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Editorial
Edição
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Originals Articles
Blood pressure control, drug therapy, and kidney disease
Gabriel Contreras, Tom Greene, Lawrence Y. Agodoa,
DeAnna Cheek, George Junco, Donna Dowie, James Lash, Michael Lipkowitz, Edgar R. Miller III, Akinlou Ojo,
Mohammed Sika, Beth Wilkening, Robert D. Toto; for the African American Study of Kidney Disease
and Hypertension (AASK) Study Group Investigators

Effects of noncardiovascular comorbidities on antihypertensive use in elderly hypertensives
Philip S. Wang, Jerry Avorn, M. Alan Brookhart, Helen Mogun, Sebastian Schneeweiss, Michael A. Fischer, Robert J. Glynn

Angiotensin-converting enzyme inhibitors and calcium channel blockers for coronary
heart disease and stroke prevention
Paolo Verdecchia, Gianpaolo Reboldi, Fabio Angeli, Roberto Gattobigio, Maurizio Bentivoglio, Lutgarde Thijs,
Jan A. Staessen, Carlo Porcellati

Association of the T8590C polymorphism of CYP4A11 with hypertension
in the MONICA augsburg echocardiographic substudy
Bjoern Mayer, Wolfgang Lieb, Anka Götz, Inke R. König, Zouhair Aherrahrou, Annett Thiemig, Stephan Holner,
Christian Hengstenberg, Angela Doering, Hannelore Loewel, Hans-Werner Hense, Heribert Schunkert, Jeanette Erdmann

Brief Reviews
Arterial aging
Is it an immutable cardiovascular risk factor?
Samer S. Najjar, Angelo Scuteri, Edward G. Lakatta

Scientific Contributions
Short- and long-term incidence of stroke in white-coat hypertension
Paola Verdecchia, Gian Paolo Reboldi, Fabio Angeli, Giuseppe Schillaci, Joseph E. Schwartz, Thomas G. Pickering,
Yutaka Imai, Takayoshi Ohkubo, Kazuomi Kario

Fifth International Workshop on Structure and Function of Large Arteries
Vascular development, pulse pressure, and the mechanism
of hypertension
Michel E. Safar, Harry Struijker Boudier
Hypertension

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A Sociedade Portuguesa de Hipertensão (SPH), como qualquer Sociedade Científica, pretende ser um forum de encontro, discussão, troca de conhecimentos e de informações dos seus associados, com vista a congregar esforços dos interessados na temática que os reúne e assim difundir o saber por toda a comunidade científica em geral. Uma das vertentes essenciais desta missão é divulgar, através de escritos, artigos, normas, a sua actividade, não descurando, também, a formação contínua dos seus associados. Assim, em boa hora, os Laboratórios Bial, cujo papel na investigação farmacológica e apoio e estímulo ao conhecimento e pesquisa bio-médica são bem conhecidos, vieram propor à S.P.H. a publicação, distribuída aos médicos portugueses, de uma das revistas do nosso foro mais prestigiosas, a Hypertension, da American Heart Association.

Esta publicação far-se-á através de uma das maiores editoras europeias, a WoltersKluwer, sob a licença da sua congénere americana, a Lippincott Williams & Wilkins, editora da revista. Foi aceite a nossa sugestão de publicar os artigos na língua original, com os sumários traduzidos e indicámos como Director desta edição portuguesa, o nosso colega do Hospital de Santa Maria e da Faculdade de Medicina de Lisboa, e velho amigo, Prof. Dr. José Manuel Braz-Nogueira, figura de renome no campo da hipertensão, a quem caberá a selecção dos artigos originais e comentário editorial.

Nos primeiros dois anos a frequência da revista será bi-anual, prevendo-se, no futuro, dar à estampa quatro números por ano. Esperamos que esta iniciativa seja do interesse dos associados da S.P.H. e de outros colegas que a venham a receber.

João Alberto Saavedra
Presidente da S.P.H
Editorial

Edição Portuguesa da Revista Hipertension

J. Braz Nogueira

“Hypertension” foi a primeira revista publicada em todo o mundo dedicada exclusivamente à problemática da hipertensão arterial.

O primeiro número data de 1979 e teve como editor-chefe Harriet Dustan e editores associados Suzanne Oparil e Henry Overbeck que definiram como seus objectivos fundamentais “…o desenvolvimento de uma revista de alta qualidade que se baseasse e abrangesse todos os múltiplos problemas no campo da hipertensão, tendo a preocupação de explorar novas áreas do conhecimento e não apenas aquelas já aceites como importantes, de estabelecer ligações multidisciplinares, de estimular controvérsias científicas, de ser um porta-voz da investigação quer laboratorial quer clínica e devendo servir a ciência da hipertensão e promover o melhor tratamento dos doentes hipertensos”.

Ao longo destes 26 anos todos esses objectivos têm sido realizados e desenvolvidos constituinte hoje em dia, sem qualquer dúvida, uma das revistas de referência no campo da hipertensão arterial.

Esta edição portuguesa do “Hypertension” que agora se inicia com o patrocínio da Sociedade Portuguesa de Hipertensão e com o apoio dos Laboratórios Bial, e de que tenho o privilégio de ser o Director por convite da Direcção daquela Sociedade que muito me honrou, vai reunir em cada um dos números alguns dos trabalhos publicados nos meses anteriores na edição original e que, por agora, serão unicamente o resumo traduzido em português. Pretende-se, também, que haja sempre um comentário editorial a um ou mais dos artigos publicados e que, segundo a Direcção da revista devam ser devidamente destacados.

Esperamos que esta edição agrade a todos quantos se dedicam com especial interesse à hipertensão arterial e possa contribuir para uma divulgação mais ampla da investigação e progressos clínicos e terapêuticas importantes que se têm registado nestes últimos anos nas várias áreas da hipertensão.

Relativamente a este primeiro número salientamos dois artigos que têm Veredechia como primeiro autor. Num deles este autor e Schwartz, Pickering, Kario entre outros analisam o risco de AVC em hipertensos de bata branca, num conjunto de vários grupos populacionais, durante um período de “follow-up” médio de cerca de 6 anos, tendo verificado que, embora inicialmente o risco seja idêntico ao dos normotensos, após o 6.º ano parece existir um risco maior nos hipertensos de bata branca o que leva estes autores a pôr em dúvida a aparente benignidade desta entidade, que sempre tem defendido, no longo prazo.

No outro artigo de Veredechia e colabs. faz-se uma meta-análise de 28 estudos prospectivos publicados até Dezembro de 2004, que fazem a comparação entre terapêutica anti-hipertensiva com antagonistas do cálcio ou inibidores da enzima de conversão da angiotensina (IECA) “versus” placebo ou diuréticos e/ou bloqueadores beta relativamente à prevenção de doença coronária e de AVC. Mais uma vez fica demonstrado o efeito primordial da diminuição da pressão arterial, embora pareça evidenciar-se alguma superioridade dos antagonistas do cálcio na prevenção de AVC e dos IECA na prevenção de doença coronária.

Interessante é, também, o trabalho de Mayer e colabs., que vem confirmar, na população envolvida na avaliação ecocardiográfica do estudo MONICA Augsburg, a associação de um polimorfismo genético do gene CYP4A11 com a elevação tensional, embora não tenha evidenciado qualquer influência na estrutura e função do ventrículo esquerdo. Este artigo é mais um exemplo da intensa investigação presentemente em curso no campo da genética da hipertensão essencial e suas repercussões orgânicas.

Finalmente o artigo de revisão de Najjar, Scuteri e Lakatta sobre a íntima inter-relação entre envelhecimento arterial e doenças cardiovasculares, com referência particular aos progressos em biologia vascular que têm demonstrado um conjunto de alterações moleculares, bioquímicas, enzimáticas e celulares comuns ao processo de envelhecimento vascular e à hipertensão e aterosclerose, merece de igual modo ser destacado em especial pela mensagem de esperança de que a idade possa, no futuro, ser considerada um factor de risco cardiovascular modificável.
Blood Pressure Control, Drug Therapy, and Kidney Disease

Gabriel Contreras, Tom Greene, Lawrence Y. Agodoa, DeAnna Cheek, George Junco, Donna Dowie, James Lash, Michael Lipkowitz, Edgar R. Miller III, Akinlou Ojo, Mohammed Sika, Beth Wilkening, Robert D. Toto; for the African American Study of Kidney Disease and Hypertension (AASK) Study Group Investigators

Abstract—The African American Study of Kidney Disease and Hypertension (AASK) used a 2×3 factorial design to examine the effect on decline in renal function of 2 blood pressure (BP) goals, defined by a mean arterial pressure (MAP) ≤92 mm Hg or 102 to 107 mm Hg, and of 3 different first-line antihypertensive agents, ramipril, amlodipine, and metoprolol, in African-Americans with chronic kidney disease (CKD) attributed to hypertensive nephrosclerosis.1,2 The rationale for this hypothesis comes from animal3 and human data, 4 suggesting that renal disease progression and proteinuria reduction may differ between angiotensin-converting enzyme inhibitors (ACEIs) and dihydropyridine calcium channel blockers (DHP-CCBs) at higher blood pressure levels but are similar at lower blood pressures corresponding to those achieved in the low goal of the AASK Study. The factorial design of the AASK trial provides a unique opportunity to address this hypothesis for a wide range of outcomes.5 The primary purpose of this investigation is to evaluate the effect of the BP intervention on the clinical composite outcome and its specific components separately within each of the 3 drug groups. In addition, this investigation compares amlodipine versus ramipril or metoprolol within each of the 2 BP groups.

Methods

Population

The AASK study population has been previously described.1,2 Briefly, participants were self-identified African-Americans with hypertensive renal disease (n=1094), aged 18 to 70 years, with a...
baseline GFR between 20 to 65 mL/min per 1.73 m² and no other clinically identified causes of renal insufficiency. The institutional review board at each center approved protocol and procedures, and all participants gave written informed consent. Participants’ enrollment began in February 1995 and ended in September 1998. Planned follow-up to the end of the study in September 2001 was 3 to 6.4 years.

