patients with LVH were treated for 1 year either with the Coversyl/indapamide combination or with enalapril, at equihypotensive dosages. At the end of follow-up, reduction in left ventricular (LV) mass index was significantly greater with the Coversyl/indapamide combination than with enalapril (P<0.001). Furthermore, treatment of hypertensive patients with the Coversyl/indapamide combination has been shown to restore coronary reserve to normal values and thus, to increase myocardial perfusion.

Coversyl was chosen among the available ACE inhibitors for the landmark ASCOT-BPLA trial because of its true 24-hour antihypertensive efficacy with once-daily dosage. ASCOT-BPLA was the first trial to study the comparative effects of the amlopidine/Coversyl combination and a conventional combination of atenolol/thiazide despite being a more antihypertensive drugs, and in the amlopidine/Coversyl arm most patients received Coversyl. ASCOT-BPLA was stopped earlier than scheduled due to the significantly lower mortality observed on amlopidine/Coversyl therapy, thus decreasing the statistical power of the study with respect to its primary end point. However, risk for all prespecified secondary and tertiary end points was lower on amlopidine/Coversyl therapy, including a significant 24% reduction in cardiovascular death (P=0.001), 13% reduction in total coronary events (P=0.007), 23% reduction in stroke (P=0.0003), and 15% reduction in new-onset renal impairment (P<0.002). The benefits on amlopidine/Coversyl were consistent among all prespecified subgroups of hypertensive patients and remained significant after adjustment for SBP. The effects on central aortic BP — considered to accurately reflect target-organ damage in hypertension — have been assessed in the CAFE (Conduit Artery Function Evaluation) sub-study of ASCOT-BPLA, which included 2199 patients. In this sub-study, amlopidine/Coversyl therapy was more effective in reducing central systolic and pulse pressures than atenolol/thiazide despite a similar reduction in brachial pressures on both treatments. Central aortic pressure reduction in CAFE was associated with a reduction in a composite end point of major cardiovascular and renal outcomes and death (P<0.01).

Finally, in ASCOT, analysis of 14120 hypertensive patients who did not have diabetes at the time of inclusion showed that there were significantly fewer new cases of diabetes on amlopidine/Coversyl in comparison with atenolol/thiazide (relative risk reduction 34%; P<0.001). This was attributed by the investigators to a composite of the adverse effects on risk produced by atenolol and thiazide, with the protective effects of Coversyl and amlopidine probably playing a neutral role.

**Patients with type 2 diabetes mellitus**

It has been clearly established that the coexistence of hypertension and diabetes substantially increases the risk of developing renal and other organ damage, leading to a much higher incidence of stroke, coronary heart disease, congestive heart failure, peripheral artery disease and cardiovascular mortality. Although BP lowering per se provides a remarkable cardiac protective effect in type 2 diabetic patients with hypertension, the renin-angiotensin-alderosterone system (RAAS) inhibitors should be the preferred antihypertensive monotherapy and a regular component of combination treatment, because of their specific renal protective properties.

In diabetic patients with hypertension, Coversyl provides dose-dependent improvement in structure and function of conduit arteries. Coversyl appears to be more effective than ARBs with respect to improvement of insulin sensitivity and fibrinolytic balance. Coversyl has been shown to prevent progression of diabetic renal disease through its direct renal protective effects such as prevention of interstitial collagen expansion and reduction in transforming growth factor–β (TGF-β) activation.

In view of the currently recommended tighter BP goals (below 130/80 mm Hg), early use of combination treatment is perfectly adapted to the needs of diabetic hypertensive patients. Robust data confirm that Coversyl, in combination with the only glucose-friendly thiazide-like diuretic indapamide, ensures antihypertensive efficacy, reduction in renal and other target-organ damage, and prevention of cardiovascular outcomes in patients with type 2 diabetes mellitus. In the PREMIER study (PREterax in albuMinuria rEgRession), 482 type 2 diabetic patients were treated with Coversyl/indapamide or enalapril for 1 year. Coversyl/indapamide reduced albumin excretion rate to a significantly greater extent than enalapril (~42% vs ~27%, respectively, P=0.002). This effect was maintained after adjustment for the decrease in mean BP, suggesting a specific renal protective effect of the Coversyl/indapamide combination. At 1 year, significantly fewer patients experienced clinical cardiovascular adverse events (myocardial infarction, stroke, heart failure, cardiovascular death) in the Coversyl/indapamide group than in the enalapril group (2.5% vs 6.3%, respectively, P=0.036).

Recently, the ADVANCE trial (Action in Diabetes and Vascular disease: PreterAx and Diamicron® MR Controlled Evaluation) confirmed morbidity-mortality benefits with the Coversyl/indapamide combination in type 2 diabetic patients. ADVANCE, which included 11,140 diabetic patients, both with and without hypertension, is the largest morbidity-mortality trial ever performed in type 2 diabetes.
The BP arm of ADVANCE assessed the effects of the Coversyl/indapamide combination vs placebo on top of other therapies, including antihypertensive agents, aspirin, and lipid-lowering drugs. Over 4.3 years of follow-up, Coversyl/indapamide significantly reduced risk of macrovascular and microvascular events in comparison with placebo (relative risk reduction 9%, \( P=0.04 \)). This was accompanied by a 14% reduction in all-cause mortality (\( P=0.005 \)), 18% reduction in cardiovascular mortality (\( P=0.03 \)), 14% reduction in the risk of coronary events (\( P=0.02 \)), and 21% reduction in total renal events (\( P<0.01 \)).[16]

Benefits obtained in other large morbidity-mortality trials with Coversyl either in monotherapy, or in combination with indapamide or amlodipine, were consistent in diabetic patients with hypertension, as well as in diabetic patients with cerebrovascular or coronary artery disease.[3,5,14]

It should be pointed out that the consistent benefit of Coversyl regarding cardiovascular outcomes are not confounded by the presence or absence of risk factors such as hypertension or diabetes mellitus (Figures 1A and 1B).[2,5,10,13]

**Coversyl in patients with established cardiovascular disease**

**Patients with cerebrovascular disease**

PROGRESS (the Perindopril PROtection Against Recurrent Stroke Study) was the first study to assess the effects of ACE-inhibitor–based treatment on recurrent stroke in patients with cerebrovascular disease. Coversyl was chosen because of its true 24-hour BP-lowering efficacy,\textsuperscript{5} its safety, attributable to the maintenance of cerebral blood flow in post-stroke patients,\textsuperscript{35} and its well-documented improvement in endothelial function and correction of vascular remodeling.\textsuperscript{17,18} PROGRESS randomized 6105 patients with previous stroke or transient ischemic attack, either with or without hypertension, to Coversyl/indapamide or placebo. At 4 years, risk reduction of recurrent stroke was 28% (\( P<0.0001 \)) with Coversyl-based treatment.\textsuperscript{4} Benefits were observed for all stroke types and were consistent across all patient subpopulations, including diabetics.\textsuperscript{21,26} Coversyl-based treatment also reduced the risk of dementia and cognitive decline associated with recurrent stroke.\textsuperscript{37} The PROGRESS Magnetic Resonance Imaging substudy revealed that Coversyl-based treatment stopped or delayed the progression of white matter hyperintensities, ie, of the brain abnormalities associated with cognitive decline or dementia.\textsuperscript{28} A substantial reduction in the risk of cardiac outcomes was also reported, irrespective of the presence or absence of history of hypertension or coronary heart disease.\textsuperscript{29} Coversyl-based therapy significantly reduced the risk of major coronary events by 26% and of nonfatal myocardial infarction by 38%. In a subgroup of patients with atrial fibrillation, Coversyl-based treatment offered protection against major vascular events irrespective of the use of anticoagulant therapy or of the presence of hypertension.\textsuperscript{4} To conclude, PROGRESS showed Coversyl-based treatment to be effective, safe, and well tolerated across all the study’s subgroups defined by age, sex, and region.\textsuperscript{41}

**Patients with coronary artery disease**

EUROPA (European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease) was the first trial specifically aimed at a population with established stable coronary artery disease. At the core of cardiovascular disease prevention and treatment – Aseeva

**Figure 1A.** Consistent effect of Coversyl in patients with and without diabetes mellitus.

**Figure 1B.** Consistent effect of Coversyl in patients with and without hypertension.

**Abbreviations:**

CAD, coronary artery disease; TIA, transient ischemic attack; CV, cardiovascular; MI, myocardial infarction; RRR, relative risk reduction.

**Trial acronyms:**

see box on page 70.

**Figure 1A:** based on data from references 5, 10, and 33. **Figure 1B:** based on data from references 6, 7, and 10.
In EUROPA, 12 218 patients with stable CAD were randomized to high-dose monotherapy with Coversyl or placebo on top of their current preventive treatments, which were considered standard at that time (antiplatelets, lipid-lowering agents, β-blockers after myocardial infarction). After 4.2 years of treatment with Coversyl, the incidence of the primary outcome (a composite of cardiovascular death, nonfatal MI, or resuscitated cardiac arrest) was significantly decreased by 20%, fatal and nonfatal MI by 24%, and hospitalization for heart failure by 39%. These cardioprotective effects of Coversyl were consistent whatever the BP levels before randomization or BP changes during the course of the study and were independent of renal function at baseline. The treatment benefits of Coversyl in patients with stable CAD were thus observed across all levels of cardiovascular risk at baseline and were of the same magnitude whether patients had prior myocardial infarction or had undergone revascularization. In patients with preserved LV function (mean LV ejection fraction 57%), which made up most of EUROPA's population, the reduction in major cardiac events with Coversyl was similar to that in the overall EUROPA population.

The EUROPA substudies provide further insights into the mechanism of vascular protective action of Coversyl. In PERTINENT (PERindopril-Thrombosis, Inflammation, Endothelial dysfunction and Neurohormonal activation Trial), as early as by the 1st year, Coversyl restored the balance between angiotensin II and bradykinin in favor of bradykinin, improved endothelial function, and decreased the endothelial cell apoptosis rate. Intracoronary ultrasound findings from the PERSPECTIVE (PERindopril'S Prospective Effect on Coronary aTherosclerosis by IntraVascular ultrasound Evaluation) substudy showed that treatment with Coversyl was associated with a more stable pattern of coronary remodeling and a reduction in size of noncalcified coronary plaques. Together with data from the DAPHNET (Diabetes Artery Perindopril Hypertension Normalization Excess sTiffness) and CAFE studies in hypertensive patients, PERTINENT and PERSPECTIVE provide consistent evidence of Coversyl's action at multiple pathophysiological levels underlying the clinical cardiovascular disease continuum (Figure 2).

It is doubtful that the aforementioned cardioprotective benefits obtained in EUROPA with Coversyl are attributable to the class of ACE inhibitors as a whole. This is because of the potential long-term consequences of pharmacokinetic differences between these agents, such as duration of action and affinity for tissue versus circulating ACE. A recent comparative study of ACE inhibitors (perindopril, enalapril, ramipril, trandolapril, quinapril) indicated that when these agents were used at equipotent dosages, only Coversyl significantly reduced endothelial cell apoptosis, one of the initiating events in the atherosclerosis process. Further evidence of Coversyl's benefits in coronary disease comes from PREAMI (Perindopril and Remodeling in Elderly with Acute Myocardial Infarction), the first morbidity-mortality study of ACE inhibition in elderly patients with acute myocardial infarction and preserved LV function. Early after acute myocardial infarction (mean 11 days), 1252 elderly patients (mean age 72 years) with preserved LV function (mean LV ejection fraction 59%) were randomized to the high dosage of Coversyl or placebo on top of other therapies, including β-blockers (in 71% of patients) and followed for 12 months. Coversyl resulted in a significant reduction in the composite primary end point by 22% vs placebo, mainly attributable to the prevention of cardiac remodeling. LV end-diastolic volume increased by 0.7 mL on Coversyl versus 4.0 mL on placebo (P<0.001 for between-group difference). Analysis of the “PREAMI-like” population of EUROPA (elderly patients with prior myocardial infarction and LV ejection fraction >40%) showed a significant 36% reduction in major cardiac events with Coversyl. The high dosage of Coversyl is well tolerated, as shown by the fact that in EUROPA and PREAMI, at the end of follow up, 93% and 94% of patients assigned to Coversyl, respectively, were still on the high dosage.

**Patients with heart failure**

Coversyl's improved pharmacological profile (prolonged duration of action, higher affinity for tissue ACE, better tolerability), has a special impact in heart failure where, compared with conventional ACE inhibitors, Coversyl was not associated with systemic hypotension at the initiation of treatment, even in elderly patients. Coversyl improves systemic and regional hemodynamics in heart failure patients. The switch from enalapril to Coversyl results in significant improvement in New York Heart Association [NYHA] class. In a population-based study of 43 316 patients with chronic heart failure, in which ramipril was used as reference category for comparison, 1-year mortality was significantly higher in patients treated with enalapril or with captopril (+10% and +13%, respectively), while it was 10% lower on Coversyl.

Although the effects of ACE inhibition in patients with heart failure with systolic dysfunction were well established, until the Perindopril in Elderly People in Chronic Heart Failure (PEP-CHF) study it remained unclear how heart failure with diastolic...

Figure 3. Coversyl prevents occurrence of heart failure and/or hospitalizations for heart failure in different populations of patients with cardiovascular disease.