Study Design
Following a 2 × 3 factorial design, participants were randomized to a usual BP goal (MAP 102 to 107 mm Hg, n = 554) or to a lower BP goal (MAP ≤ 92 mm Hg lower, n = 540), and to double-blinded treatment with 1 of 3 first-line antihypertensive drugs, a sustained-release beta blocker (BB), metoprolol (n = 441), 50 to 200 mg/d, an ACEI, ramipril (n = 436), 2.5 to 10 mg/d, or a DHP-CCB, amlodipine (n = 217), 5 to 10 mg/d. If the BP goal was not achieved while the participants were taking the highest tolerated dose of randomized drug, additional unblinded drugs (furosemide, doxazosin, clonidine, hydralazine, minoxidil) were added sequentially. A 2:2:1 randomization ratio for the metoprolol, ramipril, and amlodipine groups was used because of an expected acute increase in GFR in the amlodipine group.6–8

Measurement of BP and Renal Function
Blood pressure and renal function measurements were conducted as described previously.1,2

| TABLE 1. Baseline Characteristics (Mean±SD or %) by Randomized BP Group |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
|                         | Ramipril                 | Amlodipine               | Metoprolol               |
|                         | Low Goal (n = 215)       | Usual Goal (n = 221)     | Low Goal (n = 110)       | Usual Goal (n = 107)     |
| Age, y                   | 54.21 ± 11.4             | 54.51 ± 10.5             | 54.26 ± 11.1             | 54.68 ± 10.4             | 54.96 ± 10.5             | 54.81 ± 10.3             |
| % Female                 | 35.81                    | 41.18                    | 41.82                    | 37.38                    | 38.14                    | 38.94                    |
| Systolic BP, mm Hg       | 151.0 ± 22.5             | 150.9 ± 24.1             | 152.2 ± 28.2             | 147.7 ± 21.9             | 152.0 ± 25.7             | 147.7 ± 21.4             |
| Diastolic BP, mm Hg      | 96.90 ± 13.6             | 95.12 ± 15.3             | 96.55 ± 15.1             | 94.87 ± 12.9             | 95.45 ± 15.4             | 94.47 ± 12.5             |
| MAP, mm Hg               | 115.2 ± 15.2             | 114.0 ± 16.7             | 115.3 ± 18.3             | 112.7 ± 14.7             | 114.5 ± 17.5             | 112.4 ± 14.1             |
| GFR, mL/min per 1.73m²   | 46.16 ± 12.6             | 44.58 ± 12.9             | 45.77 ± 12.9             | 45.85 ± 12.9             | 46.04 ± 13.1             | 45.65 ± 13.7             |
| Serum creatinine, mg/dL  |                          |                          |                          |                          |                          |                          |
| Male                     | 2.171 ± 0.749            | 2.192 ± 0.730            | 2.200 ± 0.798            | 2.352 ± 0.852            | 2.160 ± 0.744            | 2.125 ± 0.750            |
| Female                   | 1.701 ± 0.597            | 1.804 ± 0.583            | 1.735 ± 0.554            | 1.735 ± 0.548            | 1.737 ± 0.516            | 1.860 ± 0.574            |
| UP/Cr                    | 0.331 ± 0.483            | 0.340 ± 0.541            | 0.273 ± 0.424            | 0.319 ± 0.524            | 0.365 ± 0.555            | 0.304 ± 0.499            |
| Urine protein, g/d       | 0.223 ± 0.331            | 0.409 ± 0.630            | 0.316 ± 0.594            | 0.291 ± 0.505            | 0.322 ± 0.516            | 0.367 ± 0.562            |
| Male                     | 0.617 ± 0.946            | 0.601 ± 1.08             | 0.461 ± 0.675            | 0.678 ± 1.21             | 0.674 ± 1.20             | 0.577 ± 1.01             |
| Female                   | 0.277 ± 0.437            | 0.514 ± 0.924            | 0.377 ± 0.727            | 0.383 ± 0.742            | 0.435 ± 0.727            | 0.443 ± 0.710            |
| History of heart disease, % | 54.88                    | 47.06                    | 57.27                    | 52.34                    | 52.56                    | 48.67                    |
| Years of hypertension    | 13.16 ± 10.6             | 13.48 ± 9.24             | 15.17 ± 9.89             | 13.95 ± 10.1             | 15.32 ± 10.8             | 14.26 ± 10.0             |
| ACE inhibitors, %        | 43.26                    | 36.65                    | 41.82                    | 41.12                    | 30.70                    | 37.61                    |
| β blockers, %            | 26.51                    | 25.34                    | 30.00                    | 26.17                    | 29.30                    | 31.42                    |
| CCB, %                   | 63.72                    | 61.99                    | 64.55                    | 57.94                    | 66.05                    | 63.27                    |
| DHP-CCB, %               | 49.30                    | 43.89                    | 49.09                    | 40.19                    | 50.23                    | 45.58                    |

GFR indicates glomerular filtration rate; BP, blood pressure; MAP, mean arterial pressure; UP/Cr, the 24-hour urine protein to urine creatinine ratio; ACE, angiotensin-converting enzyme; CCB, calcium channel blocker; and DHP-CCB, dihydropyridine calcium channel blocker.

Clinical Outcome Analysis
The main clinical secondary outcome was a composite including ESRD, death, or declining GFR events defined by a 50% or 25 mL/min per 1.73 m² reduction in GFR from baseline. Additional secondary endpoints included a renal composite outcome of the declining GFR events and ESRD (while censoring deaths before ESRD), a hard endpoint composite outcome including ESRD and death, ESRD alone (censoring death), and death alone (censoring ESRD). Urinary protein excretion, expressed as urine protein to creatinine ratio (UP/Cr) from a 24-hour urine collection, was also a secondary outcome.

Statistical Methods
Glomerular filtration rate slope was analyzed using a mixed-effects model,4 which included terms for the estimation of the mean acute, chronic, and total slopes within each of the 6 cells in the 2 × 3 factorial design, adjusting for clinical center and 5 prespecified baseline covariates: proteinuria (log UP/Cr), history of cardiovascular disease, mean arterial pressure, sex, and age. We present here the differences in the mean GFR slopes between the cells corresponding to the usual and lower BP interventions separately for each of the 3 drug groups and compare the differences in mean slope between the 2 BP interventions among the 3 drug groups to evaluate the interaction of the BP and drug interventions.

The effects of the drug and BP interventions on the main clinical composite outcome including declining GFR events, ESRD, or death, and on components of this outcome were analyzed by Cox regression analysis. Each Cox regression model included appropriate indicator variables for the randomized treatment groups and the same (chronic phase). The chronic slope and the mean total slope from baseline (including both the acute and chronic phases) were designated as co-primary outcomes.

Primary Renal Function Analysis
The primary analysis of renal function is based on the rate of change in GFR (GFR slope), which was evaluated separately during the first 3 months after randomization (acute phase) and after 3 months (chronic phase). The chronic slope and the mean total slope from baseline (including both the acute and chronic phases) were designated as co-primary outcomes.
interval on the assigned randomized drug during follow-up (Table 2).

**Results**

**Baseline and Treatment Characteristics**

Baseline participant characteristics were similar in the 2 BP groups within each of the 3 drug groups (Table 1). After randomization, the difference in mean achieved MAP between BP groups was maintained at \( \approx 10 \) mm Hg in all 3 drug groups, although mean MAP for the lower BP goal was 94 mm Hg in the amlodipine group versus 95 mm Hg in the other 2 groups. Participants were prescribed more antihypertensives for the lower than usual BP goal (Table 2). Those participants assigned to the low MAP goal were more commonly on the highest dose of the randomized drug compared with those assigned to the usual MAP goal. There was no difference in the percentage of participants remaining on the assigned randomized drug during follow-up (Table 2).

**Primary Analysis of GFR Slope**

As reported previously, the mean chronic and total GFR slopes decline did not differ significantly between the lower and usual BP goal groups when averaged across the 3 drug groups, and the differences in mean slopes between the BP groups did not differ among the 3 drug groups (interaction \( P=0.64 \) for the chronic slope, \( P=0.61 \) for the total slope) (Figure 1).

**Clinical Outcome Analysis**

As reported previously, the overall effect of the BP intervention on the main clinical composite outcome (including ESRD, death, or GFR decline by 50% or by 25 mL/min per 1.73 m\(^2\)) was not statistically significant when all 3 drug groups were combined, and the BP effect on the clinical composite did not differ significantly among the 3 drug groups (interaction \( P=0.17 \)) (Figure 2A). However, the rate of the ESRD or death composite was higher for patients in the amlodipine group assigned to the usual BP goal (0.087 per patient-year) than for the amlodipine patients assigned to the

### Table 2. Antihypertensive Therapy and Blood Pressure During Follow-Up (Mean±SD or %)

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<th>Ramipril</th>
<th>Amlodipine</th>
<th>Metoprolol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Goal</td>
<td>Usual Goal</td>
<td>Low Goal</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>95.28±8.19</td>
<td>104.2±8.47</td>
<td>93.71±6.11</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>128.2±12.0</td>
<td>140.7±14.5</td>
<td>126.0±9.52</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>78.52±8.35</td>
<td>85.70±8.18</td>
<td>77.22±7.13</td>
</tr>
<tr>
<td>% visits MAP in goal</td>
<td>48.91</td>
<td>38.33</td>
<td>54.59</td>
</tr>
<tr>
<td>% visits MAP&lt;107 mm Hg</td>
<td>79.12</td>
<td>62.88</td>
<td>85.96</td>
</tr>
<tr>
<td>% visits Sys/Dia&lt;140/90</td>
<td>66.75</td>
<td>34.50</td>
<td>74.16</td>
</tr>
<tr>
<td>% visits Sys/Dia&lt;125/75</td>
<td>25.05</td>
<td>6.482</td>
<td>22.07</td>
</tr>
<tr>
<td>% visits on assigned therapy</td>
<td>79.33</td>
<td>80.02</td>
<td>82.83</td>
</tr>
<tr>
<td>% visits on high dose</td>
<td>62.13</td>
<td>48.24</td>
<td>67.50</td>
</tr>
<tr>
<td>Total # of drug classes</td>
<td>2.949±1.15</td>
<td>2.413±1.22</td>
<td>3.044±1.17</td>
</tr>
<tr>
<td>Any other 2 classes</td>
<td>12.36</td>
<td>7.10</td>
<td>8.379</td>
</tr>
<tr>
<td>ACEi</td>
<td>0.000</td>
<td>0.000</td>
<td>5.208</td>
</tr>
<tr>
<td>BB</td>
<td>4.852</td>
<td>2.492</td>
<td>5.452</td>
</tr>
<tr>
<td>CCB</td>
<td>10.33</td>
<td>6.162</td>
<td>0.000</td>
</tr>
<tr>
<td>% visits on level 2</td>
<td>81.82</td>
<td>67.23</td>
<td>78.23</td>
</tr>
<tr>
<td>% visits on level 3</td>
<td>50.35</td>
<td>34.07</td>
<td>62.59</td>
</tr>
<tr>
<td>% visits on level 4</td>
<td>40.02</td>
<td>29.34</td>
<td>43.43</td>
</tr>
<tr>
<td>% visits on level 5</td>
<td>30.97</td>
<td>22.94</td>
<td>28.96</td>
</tr>
<tr>
<td>% protocol visits held</td>
<td>90.37</td>
<td>87.04</td>
<td>91.33</td>
</tr>
<tr>
<td>% GFRs done</td>
<td>83.22</td>
<td>79.97</td>
<td>85.07</td>
</tr>
</tbody>
</table>

All groups censored on September 22, 2000. Blood pressure summaries include visits after three months and exclude GFR visits. Medication summaries include all visits starting at month one. GFR indicates glomerular filtration rate; BP, blood pressure; MAP, mean arterial pressure; Sys/Dia, systolic over diastolic blood pressure; ACEi, angiotensin-converting enzyme inhibitor; BB, \( \beta \) blocker; CCB, calcium channel blocker.
low BP goal (0.046 per patient-year), or for patients assigned to either BP goal in the metoprolol or ramipril groups (with event rates ranging from 0.041 to 0.050 per patient-year). A similar pattern can be seen for ESRD alone (Table 3). Hence, the effect of the BP intervention differed significantly among the 3 drug groups for the composite of ESRD or death (interaction $P=0.035$) and for ESRD alone ($P=0.021$) (Table 4). For participants in the amlodipine group, there was a significantly lower risk of ESRD or death (risk reduction 51%; 95% CI, 13% to 73%) and of ESRD alone (54%; 95% CI, 8% to 77%) in those assigned to the lower BP goal. By contrast, there was no significant difference in outcomes between BP groups within the metoprolol or ramipril groups.

As reported previously, among both BP goals combined, the ramipril group had a significantly reduced risk of the main clinical composite outcome compared with the amlodipine group, and both the ramipril and metoprolol groups had significantly reduced rates of ESRD or death and of ESRD alone compared with amlodipine. Consistent with the effects noted, the differences between amlodipine and the other 2 drug groups were larger for the composite of ESRD or death and for ESRD alone for participants assigned to the usual BP goal than for participants assigned to the low goal. For participants in the usual BP group, there was a significant benefit of ramipril compared with amlodipine for the ESRD or death outcome (risk reduction 68%; 95% CI, 47% to 80%) and the ESRD alone outcome (risk reduction 77%; 95% CI, 59% to 88%). Likewise, there was a significant benefit of metoprolol compared with amlodipine for the ESRD or death outcome (risk reduction 56%; 95% CI, 29% to 73%) and ESRD alone outcome (risk reduction 69%; 95% CI, 45% to 83%) in the usual BP group. However, the effects of drug group intervention were not significantly different within the lower BP group for these secondary outcomes. There were no significant differences in the rates of the outcome of death alone between the 2 BP groups or among the 3 drug groups.

**Proteinuria**

Within each drug group, the risk reductions for any secondary clinical outcome of the low versus usual BP goal were not
significantly different between patients with baseline UP/Cr ≤0.22 and >0.22 (P=not significant). Effects of the BP intervention within each drug group on the change in proteinuria during follow-up are illustrated in Figure 3.

Discussion
Using the factorial design of the AASK trial, we have investigated whether reducing BP level has different effects on the progression of hypertensive renal disease depending on the type of first-line antihypertensive used. No significant differences were observed among the 3 AASK drug groups in the effect of the BP intervention on several key outcomes, including GFR slope, the main clinical composite, all-cause mortality, and change in proteinuria. However, the low BP intervention appeared to reduce the incidence of primarily ESRD in those participants assigned to amlodipine as the first-line antihypertensive, but not for participants assigned to ramipril or metoprolol. The low BP intervention in participants assigned to amlodipine also reduced significantly the level of UP/Cr in those with hypertensive nephrosclerosis in the absence of proteinuria during follow-up.

The differential effects of antihypertensive drugs on glomerular microcirculation provide a plausible biological basis to better understand why the effects on progression to ESRD of BP control might differ by type of antihypertensive drug. In the setting of systemic hypertension, autoregulation of blood flow protects against glomerular hypertension by increasing afferent arteriolar tone and thus preventing the transmission of high systemic pressure to the glomerular capillary circulation. DHP-CCBs impair the autoregulatory vasoconstrictor response of the afferent arteriole in experimental models.3,10 Impairment in this protective mechanism by a DHP-CCB could theoretically exaggerate the glomerular capillary exposure to systemic hypertension and result in glomerular capillary hypertension, hyperfiltration, accelerated glomerulosclerosis, and progression of kidney disease.11,12 We have some evidence that in rats with experimental hypertensive kidney disease, the risk of glomerulosclerosis attributed to hypertension, is similar between DHP-CCB and ACEIs when systolic BP is lowered to a level <120 mm Hg.3,13 In the AASK, lowering systemic BP to only 140/86 mm Hg in the usual BP goal/amlodipine group may not have been protective against transmission of high BP to the glomerular capillary circulation. In contrast, lowering systemic BP to 126/77 mm Hg in the low BP goal/amlodipine group would be expected to mitigate the pressure load to the glomerular capillaries and theoretically mitigate glomerular injury.

ACEIs and angiotensin II receptor blockers (ARBs) preferentially dilate the postglomerular vasculature and should have a salutary effect because of a proportionally greater reduction in glomerular capillary pressure for any given

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Metoprolol</th>
<th>Ramipril</th>
<th>Amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR event, ESRD, or death*</td>
<td>209</td>
<td>209</td>
<td>209</td>
</tr>
<tr>
<td>% Risk Reduction (95% CI)</td>
<td>0.74</td>
<td>0.66</td>
<td>0.64</td>
</tr>
<tr>
<td>P Value</td>
<td>0.42</td>
<td>0.06</td>
<td>0.14</td>
</tr>
<tr>
<td>GFR event or ESRD</td>
<td>192</td>
<td>192</td>
<td>192</td>
</tr>
<tr>
<td>% Risk Reduction (95% CI)</td>
<td>0.61</td>
<td>0.61</td>
<td>0.61</td>
</tr>
<tr>
<td>P Value</td>
<td>0.11</td>
<td>0.03</td>
<td>0.18</td>
</tr>
<tr>
<td>ESRD or death*</td>
<td>209</td>
<td>209</td>
<td>209</td>
</tr>
<tr>
<td>% Risk Reduction (95% CI)</td>
<td>0.61</td>
<td>0.61</td>
<td>0.61</td>
</tr>
<tr>
<td>P Value</td>
<td>0.11</td>
<td>0.03</td>
<td>0.18</td>
</tr>
<tr>
<td>ESRD alone</td>
<td>192</td>
<td>192</td>
<td>192</td>
</tr>
<tr>
<td>% Risk Reduction (95% CI)</td>
<td>0.61</td>
<td>0.61</td>
<td>0.61</td>
</tr>
<tr>
<td>P Value</td>
<td>0.11</td>
<td>0.03</td>
<td>0.18</td>
</tr>
<tr>
<td>Death Alone</td>
<td>209</td>
<td>209</td>
<td>209</td>
</tr>
<tr>
<td>% Risk Reduction (95% CI)</td>
<td>0.61</td>
<td>0.61</td>
<td>0.61</td>
</tr>
<tr>
<td>P Value</td>
<td>0.11</td>
<td>0.03</td>
<td>0.18</td>
</tr>
</tbody>
</table>

GFR indicates glomerular filtration rate; ESRD, end-stage renal disease.
All risk reductions were adjusted for the prespecified baseline covariates: proteinuria, mean arterial pressure, sex, history of heart disease, and age. Risk reductions for ESRD or death composite or ESRD alone were also adjusted for baseline GFR. All groups censored on Sept 22, 2000.

*Deaths prior to dialysis.
Adequate BP control.1,2,4,15 Pertensive drug and its benefit is beyond their effect of tensin system with ACEIs and ARBs reduced the progression of patients have demonstrated that blockade of the renin-angiotensin system with ACEIs and ARBs reduced the progression in systemic BP.14 Several multicenter trials in CKD patients have demonstrated that blockade of the renin-angiotensin system with ACEIs and ARBs reduced the progression of kidney disease to a greater extent than any other antihypertensive drug and its benefit is beyond their effect of adequate BP control.1,2,4,15–20 Consistent with these findings, in the Renoprotective Effect of the Angiotensin-Receptor Antagonist Irbesartan in Patients with Nephropathy due to Type 2 Diabetes (IDNT) study,16 irbesartan treatment reduced the incidence of doubling of the serum creatinine concentration (risk reduction 37%; P=0.001) and ESRD (risk reduction 23%; P=0.07) compared with amiodipine treatment. These differences were not explained by differences in the BPs that were achieved. Evidence of a renoprotective effect of angiotensin blockade independently of BP control was also seen in the overall drug group comparisons of the AASK trial, in which assignment to the ramipril group significantly reduced the risk of the main composite clinical outcome compared with the amiodipine and metoprolol groups.1,2 In the IDNT, there were no significant differences between the amiodipine and placebo groups in the rate of doubling of the serum creatinine concentration and ESRD (P=not significant). In that study, achieved mean BP of 141/77 mm Hg in the amiodipine group was similar to achieved BP in the usual BP goal/amiodipine group in the AASK study.

We view the secondary analyses suggesting a benefit of the low BP goal for participants in the amiodipine group as potentially important but as hypothesis-generating. The implications of these findings are limited by several factors. First, this was a post hoc analysis stemming from the hypothesis that the BP effect is different specifically in the amiodipine group compared with the other 2 groups. However, as described previously, this analysis is based on a biologically plausible mechanism and is consistent with findings in some animal models as noted. Second, the interaction test between the BP and drug group interventions did not approach statistical significance for any outcome including GFR measurements. It is possible that effects on GFR were obscured by the initial effects of the interventions on GFR during the acute phase, especially those of amiodipine, which were likely hemodynamic effects without clinical significance (Figure 1).2 However, this hypothesis does not appear to be able to account for the absence of a difference in the effect of the BP intervention on the chronic GFR slope among the drug groups. One could argue that the AASK follow-up time from 3 to 6.4 years was short to show possible difference in outcomes including GFR measurements. This is an important question undergoing study in the AASK cohort study, an ongoing National Institutes of Health-sponsored follow-up to the AASK trial. Third, the multiple comparisons of the various combinations of the components of the main secondary clinical composite outcome between different treatment groups caution conservative interpretation of the nominally significant probability values caused by the risk of type I error. Finally, hypertensives patients with renal disease who might receive a DHP-CCB must also be receiving an ACEI (or an ARB), and the protocol precluded evaluation of this combination. Thus, it is unclear whether the interaction of BP goal and amiodipine on the progression to ESRD is evident in patients using an appropriate renoprotective antihypertensive regimen.