Evidence for RAAS inhibition along the cardiovascular disease continuum

Usefulness of ACE inhibitors in prevention and treatment of cardiovascular disease is supported by the bulk of evidence from large randomized clinical trials. Findings from recent studies with ARBs lead to the conclusion that they are not as effective as the ACE inhibitors in preventing cardiovascular events in patients with vascular disease. In the PROFESSION (PRevention Regimen For Effectively avoiding Second Stroke) trial in patients after an ischemic stroke, telmisartan did not reduce the risk of subsequent stroke, major cardiovascular events, or, new-onset diabetes, despite greater BP reduction in comparison with placebo. In ONTARGET (ONGOing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial), there was no significant difference between telmisartan alone or the telmisartan/ramipril combination versus ramipril on the primary outcome in high-risk patients with vascular disease or diabetes despite differences in BP reduction in favor of telmisartan. In a population of patients intolerant to ACE inhibitors similar to that of ONTARGET, TRANSCEND (Telmisartan Randomized AssessmeNT Study in ACE iNtolerant trial subjects with cardiovascular Disease), telmisartan did not reduce the risk of cardiovascular death, myocardial infarction, stroke, or hospitalization for heart failure in comparison with placebo, despite a significant reduction in BP. Surprisingly, both in the TRANSCEND and PROFESSION trials, there was no effect of angiotensin receptor blockade on hospitalization for heart failure. In contrast with these findings, treatment with Coversyl systematically leads to reduction in hospitalization for heart failure or occurrence of heart failure in patients with cardiovascular disease (Figure 3),

Recent trials have confirmed previous findings of a lesser protection against coronary heart disease with ARBs in comparison with ACE inhibitors. Overall, data supporting the use of ARBs to prevent vascular events in various groups of cardiovascular patients, other than those with heart failure, are incomplete.

Conclusion

Recent trials have shown that the clinical effects of ARBs are less robust than those of ACE inhibitors. Therefore, ACE inhibitors should remain the preferred RAAS inhibitors for the prevention of cardiovascular events. Coversyl, alone among the ACE inhibitors, has been extensively studied for its effects all along the cardiovascular disease continuum, from risk factors, such as hypertension or diabetes (ASCOT-BPLA, ADVANCE), to established cardiovascular disease (PROGRESS, EUROPA), Coversyl, whether as monotherapy or in combination with the long-acting CCB amlodipine (Coveram) or the only metabolically friendly thiazide-like diuretic indapamide, reduces the risk of cardiovascular events in a broad population of patients with cardiovascular disease or risk factors. With its proven beneficial action on arterial structure and function, Coversyl is able to oppose at their early stages the pathophysiological processes that lead to target-organ damage and established cardiovascular disease.

REFERENCES
3. PEP-CHEF, despite statistical limitations due to the loss of randomization power after 1 year, showed a reduction in unplanned heart failure–related hospitalization and an improvement in functional capacity and symptoms in patients treated with Coversyl. There was also a strong tendency for improvement in the primary end point (all-cause mortality and unplanned heart failure–related hospitalization) of similar magnitude to that in SOLVD (Studies Of Left Ventricular Dysfunction) in patients with heart failure with LV systolic dysfunction. Coversyl significantly reduced the end point of cardiovascular mortality and unplanned heart failure–related hospitalization by 18% at 1 year. Taking into account the scarcity of morbidity-mortality data in heart failure with preserved LV function, Coversyl appears to be a valuable therapy in this particular population.

Coversyl: at the core of cardiovascular disease prevention and treatment – Aseeva

Medicographia, Vol 31, No. 1, 2009
based clinical trial.

829-840.

patients with type 2 diabetes mellitus (The ADVANCE 10.

ter dosing.

hypertension: effects on blood pressure 6 and 24 h af-

15.

tiovascular function.

Guo W, Turlapaty P, Shen Y, et al. Clinical expe-

14.

Cohn JN, Julius S, Neutel J, et al. Clinical expe-

13.

Coversyl: at the core of cardiovascular disease prevention and treatment –

7.

imen among 6165 individuals with previous stroke or transient ischaemic attack. Lancet. 2003;358:1033-1041.

8. Fox KM; EURopean trial On reduction of cardiac events among patients with previous stroke or transient ischaemic attack. Lancet. 2003;358:1033-1041.


17. Langham RG, Kelly DJ, Gow RM, et al. Transforming growth factor-β in human diabetic nephropa-

40.

Coversyl: at the core of cardiovascular disease prevention and treatment –

20.


men on the risk of recurrent stroke according to stroke type. Stroke. 2004;35:116-121.


23. Poultier NR, Wedel H, Dalhoff B, et al. Role of blood pressure and other variables in the differential cardiovascular event rates noted in the Anglo-Scan-

25.


sians randomized to two different antihypertensive regimens (the ADVANCE trial). J Hypertens. 2007;25:2006-2021.

27. Fogan R, Mugellini A, Zappi A, et al. Losartan and perindopril effects on plasma plasminogen activator inhibitor-1 and relative influence of antihypertensive type 2 di-


dopril in hypertensive insulin-treated diabetic pa-

29.

30. Cordonnier DP, Pline N, Barro C, et al. Expansion of cortical interstitium is limited by converting en-


31. Langham RG, Kelly DJ, Gow RM, et al. Transforming growth factor-β in human diabetic nephropa-

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ACE INHIBITION AND ATRIAL FIBRILLATION

Interview with J.C. Tardif and K. Najem, Canada

What is the relationship between atrial fibrillation and hypertension?

Atrial fibrillation (AF) and hypertension are frequently linked to each other. In fact, hypertension is the most prevalent, independent, and potentially modifiable risk factor for AF. Chronically elevated blood pressure leads to left ventricular (LV) hypertrophy, diastolic dysfunction, and increased left atrial pressure and enlargement. The latter events increase the probability of AF, but also of thrombosis and systemic embolism. In addition, LV mass is an independent predictor of AF in hypertensive patients. In the Framingham Study, a 4-mm increase in LV wall thickness resulted in a 28% increase in the risk of developing AF. In that study, left atrial enlargement was also recognized as a predisposing factor for AF, with a 5-mm increase in left atrial size increasing by 39% the risk of developing AF. Other studies have demonstrated that the degree of left atrial enlargement correlates with the severity of hypertension. Moreover, atrial stretching and electrophysiological remodeling comprising changes in atrial refractoriness and conduction are thought to contribute to AF maintenance. Atrial stretching is involved in the pathophysiology of AF by shortening the effective refractory period and lengthening intra-atrial conduction time. Angiotensin II increases left atrial pressure and stretch and can promote fibrosis, which renders the atrium structurally susceptible to reentry loops that are characteristic of AF. Those intra-atrial conduction abnormalities arising from fibrosis of the atrial walls are due to the action of angiotensin II through cardiac myoblast proliferation, reduced collagenase activity, and activation of extracellular signal-regulated and mitogen-activated protein kinases (MAPK). Finally, increased angiotensin-converting enzyme (ACE) expression has been found in the atria of patients with AF. Thus, angiotensin II is a key hormone linking AF and hypertension.

What are the major difficulties in the management of patients with atrial fibrillation and hypertension in clinical practice?

At present, the treatment of patients with AF is inappropriate: more than 50% of patients have recurrences of their arrhythmia within 12 months despite therapy with standard antiarrhythmic drugs. In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, rhythm control and rate control strategies of treatment were compared. The former was aimed at maintaining sinus rhythm through cardioversion, antiarrhythmic drugs, or atrial catheter ablation, and the risk of related hospitalization in hypertensive patients in a usual care setting. However, sufficient clinical data do not exist to justify their use as a standard approach to prevent AF. The ongoing Canadian Trial on Atrial Fibrillation–2 (CTAF-2) is prospectively testing the hypothesis that the ACE inhibitor perindopril will prevent recurrences of AF in patients with hypertension.

Selected abbreviations and acronyms

- AF: atrial fibrillation
- AFFIRM: Atrial Fibrillation Follow-up Investigation of Rhythm Management [Trial]
- AV: atrioventricular
- CCB: calcium channel blocker
- CTAF-2: Second Canadian Trial on Atrial Fibrillation
- RACE: Rhythm Control versus Electrical cardioversion [Trial]

Keywords: atrial fibrillation; arrhythmia; stroke; mortality; antiarrhythmic drug; ACE inhibitor; clinical trial

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tion, whereas the latter was aimed at controlling the ventricular response rate of AF by means of atrioventricular (AV) node blocking agents or ablation of the AV junction and pacemaker implantation. The study showed that rate control was as effective as a rhythm control strategy that incorporated currently used standard antiarrhythmic drugs. This comparison could not take into account the use of drugs that may prevent AF without the side effects or potentially proarrhythmic effects of standard antiarrhythmic agents. In addition, a rate-control strategy is often inadequate for patients who experience severe palpitations or who remain dyspeptic despite a controlled ventricular response. Rhythm control has been shown to reduce symptoms related to AF and improve exercise tolerance and overall quality of life. The best rhythm control strategy is one that would prevent development of the substrate for AF or induce its regression. Limitations of the different therapeutic approaches for AF are summarized in Table I.

Patients with AF and hypertension are at greater risk of thromboembolic complications than normotensive patients with AF, especially in patients with atrial fibrillation (AF). ACE inhibitors reduce the incidence of new-onset atrial fibrillation and thus can lead to accumulation of fibrous tissue. Several studies have shown that there is increased expression of angiotensin II13 and extracellular signal-regulated kinase (ERK) and not through its Angiotensin II type 1 (AT1) receptor. The angiotensin II type 1 (AT1) receptor is downregulated and regulates the receptor expression at the cell surface. When angiotensin II binds to AT1, the complex is internalized, therefore decreasing the occurrence of AF in hypertensive patients.

What is the pathophysiological evidence to suggest that ACE inhibition may reduce the incidence of new-onset atrial fibrillation as well as its recurrence? ACE inhibitors elicit antiarrhythmic effects in AF by at least three mechanisms: (i) reduction in atrial stretch; (ii) reduction in atrial fibrosis; and (iii) regulation of ion channel function.

Reduction in atrial stretch
ACE inhibitors induce systemic arteriolar dilatation, increase large artery compliance (hemodynamic effects), and decrease systolic blood pressure and left atrial pressure. In acute hypertension, atrial stretch contributes to AF maintenance by shortening the effective refractory period through the presumably opening of stretch-activated channels.

Reduction in atrial fibrosis
Transforming growth factor–β1 (TGF-β1) appears to play a significant role in the pathophysiology of atrial fibrosis. Angiotensin II stimulates TGF-β1 production and thus can lead to accumulation of fibrous tissue. Several studies have shown that there is increased expression of angiotensin II13 and extracellular signal-regulated kinase (ERK) and not through its hemodynamic effects. Overall, ACE inhibition reduces atrial fibrosis, intra-atrial conduction abnormalities, and susceptibility to AF.

Regulation of ion channel function
The angiotensin II type 1 (AT1) receptor forms a complex with a pore-forming ion-channel (Kv4.3), which is responsible for the transient outward potassium current (Ito) and regulates the receptor expression at the cell surface. When angiotensin II binds to AT1, the complex is internalized, therefore decreasing Ito and promoting depolarization of the cell membrane. In AF-induced remodeling, the transcription of Ito is downregulated due to the action of angiotensin II. ACE inhibition favorably impacts on electrophysiological remodeling in AF.

Do we have sufficient clinical data to support the usefulness of ACE inhibition in hypertensive patients with AF?
ACE inhibitors are an excellent treatment for hypertension. Experimental and initial clinical studies suggested that ACE inhibition may also prevent the development of AF. Based on this knowledge, we carried out a retrospective, longitudinal cohort study to evaluate the impact of ACE inhibitors on the occurrence of AF in hypertensive patients. The study compared the outcomes in patients with hypertension treated with ACE inhibitors versus long-acting calcium-channel blockers (CCB). A total of 10,926 eligible participants were taken from an integrated medical and pharmacy claims database of over 8 million subjects in the USA and were equally matched in each group of medication (5463 patients in each group). Eligibility required a diagnosis of hypertension during the 6 months prior to the study and a filled prescription for either class of medication. The patients had a mean age of 65 years and were followed for an average of 4.6 years for the ACE inhibitor group and 4.2 years for the CCB group.

Our results showed a significantly lower incidence of new-onset AF in the ACE-inhibitor group compared with the CCB group. The onset of AF occurred at an average of 29.5 months in the ACE-inhibitor group versus 26.1 months in the CCB group. The incidence rate of AF-

Table I. Limitations of different treatment modalities for atrial fibrillation...

Abbreviations: AF, atrial fibrillation; AV, atrioventricular; HF, heart failure.

<table>
<thead>
<tr>
<th>RHYTHM CONTROL</th>
<th>RATE CONTROL</th>
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<tr>
<td><strong>Antiarrhythmic drugs</strong></td>
<td><strong>AV-node blocking agents</strong></td>
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<tr>
<td>Class I</td>
<td>Digoxin</td>
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<tr>
<td>✷ Risk of proarrhythmia</td>
<td>✷ Efficacy reduced in states of increased sympathetic tone (acute AF, exercise)</td>
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<td>✷ Aggravation of heart failure (HF)</td>
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<tr>
<td>Class III</td>
<td>β-Blockers</td>
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<td>Amiodarone</td>
<td>✷ Nondihydropyridine calcium antagonists</td>
</tr>
<tr>
<td>✷ Bradycardia</td>
<td>✷ Both classes are associated with different side effects</td>
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<tr>
<td>✷ Increased plasma level of warfarin</td>
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<td>✷ Side effects and potential toxicity (lung, thyroid, etc) with chronic use</td>
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<tr>
<td><strong>Cardioversion</strong></td>
<td>Ablation of AV node</td>
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<tr>
<td>✷ High risk of AF recurrence</td>
<td>✷ Necessity of pacemaker implantation</td>
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<tr>
<td><strong>Atrial catheter ablation</strong></td>
<td>✷ Permanent loss of AV node conduction</td>
</tr>
<tr>
<td>✷ Recurrence of AF</td>
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<tr>
<td>✷ Rare, but clinically significant complications (tamponade, pulmonary vein stenosis)</td>
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<tr>
<td>✷ Effective for patients without significant structural heart disease</td>
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related hospitalizations was also lower with ACE inhibitors than with CCBs (8.5 vs 11.9 per 1000 patient-years, respectively). Furthermore, a greater benefit of ACE inhibitors compared with CCBs was observed in patients with previous history of AF. Thus, this cohort study demonstrated that ACE inhibitors reduced the incidence of AF and the risks of related hospitalizations in hypertensive patients in a usual care setting. However, data definitively demonstrating the beneficial effects of ACE inhibition for the prevention of AF in a randomized controlled trial are currently lacking. These data are necessary before we can recommend the widespread use of ACE inhibition for the prevention of AF.

Could you explain the rationale and design of the CTAF-2, trial, which you are chairing, and what its status is?