In conclusion, the secondary analyses presented in this report raise the possibility that the effects of BP control differ by class of antihypertensive medication in the AASK study population. The results do not alter the main conclusions from the AASK trial, namely that there was a significant overall benefit of the use of ramipril compared with amiodipine (risk reduction 38%; P=0.004) or metoprolol (risk reduction 22%; P=0.04) in reducing the rate of the main clinical composite outcome, but no significant overall benefit of lowering MAP to ≤92 mm Hg.1,2

Perspectives

Hypertension is an independent risk factor for progressive CKD21 and is the second leading cause of ESRD in African-Americans22,23 in whom the risk of ESRD is graded as a function of BP level.23 The AASK trial simultaneously compared 3 classes of antihypertensive agents (ACEI, DHP-CCB, and BB) and 2 levels of BP control (usual BP and low BP) on the progression of CKD. The AASK trial previously documented its main results, namely, that an ACEI was more effective than either DHP-CCB or BB in reducing the risk for rapidly declining renal function, ESRD, or death from any cause and that the low BP goal had the same effects on GFR decline as the usual (traditional) BP goal. This article explored the possibility that the drug effects (ACEI, DHP-CCB, and BB) might differ by BP goal. In secondary analyses that focused on the occurrence of ESRD or death, it appeared that among patients assigned to amiodipine, those randomized to the low BP goal had fewer ESRD or death events than those randomized to the usual BP goal. This intriguing finding, while biologically plausible, should be interpreted cautiously, in part because the analyses were post-hoc (not specified in the protocol) and because parallel analyses with other outcomes were inconsistent.
Acknowledgments

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References


Effects of Noncardiovascular Comorbidities on Antihypertensive Use in Elderly Hypertensives

Philip S. Wang, Jerry Avorn, M. Alan Brookhart, Helen Mogun, Sebastian Schneeweiss, Michael A. Fischer, Robert J. Glynn

Hypertension afflicts $\approx$ 65 million Americans, including the majority of elderly, and imposes enormous burdens through associated myocardial infarctions, heart failure, stroke, and kidney disease. Although the benefits of antihypertensive medications are clearly established, only 60% of hypertensive patients are currently treated, and only 34% are adequately controlled. Identifying reasons for this underutilization is a critical first step in developing interventions to improve use of this highly effective therapy.

Multiple chronic conditions are present in $>60\%$ of older persons. Studies have begun recently to shed light on the impact that comorbid illness can exert on use of treatments such as antihypertensive medications. One investigation found that having multiple conditions substantially increases the risk of avoidable hospitalizations and preventable complications during hospitalizations, leading the authors to hypothesize that comorbidity decreases the use of preventive therapies. Some studies have indeed found reduced use of cardiovascular treatments such as aspirin and thrombolysis when comorbidity is present.

Results concerning the impact of comorbidity on specifically antihypertensive use in the elderly are limited and mixed. Most previous research has focused exclusively on the impact of comorbid cardiovascular conditions. Not surprisingly, comorbid coronary artery disease, congestive heart failure, cerebrovascular disease, diabetes, and hyperlipidemia are associated with increased antihypertensive use as a result of compelling evidence of benefits when such indications are present.

On the other hand, research examining the impact of noncardiovascular comorbidities on antihypertensive use has been lacking. One study reported reduced antihypertensive use when physical or cognitive impairment was present, although it is not clear whether and what comorbid conditions may have been responsible. Reasons for such findings are uncertain, but some investigators have proposed that primary conditions are neglected by patients and providers when unrelated chronic medical illnesses are copresent.

The current study had 3 aims. First, we sought to investigate whether comorbidities, unrelated to indications for antihypertensive therapy or sequelae of hypertension, decrease antihypertensive use. We purposefully chose 4 unrelated conditions that are symptomatic: asthma/chronic ob-
restrictive pulmonary disease (COPD), depression, gastrointestinal (GI) disorders such as dyspepsia and ulcerative disease, and osteoarthritis. Our a priori hypothesis was that symptomatic comorbidities especially reduce antihypertensive use because the asymptomatic nature of hypertension may spuriously make it seem less pressing to treat.20 Our second aim was to determine whether there are differences across the 4 conditions in terms of their impacts on antihypertensive use. Some investigators have suggested that mood disorders and chronic airway diseases may be particularly associated with underutilization of health care despite their high levels of disability.21 Finally, without information on blood pressures, we could not be certain that lower rates of antihypertensive use in patients with comorbidities truly represented underuse. Therefore, our third aim was to examine whether comorbidities deter antihypertensive use in subgroups with clear cardiovascular indications.

Methods

Data Sources

**Pennsylvania Pharmaceutical Assistance Contract for the Elderly Program**
The Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE) program is the largest state prescription benefits program for the elderly in the United States. Information was available from January 1, 1999, to December 31, 2000, and included demographic characteristics and data for all filled prescriptions (including medication, quantity dispensed, and days supply). The PACE program has no deductibles and no maximum annual benefit. There is a modest copayment of $6 for each prescription. The income ceiling for PACE eligibility is $14,000 if single and $17,200 for a couple, resulting in a recipient population that is inclusive of indigent as well as nonindigent elderly. These benefits and eligibility requirements for enrollment result in essentially no out-of-pocket (ie, out-of-system) medication.

**Pennsylvania Medicare**
Medicare data used in the present study included Medicare part A data on hospitalizations and nursing home stays, and Medicare part B data on outpatient professional services and procedures. These data were available for all Pennsylvania residents ≥65 years of age enrolled in the PACE program during January 1, 1999, to December 31, 2000. We first identified all Medicare beneficiaries ≥65 years of age who were also enrolled in the PACE program (because the latter program, but not Medicare, provides comprehensive data on all prescription drug use). Data on all filled prescriptions, procedures, physician encounters, hospitalizations, and long-term care were assembled into a relational database using Sybase software. All traceable person-specific identifiers from both programs were transformed into anonymous, coded study numbers to protect the privacy of subjects. This study was approved by the institutional review board of the Brigham and Women’s Hospital.

Study Population

The study population consisted of all individuals ≥65 years of age who had ≥1 International Classification of Diseases, 9th revision (ICD-9) diagnoses of hypertension in their administrative records and fulfilled the following criteria from January 1, 1999, to December 31, 1999, for entry into 1 of 5 mutually exclusive cohorts.

**Asthma/COPD**
The asthma/COPD cohort received ≥1 ICD-9 diagnosis of asthma or COPD, filled ≥1 prescription for an inhaled corticosteroid or an inhaled β-agonist, and had no diagnoses or treatments for depression, GI disorders, or osteoarthritis during the calendar year.

**Depression**
those in the depression cohort received an ICD-9 diagnosis of depression, filled ≥1 prescription for an antidepressant drug, and had no diagnoses or treatments for asthma/COPD, GI disorders, or osteoarthritis during the calendar year.

**GI Disorders**
The GI disorders cohort received an ICD-9 diagnosis for dyspepsia or GI ulcerative disease, filled ≥1 prescription for a proton pump inhibitor or histamine-2 blocker, and had no diagnoses or treatments for asthma/COPD, depression, or osteoarthritis during the calendar year.

**Osteoarthritis**
The osteoarthritis cohort received an ICD-9 diagnosis of osteoarthritis, filled ≥1 prescription for a nonsteroidal anti-inflammatory drug, including selective cyclooxygenase-2 inhibitors, and had no diagnoses or treatments for asthma/COPD, depression, or GI disorders during the calendar year.

**No Evidence of the 4 Comorbidities**
Finally, those with no evidence of the 4 comorbidities had no diagnoses or treatments for asthma/COPD, depression, GI disorders, or osteoarthritis as defined above during calendar year 1999.

To ensure uniform periods of eligibility during calendar years 1999 and 2000, during which covariates and the study outcome could be assessed, all subjects were required to have used ≥1 health care service and filled ≥1 prescription in each of the following 4 time periods: the first 6 months of 1999, the second 6 months of 1999; the first 6 months of 2000; and the second 6 months of 2000.

**Definition of Antihypertensive Drug Use During the Follow-Up Year**
We began by identifying all prescriptions filled by subjects during calendar year 2000. We then defined antihypertensive medication use during 2000 as filling ≥1 prescription for β-blockers, calcium antagonists, or diuretics typically used to treat hypertension in ambulatory settings.

**Other Covariates**
We defined the following variables during calendar year 1999.

**Sociodemographic Characteristics**
Program enrollment information was used to determine each subject’s age, gender, and race.

**Cardiovascular Conditions**
We scanned all ICD-9 diagnostic information and use of all treatments and services to assess the presence in 1999 of the following cardiovascular conditions potentially related to use of antihypertensive medications: coronary artery disease, cerebrovascular disease, congestive heart failure, and diabetes.

**Other Clinical Comorbidity**
We scanned all ICD-9 diagnostic information from subjects’ inpatient and outpatient encounters in 1999 to calculate a modified Charlson score, a commonly used measure of the extent of comorbid illness.22 Charlson scores were calculated such that none of the diagnoses of primary interest (ie, asthma/COPD, depression, GI disorders, or osteoarthritis) or cardiovascular conditions described above contributed points to subjects’ scores.

**Health Care Utilization**
The extent of specific forms of health care utilization was assessed during calendar year 1999, including the number of medications used (excluding medications used to define the 4 comorbidity cohorts of interest), days hospitalized, days spent in a nursing home, and physician visits.
Analyses
Initially, we identified the distributions of sociodemographic, clinical, and health care utilization characteristics among the 5 study cohorts during calendar year 1999. We then calculated the frequency of use of antihypertensive drugs in the 5 cohorts of interest during calendar year 2000. To examine the independent effects of the 4 comorbidities of primary interest (sociodemographic characteristics, cardiovascular conditions, other comorbidity, and health care utilization variables on antihypertensive use), we constructed multiple logistic regression models of antihypertensive drug use during calendar year 2000. Variables representing the 4 comorbidities of primary interest were included. Models also contained age, gender, race, individual cardiovascular conditions, Charlson comorbidity score, total number of medications, days hospitalized, days in nursing homes, and physician visits in 1999. To directly compare the effects of the individual comorbid conditions on antihypertensive use in 2000, we constructed additional multivariable models in which subjects with none of the 4 comorbidities were excluded and those with osteoarthritis served as the referent. We also conducted analyses restricted to just patients with coronary artery disease, cerebrovascular disease, peripheral vascular disease, or diabetes mellitus to study whether comorbidities have deterring effects on antihypertensive use in patients with clear indications. The statistical significance of relationships was assessed with 95% confidence intervals (CIs).

Results
Table 1 presents the distributions of demographic, clinical, and health care utilization characteristics among the 5 study cohorts. Approximately half of subjects in all cohorts were 75 to 84. Mean ages in the cohorts with asthma/COPD, depression, GI disorders, osteoarthritis, and none of the 4 comorbidities were 78.3, 79.6, 79.6, 79.8, and 79.9, respectively. Women made up the large majority, more so in the cohorts with osteoarthritis and depression cohorts and less so in cohorts with asthma/COPD, GI disorders, and none of the 4 comorbidities. The majority of cohorts were of white race. Proportions with coronary artery disease ranged from a high of 27.0% in those with GI disorders to a low of 13.7% among those with none of the 4 comorbidities. The presence of cerebrovascular disease ranged from 29.6% of those with depression to 15.0% of those with none of the 4 comorbidities. Congestive heart failure prevalence ranged from 52.4% of those with asthma/COPD to 28.6% of those with none of the 4 comorbidities. Diabetes was most prevalent in those with GI disorders (32.6%) and least prevalent in those with asthma/COPD (29.6%). Subjects without any of the 4 comorbidities had lower Charlson comorbidity scores than other cohorts. Those without the 4 comorbidities also had less utilization of health care in 1999 than other cohorts, including their total number of medications, days hospitalized, days in a nursing home, and physician visits. On the other hand, a greater proportion of the cohort without the 4 comorbidities used antihypertensives in 2000, relative to the cohorts with 1 of the comorbidities of interest.

Results from a multivariable logistic regression model of the independent effects of patient sociodemographic, clinical, and health care utilization characteristics assessed in 1999, on antihypertensive use in 2000, are shown in Table 2. Younger
Discussion

We found that chronic conditions unrelated to indications for antihypertensive therapy or the sequelae of hypertension appear to have deterring effects on antihypertensive use. Elderly hypertensive patients with these unrelated comorbidities were generally half as likely to receive this already underused class of treatments. These results are problematic in light of the very clear evidence of the benefits of antihypertensive therapy for primary and secondary prevention at multiple end organs.

Significant reductions in antihypertensive use were seen consistently across the 4 comorbidities examined, suggesting that other conditions not studied here are also likely to reduce antihypertensive use. This possibility that unrelated comorbidity in general diminishes antihypertensive use is further supported by the significant reduction in antihypertensive use with higher Charlson comorbidity scores. Comorbid conditions are present in as many as 60% of older populations. This high frequency makes any general deterring effect of comorbidities on use of beneficial treatments an important public health issue to address.

Although all 4 conditions were associated with diminished antihypertensive use, the retarding effects of asthma/COPD and depression were significantly larger than for osteoarthritis or GI disorders. This confirms some previous findings that identified mood disorders and chronic airway diseases as being especially associated with underuse of health care in general and treatments for cardiovascular conditions in particular.

Potential mechanisms underlying these findings should be considered. One possibility is that biological or physiological bases explain these findings (eg, lower blood pressures have been observed in some but not other studies of depressed patients). However, this is unlikely to explain the equally strong deterring effects of comorbidity on antihypertensive use we observed in subgroups with more clear cardiovascular indications. Furthermore, the limited evidence that does exist suggests the comorbidities examined here or their treatments

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**TABLE 2. Independent Predictors of Using Antihypertensive Medications in 2000**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR* (95% CI*) of Using Antihypertensives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>65–74</td>
<td>1.09 (1.03–1.16)</td>
</tr>
<tr>
<td>75–84</td>
<td>0.99 (0.94–1.05)</td>
</tr>
<tr>
<td>&gt;85</td>
<td>0.92 (0.86–0.99)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.09 (1.03–1.16)</td>
</tr>
<tr>
<td>Male</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.15 (1.04–1.26)</td>
</tr>
<tr>
<td>Nonwhite</td>
<td></td>
</tr>
<tr>
<td>Comorbid conditions†</td>
<td></td>
</tr>
<tr>
<td>Asthma/COPD</td>
<td>0.43 (0.40–0.47)</td>
</tr>
<tr>
<td>Depression</td>
<td>0.50 (0.45–0.55)</td>
</tr>
<tr>
<td>GI disorders</td>
<td>0.59 (0.54–0.64)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>0.63 (0.59–0.67)</td>
</tr>
<tr>
<td>Cardiovascular conditions</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.31 (1.23–1.40)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1.03 (0.97–1.10)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1.05 (0.99–1.11)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.16 (1.10–1.22)</td>
</tr>
<tr>
<td>Charlson comorbidity score‡</td>
<td>0.98 (0.96–0.99)</td>
</tr>
<tr>
<td>Health care use in 1999§</td>
<td></td>
</tr>
<tr>
<td>Total No. of medications</td>
<td>2.15 (2.01–2.30)</td>
</tr>
<tr>
<td>Hospital days</td>
<td>0.90 (0.87–0.93)</td>
</tr>
<tr>
<td>Nursing home days</td>
<td>0.94 (0.92–0.97)</td>
</tr>
<tr>
<td>Physician visits</td>
<td>0.82 (0.79–0.85)</td>
</tr>
</tbody>
</table>

*From a multivariable logistic regression model incorporating all variables shown; referent is not having any of the 4 conditions; ORs shown are per 1 unit increase in Charlson scores; ORs shown are per 10 unit increases in the variable shown.

---

**TABLE 3. Comparison of the Effects of Individual Comorbidities on Antihypertensive Use in 2000**

<table>
<thead>
<tr>
<th>Comorbid Condition</th>
<th>Adjusted OR* (95% CI*) of Using Antihypertensives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma/COPD</td>
<td>0.70 (0.65–0.76)</td>
</tr>
<tr>
<td>Depression</td>
<td>0.79 (0.72–0.87)</td>
</tr>
<tr>
<td>GI Disorders</td>
<td>0.93 (0.86–1.01)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>1.00 —</td>
</tr>
</tbody>
</table>

*From a multivariable logistic regression model adjusted for age, gender, race, cardiovascular conditions (coronary artery disease, cerebrovascular disease, congestive heart failure, and diabetes), Charlson comorbidity score, and health care use in 1999 (No. of medications, hospital days, nursing home days, and physician visits).
may actually increase risks for negative cardiovascular outcomes and cardiovascular disability.31–38

Factors related to patients, providers, and health care systems may more readily explain these results. Patients with a greater number of conditions have less time and resources to attend to each.20 Symptomatic comorbidities may also become a higher priority for patients and providers than asymptomatic but no less serious conditions such as hypertension.39,40 It is important to keep in mind that PACE recipients do not pay much for their medications; other elderly may face much larger financial barriers, leading to even less antihypertensive use, especially among those constrained by multiple comorbidities. Widespread poor adherence and premature discontinuation may also cut utilization short among elderly patients who initiate antihypertensives.41–42

Important changes have occurred in primary care in which most hypertension is treated, including an increase in competing demands on physicians.43,44 Physicians may perceive there will be interactions, real or otherwise, between antihypertensives and medications used to treat comorbidities.4 Features of health care systems may also be important, including the extent to which there is coordination among providers caring for patients with multiple conditions.10 Although not present in PACE, restrictions on the number of prescriptions and formularies may deter antihypertensive use in other health care systems, especially among elderly with comorbidities.45–47

This study confirmed some previous findings regarding correlates of antihypertensive use. The reduced use seen previously among the oldest old may be attributable to their more limited abilities to pay for and access care, real or perceived frailty, and even outright “ageism.”18 Greater use by nonwhites could reflect the higher prevalence and severity of hypertension or possibly the success of recent programs to increase hypertension awareness and treatment in these populations.49,50 The diminished antihypertensive use observed among males may be attributable to their greater reluctance to receive such therapies but is paradoxical in light of their potentially greater needs.18

As expected, we observed that some cardiovascular indications for antihypertensives (therapy, ie, coronary artery disease and diabetes) were associated with increased use, although probably short of what should be expected in such high-risk populations.12–15 Greater antihypertensive use has been observed among those receiving more medications generally,18 whereas nursing homes have been identified previously as settings with low-intensity use of several medication classes.51,52 Hospitalizations and ambulatory visits may be markers of more severe comorbidity and have been associated with diminished antihypertensive use previously.14

These results should be interpreted with the following 4 sets of potential limitations in mind. First, although most evidence5 suggests that antihypertensives are underused in the elderly, we were unable to assess blood pressures in the study population. For this reason, we cannot say with certainty that the lower proportions of antihypertensive use observed among patients with comorbidities represent underuse; alternatively, the higher proportions observed among those without comorbidities could represent overuse. Our requirements for ≥1 diagnosis of hypertension in 1999 may have minimized the latter possibility. Furthermore, the equally strong deterring effects of comorbidities in subgroups with clear indications provides additional evidence that the lower rates of antihypertensive use in our main analyses do represent underuse. Second, although we believe our adjustments corrected any imbalances in the distribution of indications for antihypertensives across our cohorts, the possibility of residual or unmeasured confounding should be considered. Third, medications that we presumed were being prescribed for hypertension may actually have been given to patients exclusively for other cardiovascular indications. Requiring ≥1 hypertension diagnosis in patients’ administrative records may have decreased this possibility; however, if patients with other cardiovascular indications were not intentionally prescribed and using their medications to also treat specifically hypertension, we may be underestimating the degree to which antihypertensives are poorly used. Finally, the applicability of these results to other older populations is enhanced by the facts that Pennsylvania is second only to Florida in terms of the proportion of its citizens ≥65 years of age, PACE is the largest state medication benefit program for elderly in the United States, and PACE includes a wide range of socioeconomic strata because of its generous eligibility requirements.53 Nonetheless, the use of antihypertensives may be substantially different in other states and health care systems.

Despite these potential limitations, our findings suggest that the negative impact of comorbidity on antihypertensive use may be an important intervention target. Assuming 60% of elderly are afflicted by multiple comorbid conditions54–59 that reduce antihypertensive use by as much as the 50% observed in this study, successful interventions on these deterring effects have the potential to improve antihypertensive underuse in the elderly by approximately one third.54 One effective strategy may be to emphasize antihypertensive use by patients with comorbidities in widely disseminated guidelines.3 Whether growing direct-to-consumer advertising can increase awareness in this regard could be investigated.55 Greater use of community awareness, blood pressure screening, and disease management programs to increase antihypertensive initiation in patients with comorbidities may be needed.56 Even after antihypertensives are initiated, interventions to enhance adherence should be explored, especially in light of evidence of their utility in other cardiovascular conditions.57,58 Expanding drug coverage may be needed to ease financial barriers faced by patients with multiple conditions.56,57 Drug utilization review programs could alert physicians to instances of suboptimal antihypertensive use and performance standards59 or “report cards” (eg, National Committee for Quality Assurance standards60) could help monitor the impact of interventions on antihypertensive use in patients with comorbidities. A combination of all of these may be needed if the quality of hypertension care and the clinical outcomes of vulnerable elderly with comorbidities are to be improved.61

Perspectives

Antihypertensive drugs remain underused in vulnerable older populations, making it imperative to identify potentially
modifiable determinants. In this study, we found that highly prevalent noncardiovascular comorbidities (osteoarthritis, asthma/COPD, depression, and GI disorders) were all significantly related to diminished use of antihypertensives by elderly with hypertension. Clearly, more research is necessary to elucidate the reasons for these findings, including the extent to which biologic, patient, provider, economic, and health care system factors may play a role. However, if confirmed, these results suggest that there could be substantial public health benefits from intervening on the deterring effects that unrelated comorbidities appear to have on anti-hypertensive medication use. We speculate on what future initiatives might be necessary to successfully address the negative impacts noncardiovascular comorbidities may have on the use of this highly beneficial preventive therapy.