The lack of data from randomized clinical trials demonstrating the benefits of ACE inhibitors as a potential treatment for AF in hypertensive patients has led us to launch the second Canadian Trial on Atrial Fibrillation (CTAF-2). CTAF-2 is testing the hypothesis that the ACE inhibitor perindopril among other ACE inhibitors (CTAF-2) is presently in the phase of patient recruitment.

Several ACE inhibitors have been shown to reduce morbidity and mortality in patients with heart failure. Perindopril has been shown to improve cardiovascular outcomes in patients with stable coronary artery disease. Perindopril has also been shown to be well tolerated and associated with a low incidence of either symptomatic or asymptomatic hypotension. Perindopril was better tolerated in the early stages of treatment than captopril by patients with recent myocardial infarction, with a lower incidence of persistent hypotension and a higher percentage of target dose attainment. In addition, perindopril is an effective agent to reach blood pressure targets.

Perindopril was also shown to improve cardiac sympathetic nerve activity and decrease plasma brain natriuretic peptide levels to a greater extent than enalapril. Furthermore, prospective studies found that the combination of perindopril (2 mg) and indapamide (0.625 mg) decreased ambulatory systolic blood pressure, pulse pressure, and LV mass more efficiently than enalapril.

Given the incidence of AF and the limitations of standard antiarrhythmic drugs, there is a clear need for a novel effective approach to prevent the onset of and reduce the recurrence of this common arrhythmia, which is not associated with the risk of proarrhythmia. Several lines of evidence implicate the renin-angiotensin system in the pathophysiology of AF and suggest that ACE inhibition may prevent or treat AF. Because hypertension is the factor most frequently associated with AF, prospective confirmation in a randomized trial that ACE inhibition has a favorable effect against AF would be of major clinical importance. CTAF-2 is presently testing the hypothesis that the ACE inhibitor perindopril will prevent AF recurrences in patients with hypertension.

ACE inhibition and atrial fibrillation – Tardif and Najem

Figure 1. Study design of the second Canadian Trial of Atrial Fibrillation (CTAF-2).
INHIBITION DE L’ENZYME DE CONVERSION ET FIBRILLATION AURICULAIRE

La fibrillation auriculaire (FA), arythmie cardiaque la plus répandue, constitue un problème de santé majeur dans notre société. Elle est associée à une augmentation des taux d’hospitalisations et d’accidents vasculaires cérébraux ischémiques et double le risque de mortalité. L’hypertension, facteur de risque indépendant le plus fréquent pour la FA, a des conséquences énormes sur les systèmes de santé en touchant plus d’un milliard d’individus à travers le monde. À l’heure actuelle, le traitement de la FA n’est pas satisfaisant : l’arythmie récidive chez plus de 50 % des patients dans les 12 mois malgré un traitement antiarythmique standard. Les données expérimentales on montré que les IEC (inhibiteurs de l’enzyme de conversion) ont des effets antiarythmiques et pourraient diminuer l’incidence de la FA en diminuant l’élargissement et la fibrose auriculaires et en régulant les canaux ioniques. Une étude de cohorte de 11 000 patients a montré que les IEC permettaient de diminuer l’incidence de la FA et le risque d’hospitalisation chez des patients hypertendus dans un cadre de soins courants. Nous ne disposons cependant pas de données cliniques suffisantes pour justifier leur utilisation en prévention standard de la FA. L’étude en cours CTAF-2 (Canadian Trial on Atrial Fibrillation-2) vérifiera de façon prospective l’hypothèse selon laquelle l’IEC perindopril préviendrait les récidives de FA chez les hypertendus.
INHIBITION OF THE RENIN-ANGIOTENSIN SYSTEM—INSIGHTS FROM THE BLOOD PRESSURE LOWERING TREATMENT TRIALISTS’ COLLABORATION

by F. M. Turnbull, Australia

The Blood Pressure Lowering Treatment Trialists’ Collaboration: background and overview findings

Since the mid 1990s, there has been increasing recognition of the need for more reliable evidence about the effects of different blood pressure–lowering regimens in a diverse group of patients at risk of cardiovascular disease. Given the global prevalence of suboptimal blood pressure and extensive use of treatment, even moderate differences in treatment effects could potentially lead to the prevention of many thousands or tens of thousands of premature deaths each year.

In 1995, principal investigators of ongoing and planned major trials of blood pressure–lowering regimens established the Blood Pressure Lowering Treatment Trialists Collaboration (BPLTTC). The Collaboration was formed in response to the lack of strong evidence about the effects of specific drug classes and of blood pressure lowering in high-risk patients without “hypertension.” Although the evidence that blood pressure lowering reduced the risk of major cardiovascular disease was beyond question, there remained considerable uncertainty about the relative benefits of older drug classes (diuretics and β-blockers) compared with newer drug classes (ACE inhibitors and calcium antagonists) and of the effects of blood pressure lowering among patients with other high-risk conditions such as cerebrovascular disease, renal disease, and diabetes.

The broad goal of the BPLTTC was therefore to provide reliable information about the effects of commonly used blood pressure–lowering regimens on mortality and major morbidity in a range of patients at risk of cardiovascular disease using prospective overviews of large randomized trials. The

The broad goal of the Blood Pressure Lowering Treatment Trialists’ Collaboration (BPLTTC) is to provide reliable information about the effects of commonly used blood pressure–lowering regimens on mortality and major morbidity in a range of patients at risk for cardiovascular disease, using prospective overviews of large randomized trials. The results from the BPLTTC’s second main cycle of overviews were instrumental in clarifying the effects of different regimens (including newer agents such as angiotensin-converting enzyme [ACE] inhibitors and angiotensin receptor blockers [ARBs]) on cause-specific cardiovascular outcomes and on defining the major role of blood pressure reduction in reducing the risk of major cardiovascular events. While blood pressure reduction per se appeared to be a major component of the benefit conferred by different regimens, additional analyses were subsequently done to quantify the relative contributions of blood pressure–dependent and –independent effects for ACE inhibitors and ARBs. These analyses showed that ACE inhibitors afforded a small amount (9%) of additional protection against coronary heart disease by virtue of a blood pressure–independent effect. This drug-specific effect was equivalent to the estimated effect of an additional 3-mm Hg reduction in systolic blood pressure. The effect was not seen for the outcomes of stroke or heart failure, nor was it seen in the analyses of ARBs. These findings suggest that maximization of the benefit may therefore be achieved with a regimen that includes an ACE inhibitor together with other drugs in an effort to optimize the size of the blood pressure achieved.

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Keywords: ACE inhibitor; angiotensin receptor blocker; meta-analysis; blood pressure; major cardiovascular event; blood pressure–independent effect

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collaborative group defined the plans for these overviews and the resultant protocol was published in 1998. At the time the protocol was finalized no results had been reported from included trials. The prospective nature of the overviews therefore allowed the specification a priori of a number of important aspects of the research including the principal hypotheses and the criteria for inclusion of trials. In this way, retrospective outcome-dependent biases in study questions and trial inclusion could be avoided.

◆ The first main cycle of overviews

The first main cycle of overviews from the Collaboration was published in the *Lancet* in 2000 and was based on information from 15 trials and 74 696 patients. This first cycle showed conclusively that the benefits of blood pressure–lowering regimens were not limited to those based on diuretics and β-blockers, but extended to newer agents, including ACE inhibitors, and that these benefits were observed in a heterogeneous population of patients at high risk for cardiovascular disease.

In the overviews of placebo-controlled trials of ACE inhibitors where the weighted mean difference between randomized groups was 3/1 mm Hg, there was 20% to 30% reduction in the risk of stroke, coronary heart disease (CHD), major cardiovascular events, cardiovascular death, and total mortality with active treatment. While there was no significant reduction in the risk of heart failure, the 95% confidence intervals could not exclude a possible moderate advantage for patients receiving ACE-inhibitor therapy. The first cycle overviews of trials comparing regimens based on different active agents showed that where blood pressure differences between randomized groups were small (0-3 mm Hg), there was no evidence of a difference in the risk of composite events; major cardiovascular events, coronary heart disease (CHD), major cardiovascular death, and total mortality. However, there was some evidence of moderate, but potentially important, differences between regimens for the cause-specific outcomes of stroke, CHD, and heart failure. In the comparisons of ACE inhibitor– and calcium antagonist–based regimens, there was a 20% reduction in the risk of both CHD and heart failure with ACE inhibitor–based regimens. However, for the outcome of CHD, there was significant (P=0.01) heterogeneity among contributing trials, and for the outcome of heart failure, the risk reduc-

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<th>2nd listed Events</th>
<th>Mean ΔBP (mm Hg)</th>
<th>Favors 1st listed</th>
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<td>ACEI vs D/Bβ</td>
<td>6</td>
<td>2176/20 631</td>
<td>3067/26 799</td>
<td>+2/0</td>
<td></td>
<td></td>
<td>1.00 (0.95–1.05)</td>
<td>0.76</td>
</tr>
<tr>
<td>CA vs D/Bβ</td>
<td>9</td>
<td>2527/31 031</td>
<td>3437/37 418</td>
<td>+1/0</td>
<td></td>
<td></td>
<td>0.99 (0.95–1.04)</td>
<td>0.71</td>
</tr>
<tr>
<td>ACEI vs CA</td>
<td>6</td>
<td>1763/12 998</td>
<td>1683/12 758</td>
<td>+1/+1</td>
<td></td>
<td></td>
<td>1.04 (0.98–1.10)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Figure 1. Comparisons of active blood pressure–lowering regimens based on different drug classes.

tion was of borderline significance. Although the first cycle of overviews provided many answers to questions they were designed to address, there remained some uncertainty about others. In particular, while the overviews were able to determine important differences between active regimens in their protection against total major cardiovascular events, the effects on cause-specific events were less clear. Furthermore, this cycle did not examine the treatment effects of angiotensin receptor blockers (ARBs), which were receiving increasing attention as a new class of renin-angiotensin inhibitor.

**The second main cycle of overviews**

In the 3 years following the first cycle of overviews, a number of ongoing trials participating in the Collaboration presented or published their main findings. This resulted not only in substantial new information about the protective effects of different blood pressure–lowering regimens, including ARBs, but also a significant increase in data available to the Collaboration. So, while the first cycle of overviews had been based on data from 15 trials and 74,696 participants, by the middle of 2003, a further 14 trials collectively including 87,645 participants were added to the BPLTTC dataset, essentially doubling the number of events available for analyses.

The second cycle overviews confirmed many of the earlier findings of placebo-controlled comparisons of ACE inhibitors. For the composite outcomes of major cardiovascular events, cardiovascular death, and total mortality, ACE inhibitors conferred 22%, 20%, and 18% reductions in the risk of these events, respectively, compared with placebo. However, there were no significant differences in the protective effects of ACE inhibitors compared with other active regimens. The estimates of these treatment effects were based on tens of thousands of events and are therefore likely to be very reliable. While based on a smaller volume of data and thus less reliable, ARBs also conferred a 10% reduction in the risk of major cardiovascular events compared with “other” regimens. However, no significant reductions were seen for the risk of cardiovascular death or total mortality despite a 2-mm Hg systolic blood pressure reduction.

For all treatment comparisons, including those of ACE inhibitors and ARBs, there was a direct association between the blood pressure reduction and the risk of all outcomes, with the exception of heart failure, suggesting that the blood pressure–lowering effect of these regimens was a major component of their treatment effect. For heart failure, the lack of direct association appeared to be attributable to the adverse effects of calcium antagonists. Regimens based on ACE inhibitors and conventional therapy (diuretics and β-blockers) were both superior to regimens based on calcium antagonists for this outcome (Figure 1).

Conversely, for the outcome of stroke, there was a trend toward greater protection from regimens based on both calcium antagonists and conventional therapy compared with ACE-inhibitor–based regimens. However, this benefit was in the context of small differences in blood pressure between treatment groups, which favored both calcium antagonists and diuretics/β-blockers. For the outcome of CHD, there was no evidence of a difference in the effects of ACE inhibitors, calcium antagonists, and diuretics/β-blockers.

**Defining the blood pressure–dependent and –independent effects of ACE inhibitors and ARBs**

While the second main cycle of overviews showed that the risk of major cardiovascular events could be reduced by a broad range of blood pressure–lowering drugs, including ACE inhibitors and ARBs, and that blood pressure was a major component of the benefit, those analyses were unable to detect or refute any plausibly modest independent effects of particular classes of blood pressure–lowering drug on any cause-specific cardiovascular outcome. Thus, new analyses to determine the relative contribution of blood pressure–dependent and –independent mechanisms to the reductions in risk of stroke, CHD, and heart failure were proposed.

![Table I. Estimates of effect attributable to blood pressure and blood pressure-independent effects of ACE-inhibitors and angiotensin receptor blockers.](image)
The analyses used data from the 26 trials participating in the Collaboration, which compared an ACE inhibitor or ARB with placebo or other drug class. The association between the difference in follow-up systolic blood pressure levels and the log odds ratio for each of the three outcomes was investigated using random effects meta-regression analysis. For each outcome, the slopes of the lines for ACE inhibitors and ARBs were compared, so as to test for a differential effect of blood pressure reduction on risk in trials of ACE inhibitors compared with ARBs.

Blood pressure effects
For trials of both ACE inhibitors and ARBs, the magnitude of the risk reduction achieved for stroke, CHD, and heart failure was positively associated with the size of the blood pressure reduction (Table I, page 83). Treatment with ACE-inhibitor–based regimens achieved a 19% reduction in the risk of stroke, 16% reduction in the risk of CHD, and 27% reduction in the risk of heart failure for each 5-mm Hg reduction in blood pressure. The corresponding reductions in risk for ARBs were 26%, 17%, and 12%, respectively, although the confidence limits around these estimates were wider than for ACE inhibitors due to the smaller number of patients studied.

Blood pressure–independent effects
For CHD, there was evidence that ACE inhibitors provided protection that was greater than that which could be attributed to the blood pressure differences observed. At zero blood pressure reduction, the estimated relative risk reduction for CHD was 9% (3% to 14%, P=0.004) (Table I). There was no such effect apparent for stroke (P=0.8) or heart failure (P=0.3). For no outcome was there evidence that ARBs conferred any additional protection beyond that conferred by blood pressure reduction alone, although confidence intervals about these estimates were again wider than for the analyses of ACE inhibitors.