Acknowledgments

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References


Angiotensin-Converting Enzyme Inhibitors and Calcium Channel Blockers for Coronary Heart Disease and Stroke Prevention

Paolo Verdecchia, Gianpaolo Reboldi, Fabio Angeli, Roberto Gattobigio, Maurizio Bentivoglio, Lutgarde Thijss, Jan A. Staessen, Carlo Porcellati

Resumo—Investigamos se a protecção contra a doença da artéria coronária (DAC) e o AVC conferida pelos inibidores da enzima conversora da angiotensina (IECA) e pelos bloqueadores dos canais de cálcio (BCC) em doentes hipertensos ou de alto risco pode ser explicada pelo regime posológico específico. Extraiamos dados estatísticos resumidos referentes à DAC e ao AVC de 28 ensaios com resultados que compararam os IECA ou os BCC aos diuréticos, (-bloqueadores ou placebo num total de 179 122 doentes, 9509 casos de incidência de DAC e 5971 casos de AVC. A DAC incluiu enfarte do miocárdio e morte coronária. Em ensaios controlados por placebo, os IECA diminuíram o risco de DAC (P<0,001) e os BCC reduziram a incidência de AVC (P<0,001). Não se observaram diferenças significativas em termos de risco da DAC entre os regimes à base de diuréticos/(-bloqueadores e os regimes à base de IECA (P=0,46) ou BCC (P=0,52). O risco de AVC diminuiu com os BCC (P=0,041), mas não com os IECA (P=0,15) em comparação com os diuréticos/(-bloqueadores. Na medida em que a heterogeneidade entre ensaios foi significativa, investigamos as fontes potenciais de heterogeneidade por meta-regressão. As co-variáveis analisadas foram a redução da pressão arterial (PA) sistólica, tratamento farmacológico (IECA versus BCC), termo de interacção, sexo, idade no momento da distribuição aleatória, ano da publicação e duração do tratamento. A prevenção da ocorrência da DAC foi explicada pela redução da PA sistólica (P<0,001) e pelo uso de IECA (P=0,028), ao passo que a prevenção da ocorrência do AVC foi explicada pela redução da PA sistólica (P=0,001) e pelo uso de BCC (P=0,042). Estes resultados vêm confirmar que a diminuição da PA é fundamental para prevenir a ocorrência de DAC e AVC. No entanto, para lá da redução da PA, os IECA parecem ser superiores aos BCC na prevenção da DAC, ao passo que os BCC parecem ser superiores aos IECA na prevenção do AVC. (Hypertension. 2005;46:386-392.)

Key Words: antihypertensive therapy ■ myocardial infarction ■ stroke

Outcome trials showed that a persistent reduction in blood pressure (BP) reduces the risk of coronary heart disease (CHD) and stroke.1,2 The antihypertensive drugs tested in these trials have different pharmacological properties and mechanisms of action. Experimental studies and clinical trials with intermediate outcomes suggested that ancillary properties of antihypertensive drugs3–6 might play a role in the prevention of cardiovascular complications independent of BP. In the second cycle of meta-analyses of the Blood Pressure Lowering Treatment Trialists Collaboration (BPLTTC),7 angiotensin-converting enzyme inhibitors (ACEIs) reduced the risk of major cardiovascular events not dissimilarly from diuretics and β-blockers together, as well as from calcium channel blockers (CCBs). Because the BP reduction was slightly lesser (1 to 2 mm Hg) in patients treated with ACEIs than in those treated with other drugs, ancillary properties of ACEIs might have influenced cardiovascular outcome with mechanisms partially independent of BP lowering. The BPLTTC analysis also showed a trend toward a lesser risk of stroke with regimens based on CCBs.7

In a previous meta-regression analysis, we demonstrated that the benefit of antihypertensive drug treatment was largely attributable to BP reduction.8,9 In the present analysis, we refined our meta-regression approach. Including the most recent evidence from clinical trials, we reinvestigated the BP-dependent and BP-independent effects of ACEIs and CCBs in the prevention of CHD and stroke in patients with hypertension or high cardiovascular risk.

Materials and Methods

We searched for randomized controlled outcome trials that met all of the following prespecified criteria: (1) comparison between old antihypertensive drugs (diuretics, β-blockers) or placebo with new drugs (ACEIs or CCBs); (2) publication before December 31, 2004, in peer-reviewed journals indexed in Medline; (3) inclusion of...
patients with hypertension or high cardiovascular risk but without overt heart failure at entry; (4) prespecified and well-defined end-points, including CHD and stroke, the former being a composite of myocardial infarction and coronary death; (5) measurement of systolic BP at baseline and follow-up; (6) follow-up of ≥2 years; and (7) sample size of ≥100 subjects. We searched for eligible studies through Medline using research methodology filters.10 The final search identified 28 trials,11–40 which fulfilled all inclusion criteria. Two of us (P.V. and F.A.) extracted the data on the basis of an intention-to-treat approach. We accepted the definition of CHD and stroke as reported in the individual reports.

To also investigate the effects of BP lowering per se, our quantitative review included placebo-controlled as well as actively controlled trials. Reference treatment consisted of old antihypertensive drugs (diuretics or β-blockers) or placebo. Experimental treatment was based on new antihypertensive drugs (ACEIs or CCBs). We calculated odds ratios (ORs) and 95% confidence intervals (CIs) for CHD and stroke for each trial separately and for combinations of studies according to fixed- and random-effect models. We tested the null-hypothesis of homogeneity across individual studies by the Q test. In the presence of significant heterogeneity, we used a random-effect model. We assessed the influence of individual studies on pooled effect sizes by excluding 1 study at the time according to Tobias’ method.41 If the point estimate of the combined effect size with 1 study omitted lies outside the CI of the overall estimate with all available trials contributing, then the study in question had an excessive influence. We tested for publication bias using the methods described by Begg42 and Egger.43 We expressed our results as mean±SD unless otherwise indicated. All P values are for 2-sided tests. Analyses were done using the Stata version 8.0 (StataCorp LP) and SAS version 8.2 (SAS Institute Inc) packages.

**Metaregression Analysis**

To investigate potential sources of heterogeneity between different trials, we performed a weighted random-effect metaregression analysis44 using the SAS mixed-model procedure and the Stata macro “metareg.” Potential effect modifiers included: (1) the baseline-corrected differences in achieved systolic BP (follow-up minus baseline) between regimens based on either ACEIs or CCBs versus the reference group; (2) drug regimen (ACEIs versus CCBs); (3) the interaction term between the change in systolic BP and the drug regimen in relation to outcome; (4) duration of follow-up; (5) sex distribution; (6) age at randomization; and (7) year of publication. We used metaregression analysis to test the relationship between outcome and these explanatory variables. For the metaregression analysis, ORs were logarithmically transformed and weighted by the inverse of the sum of the within-trial and residual between-trial variance. Final models only included covariates that significantly contributed to the between-study heterogeneity.44

**Results**

Table 1 shows the main characteristics of the 28 eligible trials, which included 179 122 patients. Overall, 4810 cases of CHD and 3044 strokes occurred among 92 446 patients randomized to ACEIs or CCBs. The 86 676 control patients randomized experienced 4699 and 2927 incident cases of CHD and stroke, respectively. In sensitivity analyses, none of the trials had a significant influential effect on the overall estimates for CHD or stroke. None of the tests for publication bias achieved significance (P>0.10).

**Coronary Heart Disease**

Overall (Figure 1), treatment with ACEIs or CCBs compared with control (diuretics/β-blockers or placebo) resulted in a 7% lower risk of CHD (OR, 0.93; 95% CI, 0.87 to 0.99; P=0.024), with significant heterogeneity across the trials (P=0.013). We also calculated pooled estimates for specific comparisons: ACEIs versus placebo,14,17–20,40 ACEIs versus old drugs,11–13,15,16 CCBs versus placebo,28,29,31,32,34–39 and CCBs versus old drugs.11,15,21–27,30,33 Treatment based on ACEIs was associated with a 21% lesser risk of CHD (OR, 0.79; CI, 0.71 to 0.88; P<0.001) compared with placebo, whereas the odds for CHD did not differ between the regimens based on ACEIs and the regimens based on diuretics/β-blockers (OR, 0.97; CI, 0.90 to 1.05; P=0.46). Regimens based on CCBs were associated with a nonsignificant 17% lower risk of CHD (OR, 0.83; CI, 0.67 to 1.03; P=0.10) compared with placebo. For CHD, there were no significant differences between the regimens based on CCBs and those based on diuretics/β-blockers (OR, 1.02; CI, 0.96 to 1.09; P=0.52). The test of heterogeneity between subgroups was statistically significant (P=0.002).

**Stroke**

Treatment with ACEIs or CCBs conferred an 11% reduction in the risk of stroke (OR, 0.89; 95% CI, 0.82 to 0.97; P=0.005) compared with diuretics/β-blockers or placebo (Figure 2). Use of ACEIs was associated with a significant decrease in stroke incidence (OR, 0.84; 95% CI, 0.72 to 0.97; P=0.020) compared with placebo. The risk of stroke was similar in treatment with ACEIs compared with diuretics/β-blockers (OR, 1.09; 95% CI, 0.96 to 1.24; P=0.15). Treatment with CCBs lowered the risk of stroke by 35% (OR, 0.65; CI, 0.55 to 0.78; P<0.001) compared with placebo and by 8% compared with old drugs (OR, 0.92; CI, 0.85 to 0.99; P=0.041). There was heterogeneity (P<0.001) among the pooled results of these subgroups of trials.