Sensitivity analyses
For the outcomes of stroke and CHD, the sensitivity analyses did not provide any evidence to indicate that the observed blood pressure–dependent and –independent effects were in any way determined by the composition of the comparator treatment regimen. For the outcome of heart failure, however, the inclusion of trials with a calcium antagonist comparator arm indicated, that with zero blood pressure reduction, there was a borderline 10% (0% to 19%; P=0.06) reduction in heart failure risk with ACE-inhibitor treatment and an 18% (9% to 27%; P=0.001) reduction with ARBs. These effects were not apparent in the trials that involved other comparator regimens.

Given the known limitations of calcium antagonists in preventing heart failure, this finding suggests a blood pressure–independent adverse effect of calcium antagonists rather than a blood pressure–independent protective effect of ACE inhibitors or ARBs.
Comparisons of ACE inhibitors and ARBs

The blood pressure–dependent and –independent effects of ACE inhibitors and ARBs on each outcome were compared to examine whether there was evidence of a difference between the two drug classes. The association between magnitude of reduction in blood pressure and size of relative risk reduction for stroke, CHD and heart failure were similar for ACE inhibitors and ARBs (all P>0.2) (Table I). There was also no evidence that ACE inhibitors and ARBs were different to each other in terms of their likelihood of providing protection independent of blood pressure lowering for stroke or heart failure (both P=0.6). A single combined regression of ACE and ARB trials was therefore calculated for stroke and heart failure (Figure 2). There was, however, evidence (P=0.002) of a difference between ACE inhibitors and ARBs for CHD, suggesting greater protection independent of blood pressure lowering with ACE inhibitors than ARBs (Table I, Figure 2).

Direct comparison

The effects of ACE inhibitors and ARBs were directly compared in the supplementary meta-analysis of three head-to-head trials, collectively including 18 447 individuals with acute myocardial infarction and/or heart failure (Figure 3). In these studies, the mean age of participants was 67 years and 70% were male. A total of 6181 major cardiovascular events contributed to the analyses. There was an estimated mean 0.7-mm Hg lower follow-up systolic blood pressure in the ARB group compared to the ACE-inhibitor group. The meta-analyses identified no differences between these two drug classes for any of the three outcomes, but confidence limits were wide and could not exclude true difference of moderate magnitude.

These analyses provide the most reliable information about blood pressure–dependent and –independent effects of ACE inhibitors and ARBs to date for two main reasons: first, the analyses include nine new ACE-inhibitor and ARB trials with data from an additional 48 745 patients; and second, they involve more sophisticated statistical methods specifically aimed at the identification of blood pressure–dependent and –independent components of the treatment effects. While the size of blood pressure reduction achieved with either drug class was directly associated with the size of the reductions in risks of stroke, CHD, and heart failure, the analyses also showed that for CHD, treatment with an ACE inhibitor provides an additional 9% relative risk reduction beyond that explained by the observed blood pressure differences. There was no such effect observed for ARBs, although the confidence limits were too wide to exclude a modest effect.

While the supplementary meta-analysis involving data from three trials that directly compared an ACE inhibitor and an ARB in patients with acute myocardial infarction or heart failure did not detect a difference between these regimens for any outcome, the confidence limits for CHD were consistent with as much as a 19% lower risk, as well as a 6% greater risk, among those assigned the ACE inhibitor. Furthermore, patients with heart failure or acute myocardial infarction may respond differently to ACE inhibitors and ARBs compared with patients selected on the basis of high blood pressure and an elevated cardiovascular risk (who made up the majority of the population in the trials contributing to the meta-regressions).

Conclusion

In summary, the BPLTTC overview analyses provide strong evidence to suggest that the size of the reduction in blood pressure achieved with either ACE inhibitors or ARBs is a major determinant of the size of the reductions in risk of CHD, stroke, and heart failure. Additionally, the analyses have identified a potentially important blood pressure inde-
REFERENCES


**Inhibition du système rénine-angiotensine : perspectives ouvertes par l’étude Blood Pressure Lowering Treatment Trials’ Collaboration**

L e BPLTTC (Blood Pressure Lowering Treatment Trials’ Collaboration) a comme objectif global d’informer de façon fiable des effets des antihypertenseurs courant sur la morbi-mortalité des patients à risque de maladie cardio-vasculaire, grâce à une analyse prospective d’études randomisées à grande échelle. Les résultats du second cycle principal d’analyse par le BPLTTC ont permis de clarifier les effets de différentes classes thérapeutiques (dont les plus récentes comme les inhibiteurs de l’enzyme de conversion de l’angiotensine [IEC] et les antagonistes des récepteurs de l’angiotensine [ARA]) vis-à-vis des événements cardio-vasculaires de cause spécifique et de la définition du rôle essentiel de l’abaissement de la pression artérielle sur la réduction du risque d’événements cardio-vasculaires majeurs. Bien que l’abaissement de la pression artérielle en elle-même
The science of genetics is said to have begun in 1866 with the work of a monk called Gregor Mendel who liked to spend time in the garden. However, as with many types of knowledge through history—an awareness of heredity and the factors influencing it had been present for much longer. For example, 2000 years earlier Aristotle and Hippocrates both wrote about the inherited nature of physical characteristics that depended upon the alternate characteristics of mother and father. However, the exponential growth of knowledge in our understanding of the human genome has been truly remarkable and has even surprised the enthusiast. Within the last 2 years the use of a new set of methodologies and laboratory techniques has allowed very large studies to be performed in patients with common diseases such as diabetes, hypertension, and coronary artery disease (CAD). These have used an approach called genome-wide association, which compares the frequency of single DNA base changes called single nucleotide polymorphisms (SNPs). The first wave of studies studied gene chips with 100 000 SNPs, while the most recent projects commonly evaluate 1 000 000 SNPs on a single chip. Importantly, the study of single SNPs that have been selected as worthy biological candidates has been largely eclipsed, as have also family-based methodologies that are predicated on the strict rules of Mendelian inheritance. This is the exciting and rapidly developing context that human genetics now finds itself in, a context within which I will seek to review current evidence for clinical significance for gene variants that code for the elements of the renin-angiotensin-aldosterone system.

The father of medicine, Hippocrates, wrote that “Where you find the love of mankind, there you will also find the love of the art of medicine.” He was well aware how this underpins the physicians’ oath to endeavor to choose treatments for the good of each patient according to the best of their ability and judgment—and above all to do no harm. Genetic profiling of patients holds the promise of improved diagnosis, risk prediction, and therefore also patient selection for treatment, as well as the ability to select treatments most likely to benefit and least likely to cause harm. However, this remains an unfulfilled dream at this point in time, with the many studies of candidate genes having had little impact on routine clinical care. Nevertheless, the last year has seen a quantum leap in understanding of the genetics of common diseases, helped by new research methods and technologies. The stage is therefore set for big advances over the next decade.

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Keywords: cardiovascular disease; coronary artery disease; hypertension; genetics; renin-angiotensin-aldosterone system; angiotensin-converting enzyme inhibitor; angiotensin receptor blocker; angiotensin receptor blocker

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of the value placed on salt. The basic skeleton of the physiological system for salt retention begins with a detector mechanism and ends with an effector mechanism. The detector mechanism includes the monitoring of sodium status by the macula densa cells of the juxtaglomerular apparatus located within close proximity to both blood and urine within the kidney. Situated adjacent to the vascular pole of each nephron (the glomerulus) and also adjacent to the distal tubule, the content and rate of flow of both blood and urine can be monitored and regulated. When the sodium content of the urine is detected as being high, the bloodborne hormone renin is released, and the RAAS pathway initiated (Figure 1).5

**Drugs and the RAAS**

Dissection and hence understanding of this system and its relevance to clinical medicine has been aided by the development of a series of drugs that block the system at various levels. These now comprise the following: (i) renin enzyme inhibitors; (ii) angiotensin-converting enzyme (ACE) inhibitors; (iii) angiotensin II type 1 (AT1) receptor antagonists (ARBs); and (iv) aldosterone receptor antagonists. All four classes have the intended and actual effect of increasing salt and water excretion through the kidney. The primary clinical benefits of this are in the treatment of hypertension and heart failure, acting much in the same way as more classic diuretics. However, while this aspect of shared efficacy is of clinical value in lowering elevated systemic blood pressure and reducing fluid retention with associated ankle swelling and breathlessness, a primary objective of all cardiovascular care is the prevention of major clinical events such as myocardial infarction, stroke, and death. In this regard these four drug classes have demonstrated important differences that appear to relate to the “off-target” effects. By their very nature, these important distinctions and differences are not easily studied and defined, with greater emphasis being placed on the effects that are judged to be similar.

**The genetic “scalpel”**

In the laboratory it is possible to genetically modify cells living in culture, whole animals or selected organs/tissues in an animal at a selected time. Protein encoding genes can be removed (knocked-out), changed into a variant form (transgene), or made to be expressed in large amounts (knock-in). This can result in the loss, the gain, or the selective alteration of function of a selected molecule/enzyme/receptor/hormone/ligand. These and other techniques have permitted a much greater understanding of the complexity of the RAAS both with regard the primary axis and also a range of other parallel effects on other molecular systems. However, it is both difficult and potentially dangerous to generalize from observations from in vitro cell systems and in vivo transgenic animal systems to human disease states. A very good example of this relates to “off-target” events mediated via the angiotensin II AT2 receptor.5

**Function of the AT2 receptor**

Angiotensin II mediates its effects through a number of receptors subtypes other than the mainly recognized AT1 receptor, activation of which aggravates...
the clinical conditions of hypertension and heart failure through the release of aldosterone. These include the AT2, AT3, and AT4 receptor subtypes. Of these, the best known and understood is the AT2 receptor. For years after the existence of this subtype was first described the role and function of the AT2 was poorly understood, having presumed significance in new vessel formation both during embryonic development and also during later tissue repair. Other comparable effects that have been attributed to this receptor subtype include the modulation of extracellular matrix, neuronal regeneration, cellular differentiation, and apoptosis. Of particular interest is the fact that in arteries damaged by atherosclerosis the expression of the AT2 receptor increases 8-fold, implicating it as having a role in the plaque biology.

The AT2 receptor gene

In humans, the AT2 receptor is located on the X chromosome, suggesting that these receptors may be involved in diseases (such as CAD) present to a greater extent in males as compared with females. The gene is composed of three exons that span a distance of more than 5 kb. Exons-1 & 2 code for a section of untranslated mRNA regions, while exon-3 codes for mRNA that is translated into the AT2 receptor. The promoter region of the gene includes a possible embryonic long terminal repeat binding protein site. In vitro study of Intron-1 using artificially induced mutations indicates that this section of the gene is necessary for efficient transcription of the gene. In particular, effect relates to a common human mutation found within intron-1 and annotated by Nishimura as +1332G/A and later by Erdmann et al as +1675 G/A.

The distribution of polymorphic alleles of the AT2 receptor gene Intron-1 SNP rs1403543 (G/A) was established. For siblings unaffected by CAD the A/AA genotype was most frequent (53.7%) and the G/GG least frequent (46.3%) while to the contrary for the siblings affected by early coronary artery disease the A/AA genotype was least frequent (47.6%) and the G/GG was most frequent (52.4%). Consequently, the G allele occurred significantly more frequently with premature CAD than would be expected if the disease susceptible locus and typed marker were unlinked (P = 0.028). This difference was driven by a highly statistically significant result in males in contrast to a negative result for females.

Alfakih et al next subcategorized patients into two groups based on the occurrence of myocardial infarction and also the extent of stenotic atherosclerosis. Group 1 consisted of patients who had had myocardial infarction with or without a coronary revascularization procedure for occlusive disease. Group 2 was made up of patients with stenotic atherosclerosis that was of sufficient severity to require revascularization by either coronary artery bypass surgery of percutaneous coronary intervention. There was a sequential increase in the prevalence of the rs1403543 G/GG genotype in Group 1 siblings as compared to the unaffected sibling and in Group 2 as compared to Group 1, both in the cohort as a whole and also separately for males and in females (Figure 2, page 90). These data help to support the hypothesis that the AT2 receptor, and its variable expression, play a role in coronary atheroma. However, to better understand what this role might be, it is necessary to reconsider the evidence derived from randomized clinical trials of: (i) ARBs, which preferentially increase AT2 receptor expression and stimulation; and (ii) ACE inhibitors, which reduce angiotensin II concentrations and thereby also AT2 receptor stimulation.

AT2 receptor gene and cardiovascular disease

Two separate genome-wide searches for regions that may be implicated in the causation of early CAD have demonstrated a statistical link (linkage) to a region (Xq23-26) on the X-chromosome where the AT2 receptor gene is located. This stimulated further research into this hypothesis by a number of clinical investigators. Alfakih et al initially described an association between rs1403543 and premature CAD in 509 families with at least one member affected by early CAD. However, that study was not sufficiently large to examine important details of this primary observation such as the relationship with other conventional nongenetic risk factors, differential effects based on gender and associations with coronary atheroma subphenotypes. All of these aspects have potential relevance to better understanding the differential effects of ACE inhibitors and ARBs with regard to the prevention of myocardial infarction and cardiovascular death.

Later, Alfakih et al studied 885 families (2662 individuals) that had been demonstrated to have appropriate Mendelian relationships and successful genotyped. The distribution of polymorphic alleles of the AT2 receptor gene Intron-1 SNP rs1403543 (G/A) was established. For siblings unaffected by CAD the A/AA genotype was most frequent (53.7%) and the G/GG least frequent (46.3%) while to the contrary for the siblings affected by early coronary artery disease the A/AA genotype was least frequent (47.6%) and the G/GG was most frequent (52.4%). Consequently, the G allele occurred significantly more frequently with premature CAD than would be expected if the disease susceptible locus and typed marker were unlinked (P = 0.028). This difference was driven by a highly statistically significant result in males in contrast to a negative result for females.
Both agents reduce the production of aldosterone and hence also attenuate hypertension and heart failure by reduced salt and water retention. However, a large literature suggests that ARBs have distinct beneficial “off-target” effects as a result of upregulation of AT2 receptor expression and stimulation. Nevertheless, an overview of the major randomized clinical trials of ARBs suggests that any such benefits do not extend to the reduction of major cardiovascular events.24

Meta-analysis designed to assess the benefits or risks of AT2 receptor activation in patients at high risk of cardiovascular events has demonstrated the absence of any net statistically significant benefit on all-cause mortality, stroke, or myocardial infarction (Table I).24 This observation was true irrespective of whether ARB treatment was compared with placebo or with all other randomized comparators. Importantly, these analyses excluded trials in which the alternate strategy of using ARB treatment on top of ACE-inhibitor therapy was assessed. Under such circumstances, the attenuating effects of ACE inhibitors are likely to have diminished ARB-associated AT2 effects. This assumption was based on the observations from the Candesartan in Heart Failure Assessment in Reduction of Mortality (CHARM) program of trials in which the ability of ARB candesartan to prevent myocardial infarction was apparent only in the presence of concomitant ACE-inhibitor treatment.20–21

A recent study looked at the blood pressure response to ACE inhibitors relative to genetic profiles for RAAS gene variants.22–25 Specifically, these related to the angiotensinogen (AGT), angiotensin receptor 1 (AGTR1), and angiotensin receptor 2 (AGTR2) genes in 1447 Chinese patients with established systemic hypertension (Figure 3). The AGT SNP rs7079 and an AGTR1 haplotype were shown to be associated with blood pressure reduction in response to ACE-inhibitor therapy, appearing to explain about 13% of the drug response. A second group looked at an even larger selection of SNPs form the RAAS and other pathways, and demonstrated a significant association between an angiotensinogen SNP and the prevention of left ventricular hypertrophy induced by the ARB irbesartan.21 Both of these studies illustrate the potential promise of pharmacogenetic profiling of patients prior to drug selection, though much larger prospectively designed studies are required in this area.

Table I. Meta-analysis results for angiotensin-converting enzyme inhibitors and ARBs assessing a range of “hard” cardiovascular end points.

<table>
<thead>
<tr>
<th>End points</th>
<th>Number at risk</th>
<th>Number of events</th>
<th>Control event rate (%)</th>
<th>Odds ratio (95% CI)</th>
<th>P value overall effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARBs vs placebo/non-ACEi comparator/ACEi</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>54 050</td>
<td>3 537</td>
<td>6.3</td>
<td>1.08 (1.01 to 1.16)</td>
<td>0.03**</td>
</tr>
<tr>
<td>Stroke</td>
<td>53 318</td>
<td>2 285</td>
<td>4.4</td>
<td>0.92 (0.79 to 1.08)</td>
<td>0.32</td>
</tr>
<tr>
<td>Global death</td>
<td>55 050</td>
<td>7 601</td>
<td>14.0</td>
<td>1.01 (0.96 to 1.06)</td>
<td>0.80</td>
</tr>
<tr>
<td>ACEi vs placebo/non-ARB comparator/ARBs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>144 790</td>
<td>8 377</td>
<td>5.8</td>
<td>0.86 (0.82 to 10.90)</td>
<td>&lt;0.003***</td>
</tr>
<tr>
<td>Stroke</td>
<td>135 803</td>
<td>5 485</td>
<td>4.2</td>
<td>0.94 (0.83 to 1.06)</td>
<td>0.31</td>
</tr>
<tr>
<td>Global death</td>
<td>150 943</td>
<td>1 643</td>
<td>13.0</td>
<td>0.91 (0.86 to 0.95)</td>
<td>&lt;0.001***</td>
</tr>
</tbody>
</table>

Figure 2. Bar chart illustrating the sequential increase in frequency of the G/GG genotype in Group 1 siblings as compared to the unaffected sibling and in Group 2 as compared with Group 1, in males and in females. *P exact = 0.067; **P exact = 0.023; ***P exact = 0.336. CAD, coronary artery disease.

The advent of gene chip technologies has already changed the face of human genetic research, though it has yet to have its full impact. Genome-wide studies performed with assays such as the Affymetrix 500K chip have covered the human genome with gene-environment, and gene-drug interactions are also being shown to have significance, in planned large-scale meta-analyses of more than 120,000 individuals.

Furthermore, important insights into gene-gene, gene-environment, and gene-drug interactions are expected.

REFERENCES
2. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. 2007;447:661-678.
Spices, diamonds, and Ayurvedic medicine
French physicians in 17th-century Mughal India

by C. Régnier, France

Until the Suez Canal opened in 1869, the only sea route to India was round the Cape of Good Hope, pioneered in 1498 by the Portuguese navigator Vasco de Gama. His expedition led to the establishment of European outposts along the Indian coast, especially by the Portuguese who secured substantial commercial privileges. Their use of light two-masted caravels allied to their familiarity with the winds and currents of the Atlantic Ocean enabled them to seize many staging posts on the voyage to India and play havoc with Arab shipping routes. In a letter to the Portuguese king Manuel I, the viceroy of India Francisco de Almeida emphasized the importance of maintaining Portuguese supremacy over the high seas: "If you are strong in ships, trade with India is yours; and if you are not strong in this domain, no fortress you may have on dry land will be of help."1,2

The birth of the East India Companies
Vasco de Gama brought cinnamon, cloves, ginger, nutmeg, and pepper back with him to Lisbon. For the first time, his voyage gave Portugal direct access to the spice producers, breaking the Venetian stranglehold on this lucrative trade (a popular expression of the time being "dear as pepper") and justifying the primary motivation behind the expedition. From the early 16th century, Lisbon became the crossroads of the spice market.

European fascination with the East Indies increased dramatically in the 16th century with the opening of the sea route. India was not only a theater of contrasting civilizations and religions, it was above all an awesome reservoir of spices and diamonds. Economic and commercial imperatives dictated the initial contacts between Europeans and the Indian rulers. This inspired the trading post strategy in which bridgeheads were established without the need for military occupation. The European adventurers who journeyed to India mainly by sea, but sometimes overland, included merchants, mercenaries, missionaries, diplomatic agents, East India Company staff, and several physicians and barber-surgeons. European medicine was still highly doctrinal and undoubtedly inferior to its Ayurvedic counterpart in terms of therapeutic efficacy. Only surgeons enjoyed any professional respect from the Mughal emperors. Yet medicine provided a number of adventurers with a calling card to the courts of the subcontinent, and the subsequent exercise of diplomatic or commercial influence. The French arrived shortly after the Portuguese, British, and Dutch. Several French physicians, notably Bernier, Destremeau, Saint-Jacques de Lapalisse, and Dallon, recorded their Indian experiences in memoirs, manuscripts, letters, reports, logbooks, and drawings, which appealed to European readers’ taste for the exotic.

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(see French abstract on page 99)
Merchants flocked from the four corners of Europe. As well as being used to preserve meat, spices appealed to Europe’s gustatory roots that reached back to the Roman Empire. The spice frenzy only faded somewhat with the arrival of new vegetables in the late 17th century and the marked fall in meat consumption. But spices continued to be prized for their medicinal and perfumery uses.3,4

As Vasco de Gama learned to his cost on his first voyage, what the Indian king on the Malabar coast wanted in return for spices was not the honey, olive oil, bronze bowls, and hats that Gama had brought, but gold and silver. Europeans used both these precious metals, mined in the Americas, to secure and maintain their economic domination.1

In the wake of the Portuguese came the British (1599), Dutch (1602), French (1604), and Danes (1616). In order to operate and organize trade with India, and make it pay, these countries set up dedicated financial structures, East India Companies, which were novel in early European capitalism. The most powerful Company belonged to the Dutch. These authentic “multinationals” maintained fleets, ports, and fortresses; they were also beholden to their shareholders who expected dividends. Their archives in Amsterdam, London, and Paris remain an extraordinary documentary source for the history of the relationships between European merchants and Indian rulers from the 17th century onwards.2,5,6

Culture shock, medicine shock
For 17th-century European adventurers, India was a land where they felt they could make a fortune. The French physicians and surgeons who went to India in the 17th century did so for a variety of motives: some wanted to see how their own practice would fare in a totally different world, while others were out to make their fortune (not necessarily by practicing medicine). Many left with no clear idea in mind other than that medicine would provide a ready income and/or open doors to local authorities. Some adventurers even lacked formal qualifications and practiced medicine or surgery with scant knowledge of either. Although Indians—Hindu and Muslim alike—distrusted European medicine, they often considered Europeans as being naturally versed in the healing arts. “They took us for physicians, which is very common in India,” wrote Louis Laurent de Féderbe, Count of Modave.2,8

Missionaries also practiced medicine, in particular the Jesuits who applied the rule laid down by Saint Francis Xavier in 1537. The practice of medicine and surgery, especially with children and the dying, brought many conversions. Father Pierre Martin testified as much: “Besides, it must not be thought that zeal and piety alone ensure that one’s labors bear fruit in the land of India (…) Knowledge (…) of mathematics, physics, and even medicine is also needed.” Jean Chardin, a jeweler’s son who arrived in India in 1667 and left a detailed and scrupulous study of local therapeutic practice, confirmed this view:

In those parts, all missionaries are taken for physicians because they dabble in prescribing treatments (…) As there are no physicians or surgeons, they have made themselves indispensable to the practice of medicine and surgery, with some being remarkably knowledgeable and practicing with great success.2,8
However, modesty was obligatory given that the therapeutic achievements of the Europeans were open to comparison with those of Indian practitioners. European physicians found it hard to gain the confidence of the Mughal courts. “Remember that before a European could be appointed physician to a prince,” wrote the Venetian merchant Niccolo Manucci who arrived in India in 1654 at the age of 15, “he had to undergo a prolonged probationary period since these princes are extremely wary and exacting in this regard.” The wealth of the Indian pharmacopoeia and the manifest achievements of Ayurvedic medicine greatly impressed the adventurer physicians from Europe who could only boast the three basic weapons in the European arsenal: bloodletting, purging, and theria. Theria was probably the world’s longest-lived and most popular drug, a universal panacea and antidote containing some 40 to 50 ingredients whose formula dated back to the Greeks in the 1st century AD. It found its way to China during the Tang dynasty (667), and was still being dispensed in Europe as late as 1884. On the other hand, the Indians were greatly impressed by European surgery, in particular lithotomy, wound cleansing, and military surgery.2,10

Among the French physicians who established themselves in India in the 17th century, four names stand out: Bernier, Saint-Jacques, Destremau, and Dellon. They shared a taste for adventure and were all curious to experience different civilizations and ways of life. They did not set out to make their fortune, and nor in the main did they achieve it, with only Destremeau dying a conspicuously wealthy man. However, they all relied on their art for an income during the journey and on arrival in India. Subsequently, they became tempted by much more lucrative activities, such as trade, diamond dealing, and diplomacy. We are indebted to them for leaving detailed writings on the civilization, botany and ethnography of Mughal India.2

François Bernier: a sophisticated observer
François Bernier (1625-1688), the son of farmers in the Anjou, was orphaned at an early age and brought up by his uncle, a priest. At the age of 15, he went to Paris, where he studied at the Collège de Clermont, and made the acquaintance of the mathematician, theologian, astronomer, and philosopher Pierre Gassendi (1592-1655). In 1652, he graduated from a 3-month intensive course at the Montpellier medical school that granted degrees on the understanding that recipients would not practice medicine in France (!) Fascinated by philosophy, he gained fame with his 8 volume “introduction” to the work of Gassendi, whose aide and secretary he had become. A year after the death of Gassendi, Bernier, with no attach left in France, set off for Constantinople and Aleppo. He stayed for a year in Syria, Palestine, and Egypt where he caught
the plague. After being imprisoned for 6 weeks in Jeddah, he reached the west coast of India in early 1659, landing at Surat, in the state of Gujarat, where the British East India Company had opened a trading post in 1608.2,11,12 Journeying to Delhi, Bernier was appointed court physician to the Mughal Emperor, Aurangzeb (literally, “Adorning the Crown”) upon the recommendation of another French physician, Saint-Jacques (about whom more later), who had practiced at the court during the previous decade. The new emperor, who had just eliminated his three brothers in a war of succession, had himself crowned under the title Alamgir (literally, “Conqueror of the Universe”). Bernier thus became a privileged witness to historic events such as the public humiliation of Dara, the emperor’s defeated brother, and the sumptuous welcome to the Persian ambassador.

Aurangzeb, who reigned from 1658 to 1707, espoused a strict interpretation of Islam. Bernier reports that the Emperor caught what was probably diphtheria: “He fell extremely ill, with a continuous raging fever that caused periods of confusion. His tongue was so paralyzed that he could barely speak and his physicians feared for his life.” By the end of 1659, Bernier had virtually given up practicing medicine in India. His notes on his medical practice are few and far between, and brief in the extreme. Later in 1659, he made the acquaintance of a wealthy scholar, Danishmand Khan, who took him under his protection. Bernier taught him European science in Persian, dissecting a sheep to demonstrate the circulation of the blood and lymph. In return, Bernier was tutored by a Hindu scholar among his protector’s retinue in the basics of Hindu philosophy and religion.2,11,12

Between 1662 and 1665, Bernier joined the 150 000-strong caravan that took Emperor Aurangzeb to convalesce in Kashmir. It included 35 000 horsemen, thousands of camels, and hundreds of elephants. Kashmir was totally unknown to Europeans. “From all that I have just said,” wrote Bernier, “it can be concluded that I am somewhat enamored of Kashmir, and that I believe there may be nothing similar nor so beautiful.” It was during this journey that he met a Tibetan physician “who had a book of concoctions that he consistently refused to sell me.”