**Discussion**

This quantitative overview confirms that ACEIs and CCBs protect against CHD and stroke mainly by reducing BP. In addition, over and beyond BP lowering, ACEIs appear
superior to CCBs for the prevention of CHD, whereas CCBs appear superior to ACEIs for protection against stroke. These data have relevant clinical implications in suggesting that the ancillary properties of these drug classes might provide specific contributions to the prevention of CHD and stroke, respectively. Other potential modifiers or confounders of the outcome results, including the patients’ age and sex distribution and year of publication of the trials, did not contribute to the variance explained by our metaregression models.

Role of BP Lowering

In a metaregression analysis of 27 major trials, we demonstrated previously that BP lowering was the major determinant of the benefits of antihypertensive treatment on all-cause and cause-specific cardiovascular outcomes. The 2003 update of this meta-analysis provided consistent results. Along similar lines, the BPLTTC reported that in studies comparing tight to usual BP control, the reduction in CHD and stroke produced by antihypertensive treatment increased with lower BP targets, and that in other trials, it was proportional to the differences in the achieved systolic BP between randomized groups. However, none of the previously published metaregression studies investigated whether, for the same degree of BP lowering, prevention of stroke was superior to the protection against CHD. We found that a 10 mm Hg decrease in systolic BP antihypertensive treatment prevented CHD and stroke to a similar relative extent. The absolute benefit (ie, the number of patients to be treated to prevent 1 event) depends

<table>
<thead>
<tr>
<th>Study</th>
<th>Reference Drug</th>
<th>No. of Patients (exp/ref)</th>
<th>No. of Male Subjects</th>
<th>Age (years)</th>
<th>Follow-Up (years)</th>
<th>No. of CHD (exp/ref)</th>
<th>No. of Stroke (exp/ref)</th>
<th>ΔSBP</th>
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<tbody>
<tr>
<td>ALLHAT</td>
<td>Diuretics</td>
<td>9054/15255</td>
<td>12951</td>
<td>67</td>
<td>4</td>
<td>796/1362</td>
<td>457/675</td>
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<tr>
<td>ANBP2</td>
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<td>2981</td>
<td>72</td>
<td>4</td>
<td>173/195</td>
<td>112/107</td>
<td>−1.4</td>
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<tr>
<td>CAMELOT</td>
<td>Placebo</td>
<td>673/655</td>
<td>962</td>
<td>58</td>
<td>2</td>
<td>14/19</td>
<td>8/12</td>
<td>5.6</td>
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<tr>
<td>CAPPPI</td>
<td>Diuretics/β-blockers</td>
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<td>5874</td>
<td>53</td>
<td>6</td>
<td>162/161</td>
<td>108/148</td>
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</tr>
<tr>
<td>PROGRESS</td>
<td>Placebo</td>
<td>1281/1280</td>
<td>3877</td>
<td>64</td>
<td>3</td>
<td>4/52</td>
<td>157/165</td>
<td>4.9</td>
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<tr>
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<td>Diuretics/β-blockers</td>
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<td>1451</td>
<td>76</td>
<td>5</td>
<td>139/154</td>
<td>215/237</td>
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<td>β-blockers</td>
<td>400/358</td>
<td>410</td>
<td>56</td>
<td>8</td>
<td>61/46</td>
<td>21/17</td>
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<td>60</td>
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<td>326/429</td>
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<tr>
<td>HOPE</td>
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<td>6465/6452</td>
<td>6817</td>
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<td>482/604</td>
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<td>61</td>
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<td>PART-220</td>
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<td>308/309</td>
<td>506</td>
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<td>6797</td>
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<td>1</td>
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<td>71/92</td>
<td>3</td>
</tr>
<tr>
<td>PROGRESS (combination with diuretics)</td>
<td>Placebo</td>
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<td>4626</td>
<td>64</td>
<td>3</td>
<td>67/102</td>
<td>150/255</td>
<td>12.3</td>
</tr>
</tbody>
</table>

exp indicates experimental; ref, reference.
on the rate of CHD or stroke in the population to which the present findings might be extrapolated. The present analysis also includes actively controlled trials in which all randomized patients received BP drugs as well as trials involving normotensive patients with high cardiovascular risk. These characteristics may have blunted the divergence between the regression lines of CHD and stroke in relation to BP gradients. Moreover, the disclosure of fully divergent relations might require a range of systolic BP gradients larger than those explored in the present overview (−5 to 15 mm Hg).

On the other hand, CHD prevention and BP reduction might be more closely related than conceived previously, particularly in high-risk patients. For example, in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, hypertensive patients, of whom 46% and 20% had a history of CHD or stroke, respectively, were randomized to an angiotensin II receptor antagonist or a CCB. Over the whole follow-up (median 4.9 years), systolic BP was on average 2.2 mm Hg higher on valsartan than amlodipine, and the rates of myocardial infarction and stroke were similarly elevated.
on valsartan by 19% and 15%, respectively. In the HOPE study, in which systolic BP was lower on ramipril than it was on placebo by 4 mm Hg at 1 month, 3 mm Hg at 2 years, and 3 mm Hg at the end of the study, incidence of myocardial infarction and stroke was lower by 20% and 32%, respectively, in the ACEI group. The central role of BP reduction also emerged in the PROGRESS study (Perindopril Protection Against Recurrent Stroke Study), in which systolic BP fell versus control by 5 and 12 mm Hg in the perindopril and perindopril plus indapamide strata, respectively, with a significant risk reduction for stroke only in the ACEI plus diuretic group.

Ancillary Properties of ACEIs and CCBs

In some but not all clinical studies, the renin-angiotensin system showed an association with the risk of CHD. ACEIs possess pharmacological properties, which could delay the development of atherosclerosis and increase plaque stability. In addition, ACEIs may shift the fibrinolytic balance from coagulation to lysis by reducing the angiotensin II-dependent production and secretion of plasminogen activator inhibitor-1. Results of our overview support the hypothesis that for the same degree of BP lowering, ACEIs might be superior to CCBs in the protection against incident or recurrent CHD. Conversely, compared with diuretics/β-blockers or placebo, CCBs might provide better protection against stroke than ACEIs. The mechanisms underlying the specific protection against stroke conferred by CCBs remain to be clarified. Lacidipine, a dihydropiridine CCB, reduced progression of carotid atherosclerosis independent of the reduction in clinic and ambulatory BP. The double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial already showed a 50% reduction in the incidence of dementia after a median follow-up of 2.0 years, a benefit overwhelmingly attributable to the prevention of Alzheimer’s disease.

Study Limitations

The benefits of ACEIs for prevention of stroke might have been underestimated because placebo was given on top of active medications in comparative trials with ACEIs, whereas placebo coincided with a no-treatment strategy in 3 trials. In addition, the latter studies have been performed in cohorts at high risk of stroke, thus providing a potential framework to maximize the benefits of CCBs. The same argument also applies for CHD in 10 trials, in which ACEIs were tested against placebo or older drugs. Other limitations inherent to all meta-analyses performed without access to individual patient data originate from potential differences between trials in the definition and validation of end points and in the clinical characteristics of the randomized patients. Finally, we did not execute a metaregression analysis for heart failure. Our overview was focused on CHD and stroke. Some heterogeneity exists across trials in the criteria used for diagnosis of heart failure.

Perspectives

In the present overview of 28 outcome trials, which compared new antihypertensive drugs (ACEIs or CCBs) with old antihypertensive drugs (diuretics or β-blockers) or placebo,
the risk of CHD was decreased by the BP reduction and the use of ACEIs. Furthermore, BP reduction and the use of CCBs independently reduced the incidence of stroke. The important clinical implication from our overview is that ACEIs might confer specific protection against CHD, and CCBs might confer specific protection against stroke, independent of their antihypertensive effect. Thus, the combination between these 2 classes of drugs could offer the rationale for a broad-spectrum cardiovascular prevention. However, BP lowering holds center stage in the prevention of major cardiovascular complications in patients with hypertension or high cardiovascular risk.

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References


Association of the T8590C Polymorphism of CYP4A11 With Hypertension in the MONICA Augsburg Echocardiographic Substudy


Resumo—As variantes genéticas da monooxigenase do ácido araquidónico CYP4A11 resultam numa síntese reduzida do ácido 20-hidroxieicosatetraenoico e em hipertensão experimental. Além do mais, nos seres humanos, o polimorfismo T8590C de CYP4A11 demonstrou estar associado à hipertensão arterial. O presente estudo teve por objectivo analisar ainda mais esta associação numa amostra com base numa população de grandes dimensões. Consequentemente, os participantes do subestudo ecocardiográfico do terceiro levantamento MONICA (MONitoring trends and determinants In Cardiovascular disease – Monitorização das tendências e determinantes na doença cardiovascular) foram estudados por meio de medições antropométricas, ecocardiográficas e bioquímicas padronizadas e determinação do genótipo para o estado do alelo T8590C de CYP4A11. As pessoas com o genótipo CC apresentam níveis mais altos de pressão arterial sistólica (CC 141,4(3,17 mm Hg versus CT 134,2(0,97 mm Hg e TT 134,3(0,53 mm Hg; P=0,03) e diastólica (CC 85,4(2,06 mm Hg versus CT 80,3(0,63 mm Hg e TT 80,7(0,34 mm Hg; P=0,02). Do mesmo modo, o rácio de probabilidades (ajustado para idade, índice de massa corporal e sexo) do genótipo CC versus os genótipos CT e TT para a hipertensão correspondeu a 3,31 (intervalo de confiança [IC] de 95%), 1,38 a 7,96; P=0,02). Do mesmo modo, o rácio de probabilidades (ajustado para idade, índice de massa corporal e sexo) do genótipo CC versus os genótipos CT e TT para a hipertensão correspondeu a 3,31 (intervalo de confiança [IC] de 95%), 1,38 a 7,96; P=0,02). Do mesmo modo, o rácio de probabilidades (ajustado para idade, índice de massa corporal e sexo) do genótipo CC versus os genótipos CT e TT para a hipertensão correspondeu a 3,31 (intervalo de confiança [IC] de 95%), 1,38 a 7,96; P=0,02). Do mesmo modo, o rácio de probabilidades (ajustado para idade, índice de massa corporal e sexo) do genótipo CC versus os genótipos CT e TT para a hipertensão correspondeu a 3,31 (intervalo de confiança [IC] de 95%), 1,38 a 7,96; P=0,02). Do mesmo modo, o rácio de probabilidades (ajustado para idade, índice de massa corporal e sexo) do genótipo CC versus os genótipos CT e TT para a hipertensão correspondeu a 3,31 (intervalo de confiança [IC] de 95%), 1,38 a 7,96; P=0,02). Do mesmo modo, o rácio de probabilidades (ajustado para idade, índice de massa corporal e sexo) do genótipo CC versus os genótipos CT e TT para a hipertensão correspondeu a 3,31 (intervalo de confiança [IC] de 95%), 1,38 a 7,96; P=0,02). Do mesmo modo, o rácio de probabilidades (ajustado para idade, índice de massa corporal e sexo) do genótipo CC versus os genótipos CT e TT para a hipertensão correspondeu a 3,31 (intervalo de confiança [IC] de 95%), 1,38 a 7,96; P=0,02). Do mesmo modo, o rácio de probabilidades (ajustado para idade, índice de massa corporal e sexo) do genótipo CC versus os genótipos CT e TT para a hipertensão correspondeu a 3,31 (intervalo de confiança [IC] de 95%), 1,38 a 7,96; P=0,02). Do mesmo modo, o rácio de probabilidades (ajustado para idade, índice de massa corporal e sexo) do genótipo CC versus os genótipos CT e TT para a hipertensão correspondeu a 3,31 (intervalo de confiança [IC] de 95%), 1,38 a 7,96; P=0,02). Do mesmo modo, o rácio de probabilidades (ajustado para idade, índice de massa corporal e sexo) do genótipo CC versus os genótipos CT e TT para a hipertensão correspondeu a 3,31 (intervalo de confiança [IC] de 95%), 1,38 a 7,96; P=0,02). Do mesmo modo, o rácio de probabilidades (ajustado para idade, índice de massa corporal e sexo) do genótipo CC versus os genótipos CT e TT para a hipertensão correspondeu a 3,31 (intervalo de confiança [IC] de 95%), 1,38 a 7,96; P=0,02). Do mesmo modo, o rácio de probabilidades (ajustado para idade, índice de massa corporal e sexo) do genótipo CC versus os genótipos CT e TT para a hipertensão correspondeu a 3,31 (intervalo de confiança [IC] de 95%), 1,38 a 7,96; P=0,02). Do mesmo modo, o rácio de probabilidades (ajustado para idade, índice de massa corporal e sexo) do genótipo CC versus os genótipos CT e TT para a hipertensão correspondeu a 3,31 (intervalo de confiança [IC] de 95%), 1,38 a 7,96; P=0,02).