Bernier observed the practice of Hindu and Muslim physicians, remaining noncommittal as to its efficacy. “I leave this to our learned Doctors to determine,” he wrote, not without irony. On the other hand, he observed that “where anatomy is concerned we can say that the Hindus know nothing at all; they simply spew out impertinent nonsense. It is therefore not surprising that they are so ignorant since they never open the body of man or animal.”2,11,12 Bernier’s observations of public health were more detailed:

The abstinence from wine observed in these parts, combined with the country’s everyday sobriety and the sweat and perspiration constantly exuding through the pores, explain why, to my mind, gout, the stone, backache, catarrh, and quartan fever are virtually unknown here, while those who, like myself, have brought such afflictions with them, are finally delivered from them; and even the pox, despite being very common, runs a less cruel and harmful course, with the result that ordinary life is generally much healthier here than at home.11

Bernier also observed frequent cases of filariasis in Indians and visitors and described the technique used to extract the worm by winding it a little further each day outside the body around a small stick.

Before leaving India, at the express request of the director of the French East India Company, Bernier compiled a Mémoire sur l’établissement du commerce dans les Indes [Report on establishing trade in India]. Dated March 10, 1668, it was addressed to Louis XIV’s minister of finance Jean-Baptiste Colbert.
Having returned to Paris, Bernier resumed his passion for philosophy and very nearly got thrown into jail for supporting René Descartes. In 1685, he traveled to England, then the Netherlands where he visited French philosopher and critic Pierre Bayle, an exiled Protestant. Bernier died in 1688, aged 68, from a stroke apparently induced by heated philosophical debate.

Bernier left one of the most detailed accounts ever written of the political, economic, and religious organization of Mughal India. Blessed with an elegant and precise style, and inspired by an educator’s desire to present an honest account of contemporary Indian history and civilization, Bernier maintained copious notes and correspondence throughout his 10-year stay. His *Voyages de François Bernier contenant la description des États du Grand Moghol* was published in 1670-1671, less than two years after his return, and translated into English the same year [*Travels in the Moghul Empire A.D. 1657-1668*] by the first secretary of the Royal Society. Bernier’s letters were known to contemporary luminaries such as Jean de La Fontaine, Racine, and Boileau. Two centuries later, his writings were to draw praise from unexpected quarters: on June 2, 1853, Karl Marx wrote to Friedrich Engels: “No one has written with more brilliance, detail, and power on the development of oriental cities than old François Bernier.” Marx relied on Bernier’s analysis of the absence of landownership to account for the decline and fall of Mughal India.²,¹¹,¹²

Saint-Jacques, physician to the Great Mughal

Few hard facts are available on the life of the French physician Saint-Jacques (1628-1694)—aka Jacques Seuillet or Jacques de La Palisse—who played a prominent role at the court of Emperor Aurangzeb. His name was mentioned by many travelers, merchants, East India Company agents, diplomats, missionaries, and other French physicians present in India at the time. He was unfailingly hospitable and never hesitated to play his princely cards when interceding on his compatriots’ behalf. He enjoyed well-recognized status at the Great Mughal’s court. Louis XIV wrote to him on October 29, 1664, asking for his help in securing a fitting welcome from Aurangzeb for the ambassador François La Boullaye Le Gouz. Bernier described Saint-Jacques as a consummate man of intrigue perfectly attuned to the political choreography of the durbar [Mughal court]. He can provide much intelligence and be of assistance in prosecuting business. He strikes me as a man not to be ignored, either at the present time or in the future.²⁷

Saint-Jacques is thought to have arrived in India around 1648—whether overland or by sea is unknown. There is no evidence that he was a physician or had ever studied medicine. He may have picked up some medical knowledge from missionaries. Hard evidence for his presence was provided by Jean-Baptiste Tavernier who in Delhi in 1665 met “a French surgeon de La Palisse, known as Saint-Jacques; he speaks Indian well and is married to the daughter of a Portuguese. The Nawab is very fond of this surgeon.” Whatever his background, Saint-Jacques practiced medicine in India, and had no other employment. When implementing Islamic law in 1668, Emperor Aurangzeb banished all Christians except physicians and goldsmiths to at least one league from Delhi. Saint-Jacques was one of those who stayed put.²,¹³ In a letter dated December 27, 1678, to his Superior in the Society of Jesus, the Portuguese priest Joseph Freyre wrote:

> In the city of Delhi lived a Christian by the name of Saint-Jacques, a Frenchman by nationality and physician by profession, to whom the palace gates had been opened in recognition of the excellence of his art. For the perfection of the care that he administered he was rewarded with the King’s gratitude complete with the title of Macebdar and an allowance of 6000 rupees a year, all of which gave him much standing and respect at Court.

Centuries-old method of extracting treating dracunculiasis (aka, guinea worm disease, or Medina worm), once the parasite has emerged from the skin, by inching it out, day after day, coiling it around a stick, a painful process that can take up to a month. © Institut Pasteur.
Saint-Jacques stayed in India for nearly 40 years and witnessed many political and military events. He married a mixed-race Portuguese woman who bore him two children. His private life appears to have been more than colorful, extending to the attempted poisoning of his wife, and as such attracting much contemporary comment. Saint-Jacques made several attempts to flee back to France, and eventually obtained the Grand Mughal’s permission to leave India in 1688. Having received substantial emoluments over the years, bought large quantities of diamonds, and sedulously advertised his appreciation of recompense for his services as a go-between, he is unlikely to have returned to France empty-handed. Saint-Jacques died on December 23, 1694.

Antoine Destremau, sultan’s surgeon and diamond dealer

Antoine Destremau (1636-1685) from southwest France (Armagnac) learned basic surgery with his brother Lucas in a brotherhood, or guild, in the adjoining province of the Béarn. According to a baptismal registry from March 10, 1687: “he served his surgery apprenticeship locally before traveling across France, as surgeons customarily do to hone their skills, then left our region around 30 years ago and never returned.” He probably left for India around 1660. Three years later, the wealthy Tavernier took him as his servant on his sixth voyage to India. Destremau was a Calvinist, like his master, and accompanied him throughout his travels in India until 1666. This gave the young surgeon the opportunity of rubbing shoulders with all the better-known Frenchmen who were visiting India or had made it their temporary home during this period, as confirmed by his name cropping up in their various accounts.2,7

Destremau spent almost 20 years in the sultanate of Golconda (Hyderabad) and was surgeon to Sultan Abul Hasan from 1672 to 1685. Being well introduced at court, he enjoyed a considerable income. A priest from one of the foreign missions, Father Jean Joret, testified as much in a letter dated December 27, 1682: “We lodged in the city with Mr Destremont, a Frenchman who is physician to the King, and a great friend of the King’s brother-in-law, who is fond of the French.” The sultanate of Golconda was courted by the Dutch and British for its diamonds, silver, copper, tin, and lead, as well as for spices such as pepper and cinnamon. Since he spoke Persian, Portuguese, and Dutch, Destremau was probably working for the French East India Company, while not hesitating to act on behalf of British interests as well. In October 1684, François Martin, director of the French East India Company’s Pondicherry trading post, confirmed that Destremau was the Company’s agent at the court of the sultan of Golconda. Of the three known letters in Destremau’s writing, not one refers to medical activity, but only to matters of trade or diplomacy. The French surgeon also dealt in diamonds, which was a highly lucrative activity. He soon amassed a considerable fortune, since he was able to come to the assistance of Admiral Jacob Blanquet de La Haye, leader of the French flotilla besieged near Madras in March 1673.2,3

Destremau died after a long fever on July 17, 1685, at the age of 49, bequeathing a substantial fortune and stipulating that he be buried in the Dutch cemetery. His will, written in Portuguese, set aside sums for the poor of his birthplace, La Houga (Gers), his brother Lucas, his sister’s children, and his friend and
fellow diamond dealer/jeweler François Guesty, whom he also appointed as his executor. Guesty was unscrupulous enough to embezzle part of the legacy, for which he was pursued by the local judiciary. In January 1689, the French naval minister undertook his own investigation into the whereabouts of the surgeon’s assets, some of which were returned to France 3 years later.11

Charles Dellon, the most medical of India’s French physicians
Born in Agde (Hérault), Charles Dellon (1650-1710) embarked at the age of 17 as second surgeon on board the Royal India Company ship, La Force. In 1673, he became a physician north of Bombay, in Daman, Portuguese India, treating the inhabitants and their governor Manuel Furtado de Mendonça:

From this moment onwards, I began seeing patients at the hospital and in their homes. At that time Daman only had a few Pandits, or Indian physicians, with very limited skills. Generally speaking, the only knowledge possessed by such physicians consisted of a few remedies that they dispensed as prescribed by tradition rather than reason. Furthermore, since Europeans enjoy high esteem in the Orient, and since I was not lacking in boldness myself, my services were called upon not only by the Portuguese, but even by the Indians who used to send for me from 10 leagues away (...) As the town of Daman is not particularly large, I was soon a familiar figure everywhere.2,12,15

In a plot hatched by the Portuguese governor of Daman, the Indian secretary of the Inquisition, and a Dominican friar, Dellon was accused on a trumped-up charge of heresy for having blasphemed against the adoration of a crucifix. He was incarcerated for 18 months by the Inquisition in Goa, excommunicated, stripped of his possessions, and sentenced to 5 years’ hard labor in Brazil and Portugal. On his return to France in 1677, he began writing his memoir, Relation de l’Inquisition de Goa [An account of the Goa Inquisition]. Published in 1687, it proved an immense popular success. It was promptly translated into German, Dutch, and English—and placed on the Vatican’s Index of banned books in 1690. Republished several times in the 18th century, it was the inspiration behind several passages in Candide by the French philosopher Voltaire in 1759.12,15

Dellon was clearly an able physician despite holding no recognized university degrees. He was one of the only French physicians in India to publish a work of medicine (Traité des maladies particulières aux pays orientaux, et dans la route, et leurs remèdes, Paris, 1685 [Treatise on the diseases specific to the Orient and travel there-to, their remedies]). Its 62 pages deal with the diseases commonly encountered during the voyage and in India itself, such as scurvy, vomiting, cholera, smallpox, snakebites, and filariasis, as well as the “exhaustion caused by sexual excess.” In addition to extolling bleeding and purging, Dellon recommended some Indian treatments such as betel leaf, betel nut, and congee, a salted ground-rice porridge for diarrhea. He also published a botanical work Curiosités (Curiosities) in 1703.12 In 1685, he became physician to the Prince of Conti, one of the Royal India Company’s major subscribers. Little is known of his final years and he is believed to have died around 1710.

Epilogue
Other genuine or self-certified French physicians were present in India in the 17th century, such as Biron, author of a learned medical treatise on Indian botany, and Séguineau, whom the French nicknamed “Doctor Too bad/So much the better,” and who was in India from 1669 to 1673. Others who should be mentioned include the surgeons of the Royal India Company based in Pondicherry, although their reputation was often disastrous.

The European medicine of the 17th century deserved the ridicule heaped on it by Molière. There was little chance of it impressing anyone, Indians included, either through the success of its treatments or the acuteness of its observations. For the men who set out for India as adventurers, explorers, and fortune-seekers, medicine remained, above all, a useful prop, calling card, or fallback.
Épices, diamants et médecine ayurvédique

MÉDECINS FRANÇAIS EN INDE MOGHOLE AU XVIIÈME SIÈCLE

he rise and fall of the European trading posts that dotted each coast of the Indian subcontinent reflected the commercial rivalries and colonial ambitions of the European powers as well as political rivalries between Indian princes. The reason why many Europeans settled on the otherwise uninviting Coromandel Coast was that it represented an important staging post on trade routes between the Mediterranean and the Far East. Pondicherry (modern Puducherry), which acted as the capital of French India during Joseph François Dupleix (1697-1763), slipped back into anonymity after the Treaty of Paris in 1763.

The India Companies

European rulers granted their merchants trading monopolies in Asia and America, creating the East and West India Companies, respectively. The West India Companies lasted only decades, whereas the East India Companies remained active for a century, and in some cases longer. Thus, the French West India Company, set up by minister of finance Jean-Baptiste Colbert in 1664, was dissolved in 1674, while its Dutch counterpart managed to survive from 1621 to 1667. In Asia, the situation proved quite different. The English East India Company, founded in 1600, lasted until 1858, and its Dutch counterpart from 1602 to 1795; the French East India Company, set up in 1664, suspended in 1769 and reorganized in 1784, finally lost its monopoly in 1791.

The five trading posts of the French East India Company were Pondicherry (modern Puducherry), its smaller districts of Karaikal, Yanam, and Mahé, and Chandernagore (modern Chandannagar) in the then wealthy Bengal. Pondicherry on the Coromandel Coast, where the French were granted leave of settlement by the Mughal emperor in 1673, was the French capital of southern India, enjoying huge prestige in the 1750s. Fertile Karaikal fed Pondicherry and supplied it with cloth. Mahé on the west coast produced pepper. Chandernagore was commercially the most active. These highly coveted trading posts were subject to the vicissitudes of European politics and their repercussions in Asia. The French East India Company took advantage of the declining Mughal Empire to intervene in Indian politics and protect its interests. The governors resided in Pondicherry. Their initial task was to contain the Dutch (1693), but their most bitter struggles were against the British, who destroyed the city in 1761. Pondicherry was returned to the French at the Treaty of Paris (1763) and rebuilt within two years. In 1902, when stepping ashore on Pondicherry beach, the writer Pierre Loti described “the melancholy induced by arriving in this distant and charming town where an entire French past dozes behind cracked walls.”

Joseph François Dupleix (1697-1763) and the Marquis de Bussy-Castelnau (1718-1785) were “remarkable administrators or war leaders who dreamed of a French empire in India, but it was a dream unshared by the French government.” The five trading posts were ceded back to India between 1949 and 1956.
**Mughal India**

India was a vast empire when the French under Louis XIV decided to establish a number of commercial outposts in the second half of the 17th century. The subcontinent was ruled by the Timurid Mughals, a Sunni Muslim dynasty of Turko-Mongol origin from Samarkand. Although descended from the notorious Timur (Tamerlane), they no longer carried his warrior genes. From the reign of Babur (1526-1530) to that of Shah Jahan (1627-1658), India became dotted with remarkable palaces, renowned for the refined lifestyle and brilliant civilization of an aristocracy that not infrequently viewed Europeans as “barbarians.”

In the era in which France turned its attention to India, the Mughal empire was foundering from a combination of sheer vastness and oversophistication. Dynastic decline proceeded apace under Aurangzeb (1658-1707). While quick to seize the opportunities on offer, France was slow to digest the long-term consequences. The protectorate policy—invented by Dupleix almost despite himself, admirably pursued by Bussy, and imitated by the British with legendary success—was never understood or supported by the French government. Paris was even shocked to discover that Pondicherry was its counterpart in Southern India, playing a capital city’s role with all the pomp that this implied at the time. Unlike Britain or the Netherlands, France was primarily a land power. It lacked the money to develop and modernize its fleet, which was only half that of Great Britain and the Netherlands. Being relatively powerless at sea, it was never really in a position to defend its overseas colonies. In all attempts to do so, it prioritized the French West Indies and Canada. Lukewarm commitment to India explained why at the Treaty of Aix-la-Chapelle (1748) France swapped Madras for Louisbourg on Cape Breton Island (Canada), in a deal that put Pondicherry in jeopardy. Understandably, the settlement of Pondicherry felt abandoned: in 1750, French influence in Southern India was immense, as was the prestige of Pondicherry itself. A show of support was all that it required to strengthen its position, but Paris was oblivious. Reinforcements were sent with the sole aim of “fighting off the British.”

**The rush for India in the 17th century**

Indian riches had always attracted foreign merchants. The Portuguese discovered the route to India in 1498. In the 17th century the Dutch, British, and Danes arrived on the Coromandel Coast to offset the Portuguese settlements in Goa and along the Bengali coast. Trade was the sole motive behind the Portuguese presence in Asia. Goa was their Asian capital. Symbolic of their determination to remain masters of trade with the East was the hanging in Goa in 1602 of two Zeeland merchants for having attempted to sell pepper.

In the 17th century bitter rivalry pitted the British against the Dutch, at a time when both were attempting to oust the Spanish and Portuguese from Asia. The British were notorious for privateering and plundering, with bases at Masulipatam on the Coromandel Coast, Bantam (modern Banten) on the western tip of Java, and Surat in the state of Gujarat, a major port with multiple connections to Indian Ocean countries.

In 1639 Francis Day—“Day of Madras”—who headed the British East India Company factory in Masulipatam, was exploring the southern coastline when he negoti-
ated the concession of some land near São-Tomé, occupied by the Portuguese. He asked the local chief, or mayak, to finance the building of a fort, promising reimbursement once the Company was installed and providing employment for the region’s weavers and dyers. Less than a year later, the new trading post of Madras was born, comprising 80 substantial houses under the imposing walls of Fort St George, which itself was not completed until 1653.

**Delayed French interest in India**

The French were slow to take interest in India. All through the 17th century, they read accounts by travelers attracted by this mysterious yet fascinating subcontinent: “They discovered the adventures of the Goan mercenary François Pyrard de Laval, the reflections of François Bernier, who had become doctor to a Mughal prince, the memoirs of the jeweler Jean-Baptiste Tavernier, or the descriptions by Melchisedec Thévenot.” But actual French settlement in India was a less simple matter.

The turning point came in 1661, when Louis XIV assumed effective control of government. Envying the Dutch their commercial success, he closed the French markets to them and used the newly founded French East India Company to encourage rival colonial companies. In 1666, the Mughal emperor Aurangzeb granted France permission to establish a trading post in Surat. François Caron, the recently appointed director general of the French East India Company, arrived there in 1668 with substantial funds, and asked for logistic support and warships. In 1670 an impressive flotilla commanded by Admiral Jacob Blanquet de La Haye embarked from La Rochelle to show the Dutch that the French meant business in Asia. However, its attempts to take Ceylon (modern Sri Lanka) or to hold on to São-Tomé after its initial capture were to prove unsuccessful.

**The founding of Pondicherry**

The founding of Pondicherry was to engrave an otherwise unsuccessful expedition in French memory. When dispatched by Admiral La Haye to seek food and munitions from local rulers, Louis Auguste Bellanger de Lеспinay obtained permission from the sultan’s governor, Sher Khan Lodi, to establish an outpost at Pudu Cherry (“new village”), a small fishing and trading village south of São-Tomé. Once the French had taken it
over, François Martin, commissioner of the French East India Company, was the driving force behind its rapid growth, beginning in 1674. He began by raising two brick and stone bastions to carry eight cannon. The site was constantly threatened. The hinterland was a battleground between Indian princes and it suffered incursions from Marathi marauders. Martin had to pay the princes protection money while maintaining enough soldiers to repulse any attack.

Franco-Indian trade
In the 17th and 18th centuries it was India’s luxury products that mainly interested France. But because India had no need for French products, the resulting trade imbalance created a deficit, which France attempted to offset by shipping precious metals to India. Like other European East India Companies, except for the Dutch, the French exported cargoes of gold bars and silver pieces.

Shipments from France to Asia
The French East India Company operated its precious-metal route by sending ships to Hispaniola (the island comprising modern Haiti and the Dominican Republic), which was rich in Spanish gold, or to Louisiana, bordering Mexico; alternatively, it bought piasters in Cadiz, the home port of the galleons returning from the West Indies and also a port of call for those on their way to India. On other occasions the Company bought a little gold in Portugal. “Over the period from 1725 to 1770, for which data are available, France carried close on 6 million marks to Asia, roughly equivalent to one quarter of the kingdom’s metal reserves on the eve of the Revolution.”

These shipments were supplemented by wines and spirits: “Pondicherry needed 8000 to 10 000 liters of Bordeaux a year, 20 000 liters of brandy and 200 000 liters of madeira,” as well as fabrics such as twilled woolen cloth from Sedan and Amiens. Shipments also comprised occasional luxury items such as gold thread and coral.

Shipments from Asia to France
Shipments for the return journey consisted of fabrics, white cloths, and muslins. Between 1730 and 1750, Company ships returned to France with 250 000 to 300 000 lengths of fabric yearly. These goods entered the kingdom freely provided they were labeled with the Company’s name. Conversely, when the Company bought “painted” or “dyed” fabrics, also known as “Indian fabrics,” it was allowed to sell them anywhere except in France, a measure designed to protect French manufacturers. To enforce the law, special checks were carried out on ships arriving from Asia. An excise sloop would meet the incoming ship, officials would climb aboard and place seals on the crew’s sea-chests and bags. Once in port, usually Lorient, nothing could be unloaded without being checked. Painted/dyed fabrics were stored in warehouses under armed guard. Despite all these precautions, every device was used to smuggle the prized Indian fabrics ashore undetected. Boats would meet the incoming ships out at sea, before the excise sloop reached them. The delightful Indian fabrics with their leaf and bright-plumed bird designs won over the French, who found them more attractive than their own geometric and floral patterns. The Lyon silk manufacturers asked
the ban to be extended to the importation of silks for the same protective reasons. Duly implemented in the late 17th century, the ban soon generated its own contraband market, as with the regular fabrics. As for food imports, pepper was by far the most important commodity, with 400,000 to 500,000 pounds being shipped from Mahé annually. Minor items included cardamom and rhubarb, for use in preparing medicines, and, more minor still, cinnamon, alum, and aloes. The two main heavy goods were Bengali saltpeter and the Maldives cowrie shells that were used as a slave trade currency and were in particular demand along the coast of Guinea. Rattan and dyewood served as ballast and also helped to keep the fabrics and pepper dry.

The annual sale
All ships left India with their return cargo in January, during the winter monsoon season, which was the best time of year for crossing the Indian Ocean. The imported goods were sold yearly in October. In the 17th century, the sale took place in Paris, then in Le Havre; in the 18th century in Saint-Malo, Nantes, and then Lorient. The major sale was followed by a “little sale,” featuring curios and spoiled goods. Up to 1730, according to Philippe Haudrère, sales barely reached 10 million livres tournois (1 livre tournois = 0.31 g fine gold). Turnover then doubled from 1730 to 1755, at which point the Company was running head to head with the British East India Company, except during the War of the Austrian Succession. After 1760 and the Seven Years War, the Company experienced financial difficulties, with sales falling back below 10 million.

The booming trading post of Pondicherry
Under François Martin, the fishing village expanded into a town. Having completed the fortifications, his main concerns were to strengthen ties with Sher Khan Lodi and establish regular trading links with the home country. The population grew with the arrival of Indians fleeing local conflicts. French expansion continued in Bengal with the founding of Chandernagore by Martin’s son-in-law, Bourreau-Deslandes, in 1688. The Surat outpost was abandoned.

In 1701, the creation of a sovereign council chaired by Martin gave Pondicherry the preeminence that it was to retain, even over the commercially more active Bengali settlements. The expansion of French presence in India was weakened by conflicts in Europe and the policy of Louis XIV, who redeclared war on the Netherlands in 1699. Martin was unable to repulse the Dutch troops and was forced to capitulate in 1693. Peace came with the Treaty of Ryswick in 1697, but the Dutch only returned Pondicherry in 1699, after much hesitation. Having already been weakened in this war, the French East India Company was then hit by another, the War of the Spanish Succession (1701-1714). Trade suffered in consequence. Nevertheless, at Martin’s death in 1706, France was left with sizeable settlements along the Coromandel Coast and in Bengal. Pondicherry, the Company’s political and administrative capital, had a population of 60,000.

The Peace of Utrecht in 1713 that put an end to the War of the Spanish Succession left the Company ruined. Martin’s successors failed to match his mettle. Hébert, for example, falsified his accounts to make the Indians appear as embezzlers, enabling him to impound their goods. Once unmasked he was forcibly repatriated to France in 1718. After his departure, Pondicherry slipped further downwards, threatening Martin’s whole achievement. However, once the Company was taken over by the Compagnie d’Occident, founded by John Law (1671-1729)—“Law of Lauriston,” France’s Scottish-born Comptroller-General of Finances—it was ready to make a fresh start.

French expansion (1721-1741)
The new Company registered two decades of increasing prosperity, thanks partly to the peace and stability that had returned to Europe. New trading posts were founded, including Mahé (1721), on the Malabar Coast (the western counterpart of Coromandel) where France already held the outpost of Calicut (modern Kozhikode), a crucial link in the pepper trade. The British, who owned the neighboring trading post of Tellicherry (modern Thalassery), found the French presence unwelcome and riposted with a series of hostilities via Indian intermediaries: incursions across Mahé’s borders, seizing of ships at sea, and blockade. A local ruler, the Rajah of Badagara (modern Vatakara), conspired with the British and in 1724 ordered the French garrison to evacuate Mahé. It returned strengthened six months later and defeated the Rajah’s
forces. On March 10, 1728, the French and British Companies agreed to stop attacking each other’s forts and ships once they were in sight of Mahé or Tellicherry. The agreement held until 1760, despite wars at home between the two countries.

Subsequently the French settled at Yanam in 1723 and at Karaikal in 1739, remaining in each case until 1954, interspersed by periods of British rule. Conflicts erupted after the death of Emperor Aurangzeb and Indians often called upon the French to help rid them of their enemies. Sahaji, the king of Tanjore (modern Thanjavur), requested support from Pierre Benoît Dumas, the governor of Pondicherry (1735-1741), offering money and the rice-growing region of Karaikal in return. Dumas set up a corps of 5000 Indian auxiliaries or sepoys, organized along European lines. French prestige was boosted when fearsome pillaging warriors, the Marathis, invaded the territory of the Nawab of the Carnatic, Dost Ali Khan (reign: 1732-1740), killing him in battle. His widow asked Dumas for shelter. When the Marathis came to Pondicherry to demand the widow and her gems, Dumas refused to hand her over. Not only did the Indian princes esteem him all the more, but a son of Dost Ali Khan was so moved by the nobility of this gesture that he gifted him some land in thanks.

Joseph François Dupleix (1697-1763), member of the French East India Company Council in Pondicherry in 1720, became Superintendent at Chandernagore in 1730, and was appointed Governor General of all the French Indies in 1741. © Frédéric Soltan/Sygma/Corbis.

Dupleix: from glory to disgrace

Dutch decline in late 17th century India strengthened the presence of the French and British. In the 18th century rival interests brought them into armed conflict on several occasions. The history of France in India was to reach its peak in the era of Joseph François Dupleix (1697-1763), but ultimately “his policy cost dearly, leading to the loss and ruin of French influence and a corresponding consolidation of the British presence.”

In order to protect trade, Dupleix sought to avoid conflict with Britain. When the French declared war on Britain in 1744, he made an agreement with the British Company: no hostile acts by either Company east of the Cape of Good Hope. But the Anglo-French entente cordiale in India could never hold. When British naval officers broke the agreement by capturing several French ships, Dupleix decided to attack Madras, sending an engineer into the city to reconnoiter its weakest points, and securing the dispatch by the governor of Mauritius of ten vessels and 2300 European troops under the command of Bertrand-François Mahé de la Bourdonnais.

Its preparations complete, the French squadron launched the siege of Madras on September 14-15, 1746. Taken by surprise, the British were unprepared and surrendered on September 21. La Bourdonnais offered to return the city for a ransom, the exact amount of which would be subject to a gentleman’s agreement. He backed his undertakings with his word of honor. But French victory was weakened by disagreement between La Bourdonnais and Dupleix, who believed that his role was that of overall commander. La Bourdonnais, on the other hand, felt that where the fate of Madras was concerned, he himself should have the last word. In this clash of viewpoints, Dupleix refused to countenance talk of ransom, since he was all too conscious of the prize that Madras represented. His aim was to cripple the city and he had no hesitation in breaking the agreement entered into by La Bourdonnais. In the ensuing trial of strength between the two men, meteorological chance came to the aid of Dupleix: a cyclone laid waste the fleet commanded by La Bourdonnais and it limped back to Mauritius. Dupleix seized on the opportunity to push forward with his plans. But without La Bourdonnais and his fleet, he had to ask the Nawab of the Carnatic to attack Madras. The British were masters of the sea and mounted a vigorous riposte. Not only did they establish a blockade along the coast, but in 1748 a British squadron under Admiral Edward Boscawen landed in Pondicherry with 8000 men. The city fought back and the British withdrew after a siege lasting 40 days, having lost 1675 men versus only 393 French dead. The treaty of Aix-la-Chapelle (1748) restored the ante bellum status quo: Madras was returned to the British in a sorry state following its partial destruction by Dupleix.

Dupleix had brilliantly defended Pondicherry, but his policies were aggressive and the local inter-Indian wars played against him. The Indian princes found it expensive to maintain troops after the war against
the British. They asked Dupleix for help in exchange for territorial concessions and economic benefits. In 1749, Dupleix backed the coalition of Chanda Shahib, a friend of France, against Anaverdi Khan, the king of the Carnatic. The French and their Indian allies won the battle, with Anaverdi Khan dying on the field. An outstanding French officer was the Marquis Charles de Bussy-Castelnau who arrived in India in 1746 and set out to “learn the language, study the customs, and familiarize himself with the competing political interests.” The situation between the French and English turned ugly. In the Carnatic, Dupleix had to grapple with a bitter enemy, Mohammed Ali, backed by the British. Bussy meanwhile was strengthening his position in the Deccan Plateau, obtaining land along the Orissa coast, by the Bay of Bengal. This took him too far to be of assistance to Dupleix. “So long as Dupleix was successful on the battlefield, the Company was happy to give him free rein, but it became concerned after the defeats at Trichinopoly in 1753. France, which was now at peace with Britain, was worried by the Anglo-French conflict in India and decided to bring Dupleix home.”

The weakening of French India

In 1754, France sent Charles Godeheu to Pondicherry to begin negotiations with the British. The two Companies agreed to take no further part in inter-Indian conflicts, to abandon their territorial ambitions, and to retain territories of similar size around Pondicherry and Madras. “Godeheu’s agreement with the British in India proved to be worth no more than the paper it was written on, since as soon as he left the British simply resumed the same expansionist policy that had been followed by Dupleix.”

The peace intended by the Godeheu treaty proved short-lived indeed: war between France and Britain—the French and Indian War or Seven Years War—broke out in 1756, although it took until October for the news to reach India. The French had around one thousand men, the British twice that. This imbalance produced some decisive British victories, notably in Bengal with the capture of Chandernagore (1757), which was razed to the ground. The most bitter fighting was in the Carnatic where the French under General Thomas Arthur Lally-Tollendal and Bussy tried in vain to retake Madras (1739). Bussy was made prisoner and Lally found refuge behind the ramparts of Pondicherry which the British then set out to starve into surrender. The besieged inhabitants survived on cats and rats, and many soldiers deserted. In 1760, fourteen British ships surrounded Pondicherry. The French held out for a year until, exhausted, they capitulated unconditionally in 1761. The British then razed the European city.

The Treaty of Paris (February 16, 1763) restored peace between France and Britain. The trading posts of Pondicherry, Karaikal, Yanam, Mahé, and Chandernagore were returned, but the British held on to the territories they had conquered. They were particularly strong in Bengal where they banned the French from restoring the fortifications at Chandernagore. The Treaty of Paris was deeply hurtful to the French because it left them with mere scraps of territory and trading posts that were largely demolished. Lally was accused of high treason, condemned to death, and executed on May 9, 1766.

**1763-1778: a new lease on life for the trading posts**

When Baron Jean/John Law of Lauriston, a distant cousin of the original John Law, took back Pondicherry in 1765 in the name of France, the city was but a heap of ruins. The combination of longstanding neglect by Paris and a catastrophic financial situation had compounded its destruction by the British. But thanks to Law, the European city was rebuilt within two years, complete with administrative buildings, private houses, and elaborate fortifications. Yet French commercial and military power was on the wane. The British were ahead in many fields, discouraging the French from launching any commercial ventures. In addition, they were devoid of scruples: “in January 1774, they had the Indian commander of the guard of the French outpost publicly flogged at every intersection in Dacca [modern Dhaka], and they made known, to trumpet blasts, that anyone claiming to live under the French flag would be summarily impaled. In December of the same year, they published, to drum rolls, a ban on weavers working for the French, on pain of death by hanging!”—hardly a propitious climate for the revival of French power in India.
From 1778 to 1962

The American War of Independence (1775-1783) hastened the collapse of French India after France intervened in the conflict pitching Britain against its American colonies. The immediate effect of this intervention was the loss of the French outposts in India. The British attacked Pondicherry and the fragile alliances that the French forged with Indian princes disappeared in smoke. After two periods of British occupation (1778-1785 and 1792-1814), Pondicherry was returned to the French in 1816. At the Treaty of Paris (1814), the British gave France back its five trading posts, but none were to shine with their former prestige. Nevertheless, a royal college was established in Pondicherry in 1826. It was the first academic institution in the French Empire, and was followed by a School of Law (1838) and the first Alliance française (1893). Chandernagore reverted to India in 1948, the year after independence, followed de facto on November 1, 1954, by the four trading posts forming the territory of Pondicherry. Although the formal transfer treaty was signed between France and India in May 1956, de jure transfer did not take place until 1962.

Daily life in the trading posts

In terms of daily life, the trading posts were embryonic French communities, from the founding of Surat onwards, according to its description by François Martin: “a little Babylon... where you see people from virtually all conceivable generations…. The streets are always chock-full with carts, elephants, camels, beasts of burden, coaches, horses, and palanquins…. Such a mixture gives an impression of greatness and wealth yet the city is very badly built, dirty, and in several places even putrid.”

Pondicherry soon sped ahead of the other trading posts, Masulipatam, Balasore, and even Chandernagore, none of which had “a typically French cityscape or colonial community, no doubt because they were much less commercially active. Things were quite different in Pondicherry.”

More than one historian was surprised by Bellanger de l’Espinay’s decision to settle this fishing village in 1673. The writer Robert Challe, traveling as ship’s purser, confided to his diary in 1690: “This is the most wretched and barren site along the Coromandel Coast,” adding “I fail to understand the intentions of the first Frenchmen who settled a place so difficult of access from the sea, so open to access from the land, and so uncomfortable in which to live.”

Although there was much common sense in these criticisms, Pondicherry’s location was not as bad as it was painted. Its shipping roads were among the best along Coromandel; the mouth of the Ariyankuppam river offered ships a safe haven; the water was excellent; and the local weavers manufactured cotton goods that delighted the French. Travelers also agreed that the location had its charm: “the coastline of fields alternating with woods is pleasing to the eye, being quite beautiful, even and flat.”

This therefore was where François Martin founded Pondicherry: “a French city enshrined in the magical colors of Oriental vegetation,” according to the Pondicherry-born soldier of mixed race Édouard de Warren. Martin was to govern with intelligence and diplomacy. By undertaking to respect ways and customs, he inaugurated what was to be known until 1954 as France’s policy towards indigenous communities. He made generous tax exemptions to weavers and granted lands to the soldier-colonists. To ensure that the city could defend itself, he completed the rectangular Fort Barlong. Between them, Capuchins, Jesuits, and foreign missions built four churches. The Company director and officers lived in the fort and several Frenchman had “decently built single-storey whitewashed houses.” Challe was particularly impressed by the whitewash, which he likened to “white marble.” When the Dutch occupied the city (1693-1699), they built a wall with six fortified turrets around the Coromandel Coast,” adding “I fail to understand the intentions of the first Frenchmen who settled a place so difficult of access from the sea, so open to access from the land, and so uncomfortable in which to live.”

After they left, Martin came back to Pondicherry where he pursued his goal of transforming the city into a genuine capital. By 1702, he’d built a new fort around the old one: “a copy of the pentagonal fort at Tournai in France... the only fort in the colonies that was built to a design by Vauban.” Between 1699 and his death in 1706, Martin created a major thoroughfare, the rue des Français (modern Dumas Road), and the rue des Capucins (modern Romain Rolland Street). To the north stretched the Indian quarter with its pagodas “and beautiful long tree-lined avenues.”
Europeans gradually began to build homes in this part of the city. Martin’s successors did not inherit his interest in town planning, and not until Pierre Lenoir did someone seek to carry his work forwards. To strengthen the city’s defenses, Lenoir built a new wall with powerful bastions.

Pondicherry, which numbered “200 Frenchmen and an indigenous population of several thousand in 1690…, grew to 30,000 inhabitants in 1705, 60,000 in 1718 and 100,000 in 1725.” The two main districts came to be known as “the white city and the black city, until the former was dubbed the business district and the latter the red light district.”

New thoroughfares were built. The long rue Madras (modern Mahatma Gandhi Road) crossed the city from north to south, and the rue Valdaour (modern Nehru Street) from east to west. At this time right-handed castes banned left-handed castes from crossing their streets on horseback or by palanquin. Lenoir did away with this ban and “proclaimed free movement of all castes on the main thoroughfares because the king wished no distinction to be made between his subjects, whatever their beliefs, race, wealth or poverty.”

To ensure that buildings stayed hygienic and attractive, Lenoir insisted on the use of bricks and tiles. Some visitors were impressed, others hoped for improvements: “it is difficult to get about in the sandy streets, some of the Indian houses are dilapidated…” Dumas strengthened the fortifications and developed the southern district where he built a hospital, a mint, and a new church (Notre Dame des Anges), as well as laying out splendid public gardens.

His successor, Dupleix, found Pondicherry “one of the most beautiful cities on the Coromandel Coast.” Before becoming governor of Pondicherry he had spent over ten years in Bengal where he had turned Chandernagore, a village of huts set among weeds, into a “a large town with two churches, two mosques, several pagodas, a hospital, quays, an arsenal, and strong fortifications. Where there were once wattle and daub huts, there were now 6000 houses, including over 2000 in brick.” In 1740 Chandernagore’s population reached 30,000.

During the first years of his governorship of Pondicherry, Dupleix completed the works undertaken by Dumas. He restored the town after the 6-week siege in 1748, when over 60,000 cannonballs had rained upon its walls. As a henceforth victorious city, Pondicherry shone like the capital of a vast empire and its gov-

The French Institute of Pondicherry

In 2005 the French Institute of Pondicherry celebrated its 50th birthday. The Institute was set up in 1955 after the agreement that ceded the French trading posts to India. From the start, in the words of Pandit Jawaharlal Nehru, it was considered “a window open on France.” It had three Departments: French Language and Civilization, as in the French Institutes in some other countries; Sciences, at the request of the host nation eager to develop a new India; and Indology, headed by the director of the French School of the Far East. Beginning in 1958, the French Language and Civilization Department has been run by the Alliance Française in Pondicherry. The Sciences Department has undertaken a vegetation mapping project on a scale of 1/10^6, built up a herbarium containing 40,000 specimens (including many endemic species), collected tropical pollens (to form one of the world’s richest biological archives for reconstructing the local paleo-environment), and gathered soil samples. The Indology Department has collected manuscripts on palm-leaves and published as well as translated Sanskrit and Tamil manuscripts.

Over the years, the Institute has come into its own. It has played a leading role in scientific cooperation between France and India. Indeed, India offers a privileged field for research in this regard, particularly in its position as the second most populated country on the planet.

The Institute is now recognized in international research circles as a particularly important observatory from which to study sustained development in South Asia. It also plays a major role in the network of cooperation that links France to India and, more generally, Europe to Asia. As a multidisciplinary institution with its own budget reporting to the Foreign Ministry, the Institute validated thirty projects in 2005. It organizes symposia and seminars, trains young Indian, French, and other national researchers, and awards doctoral grants to both Indian and European students. Since 2003, the Institute has undertaken an ambitious publication program on both paper (some 230 titles) and CD-ROM.

Not only does the sheer range of its activities set the French Institute of Pondicherry apart, but its harnessing of modern technology has made it a powerful laboratory perfectly poised to research both past and present India, given the rapid and radical mutation undergone by the subcontinent in the last decades.
error desired a palace worthy of his station. Begun in 1738 it was completed in 1752. Dupleix constantly complained about the softness of his fellow-colonists. They’d not covered themselves with honor during the siege — far from it, their courage had melted in the heat. In May and June, the “land winds” blew and transformed Pondicherry into an oven. Europeans had to contend with alternating seasons of cyclones and heat. In Pondicherry, the most devastating hurricane (1745) destroyed over 2000 homes and caused 40 deaths. Weakened by the climatic extremes, the French also lived in fear of epidemics of cholera, smallpox, and leprosy. Crocodiles lurked in the rivers and cobras were common in Pondicherry, while panthers and tigers prowled around Chandernagore.

But the major threat remained war, despite the French colonists getting on reasonably well with the other European settlers in India in peacetime. Dupleix had cordial relations with Schitermann, head of the Dutch trading post at Chinsurah, and with François de Schonamille from Antwerp, who managed the Austrian trading post at Bankibazar.

Despite the climate and insecurity, life in the trading posts was far from unpleasant and its financial advantages were undeniable. Six hundred livres a year was enough to live in style. There was no dearth of applicants. No Company employee earned less than this, and there was extra money to be made from trade within India itself. Some Frenchmen made a fortune, while soldiers earned a more basic wage.

In what setting did the settlers live and what did they eat? Wealthy Frenchmen liked fine homes with gardens and conservatories: “Some very luxurious homes were furnished with lacquer wardrobes with copper inlays, tables and consoles in local wood incrusted with ivory or mother of pearl, and screens in papier de Chine.” The walls were lined in silk from Bengal, satin from Tonkin, dyed cloth from Pondicherry or hung with Chinese prints and Persian miniatures. Craftsmen, particularly cabinet-markers, developed a recognizable Pondicherry style of furniture. This mix of oriental sophistication and teak furniture crafted by French artisans gave an undeniable charm to the interiors of the settler houses.

In the larger settler homes, wives managed a team of servants, some of whom had been bought from their families as slaves in times of famine. The Company had a vegetable garden for growing European as well as Indian crops. French wine traveled badly, and Persian wine was often preferred. The French also happily savored “the delights of Indian cooking, the chutneys, raitas, and curries... the guava and ginger jams and tarts, and a host of exquisitely tasting exotic dishes.”

Puducherry today

Today when strolling through this city with its old-world charm, the eye lingers on ornate walls, ancient balconies, colonnaded porches, and climbing bougainvillea. Visitors sense a relaxed rhythm of life unlike anywhere else. Maybe its older citizens dream back to the city’s French past as they listen to the music of the monsoon rain on the mango leaves. At any event, France remains present, not only in some fine buildings, but also in the activities of its cultural institutions such as the Alliance française and the French Institute (see box).

REFERENCES
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