Key Words: genetics ■ polymorphism ■ hypertension, arterial ■ echocardiography

A variety of gene variants has shown association with arterial hypertension. However, only small or inconsistent effects on blood pressure were observed for most of the frequent polymorphisms of hypertension-related genes. On the other hand, mutations with profound implications for blood pressure regulation were found predominantly in exceptional families. Thus, despite extensive research, genetic testing for risk assessment in hypertension is not yet advisable for routine patient evaluation. A major challenge for this field will be the identification of genetic variants with reproducible and clinically as well as epidemiologically relevant effects on blood pressure regulation that, in addition, offer the potential of therapeutic intervention.

The CYP4A arachidonic acid monooxygenase oxidizes endogenous arachidonic acid to 20-hydroxyeicosatetraenoic acid (20-HETE). Depending on its expression at renovascular or tubular sites, the 20-HETE metabolite can act in a prohypertensive or antihypertensive manner. Holla et al characterized a CYP4A14 (−/−) knockout mouse as a model of gender-specific severe hypertension. Evaluation of human homologues as potential novel genetic determinants in hypertension revealed 2 candidate genes: CYP4A11 and CYP4A22 from the CYP4A gene family. Recently, CYP4A11 but not CYP4A22 was identified as the functional active protein that catalyzes the metabolism of arachidonic acid to 20-HETE in humans. Screening for genetic variants revealed a cytosine for thymidine transition at nucleotide 8590 in exon 11, which results in a nonsynonymous phenylalanine to serine substitution at residue 434 of CYP4A11. The less frequent 8590C genotype, which corresponds to the 434S variant on protein...
level, affects the catalytic activity of the 20-HETE synthase through a loss-of-function mechanism.\textsuperscript{10} This variant was associated weakly with hypertension in the Framingham Offspring Cohort. Similar results were obtained in white participants of the Tennessee Cohort. Subgroup analyses in these studies including blacks within the Tennessee Cohort did not show significant association, most likely because of insufficient power.\textsuperscript{10}

This initial weak positive evaluation requires verification in an independent cohort to reduce the chance of being false-positive. Furthermore, the present analysis within the population-based MONICA (MONItoring trends and determinants In CArdiovascular disease) Augsburg echocardiographic substudy sample intends to evaluate the potential impact of the CYP4A11 T8590C polymorphism on echocardiographic parameters of left ventricular (LV) function and geometry.

Methods

Study Population

The subjects of this study participated in the echocardiographic substudy (total n=1674) of the third MONICA Augsburg survey 1994/1995.\textsuperscript{11–13} Subjects originated from a gender- and age-stratified random sample of all German residents of the Augsburg area. The third survey represents individuals 25 to 75 years of age and \textasciitilde300 subjects for each 10-year increment. The population was studied by physical examination, blood testing, and a standardized interview including medical history, physical activity, medication, and personal habits. Resting blood pressure was taken according to MONICA guidelines using the random-zero method and standard mercury sphygmomanometers after subjects had been in a sitting position for \textasciitilde30 minutes. Hypertension was defined as blood pressure \textasciitilde140/90 or the use of antihypertensive medications. Body weight in kilograms and height in meters were determined with subjects wearing light clothing. Written informed consent was obtained from all subjects, and a local ethical committee approved the study protocol.

Echocardiographic Measurements

A 2D guided M-mode echocardiogram recorded on a strip-chart paper at 50 mm/s was performed on each subject. LV end-diastolic (LVEDD) and LV end-systolic (LVESD) diameters, septal wall (interventricular septal [IVS]), and posterior wall dimension (PWD) thickness were measured according to the recommendations of the American Society of Echocardiography.\textsuperscript{14} LV mass (LVM) was calculated using the formula: LVM (g)=0.8×1.04[(LVEDD+ IVS+PWD)\textasciitilde2−LVESD]+0.6; as described by Devereux et al.\textsuperscript{15} LVM was indexed to body surface area. LV end-systolic volume (LVESV) and LV end-diastolic volume (LVEDV) were calculated according to the Teichholz equations.\textsuperscript{16} The ejection fraction (EF) was calculated as EF=LVEDV−LVESV/LVEDV.

Biochemical Analyses

Blood was drawn for biochemical analyses from nonfasting subjects. Creatinine was assessed quantitatively with an enzymatic colorimetric test (Hitachi 717; Boehringer Mannheim). Creatinine clearance was calculated using Cockcroft–Gault formula.\textsuperscript{17}

Genotyping

Genotyping the T8590C polymorphism was performed using the 5’-exonuclease activity (TaqMan) assay on a HT7900 (Applied Biosystems). Single nucleotide polymorphism (SNP)-assay was ordered from Applied Biosystems through the Custom TaqMan SNP Genotyping Assays (forward primer: CYP4_434-F: 5’-GTTGCTCTCTCTCGAGAAC-3’; reverse primer: CYP4_434-R: 5’-GTGTGTCTCTCTCAGGTT-3’; probe 1: CYP4_434-VIC: 5’-AAAACGGGAGGTGTC-3’; probe 2: CYP4_434-FAM: 5’-AACCGGAGGTGTC-3’). With respect to sequence homology of 97% between CYP4A11 and CYP4A22, primer and probe sequences guarantee CYP4A11-specific amplification. Probes were labeled with the fluorophore FAM or VIC. Genotyping was done on 384-well plates prepared with the GENESIS Freedom pipetting robot from TECAN. The universal polymerase chain reaction (PCR) Master Mix from Applied Biosystems was used in a 5-\textmuL total reaction volume with 10 ng DNA per reaction. Allelic discrimination was measured automatically on the ABI Prism HT7900 (Applied Biosystems) using the Sequence Detection Systems 2.1 software (autocaller confidence level 95%). A total of 10% of all genotypes were repeated in independent PCRs to check for consistency and to ensure intraplate and interplate genotype quality control. No genotyping discrepancies were detected between the repeated samples. For the present study, 1397 individuals were successfully genotyped. The overall misgenotyping rate of 16% was attributable to insufficient PCR amplification because of inadequate DNA quality or quantity.

Statistical Analysis

To determine whether the genotypes of the CYP4A11 T8590C polymorphism deviated from Hardy–Weinberg equilibrium, actual and predicted genotype counts were compared by a \chi^2 goodness-of-fit test with 1 df.

Because it could not be excluded that the study sample deviates from a representative sample and that baseline factors are unequally distributed across genotypes, a multivariate model was chosen for the analysis.

To predict hypertension (presence versus absence of hypertension), a logistic regression model with genotype, age, gender, and body mass index (BMI) as explanatory variables was developed. All 2-way interactions between the genotype and covariates (age, gender, BMI) were considered and kept in the model if P≤0.05. Based on the results by Gainer et al.\textsuperscript{16} the genotype was coded for a dominant effect (CC+CT versus TT). As a second analysis, a recessive model (CC versus CT+TT) was considered. To adjust for the multiple testing of 2 genetic models, the P values for the genotypes were adjusted according to Bonferroni–Holm.\textsuperscript{18} A 2-tailed adjusted P value of the WALD-\chi^2 test ≤0.05 was considered significant. In addition, odds ratios (ORs) and 95% WALD confidence intervals (CIs) are reported for all explanatory variables. For description OR, 95% CI and 2-tailed P values of the WALD-\chi^2 test are presented for males and females separately for both genetic models.

Least square means for systolic blood pressure (SBP) and diastolic blood pressure (DBP) adjusted for age, BMI, gender, and antihypertensive medication were calculated for all genotype groups. Furthermore, descriptive P values of a 2-tailed \textit{t} test for independent groups for a dominant model (CC+CT versus TT) and a recessive model (CC versus CT+TT) are reported.

Echocardiographical data and blood pressure measurements according to 8590TT, 8590CT, and 8590CC genotypes were compared descriptively using multiple linear regression adjusting for age, BMI, SBP, and antihypertensive medication. Descriptive P values of a 2-tailed \textit{t} test for independent groups for a dominant model (CC+CT versus TT) and a recessive model (CC versus CT+TT) are reported. Furthermore, the creatinine clearance of the individuals according to CYP4A11 T8590C polymorphism were considered by calculating least square means adjusted for age, BMI, gender, antihypertensive medication, and diabetes. The results of men and women and descriptive P values of a 2-tailed \textit{t} test for independent groups for both genetic models are reported.

Results

In total, 684 women and 713 men were genotyped. The allele frequencies of the 8590T and 8590C allele were 86.7% and 13.3%, respectively. The 8590TT, 8590CT, and 8590CC genotypes were found in 75.5%, 22.4%, and 2.1% of the population. These frequencies do not deviate from those
TABLE 1. Baseline Characteristics of the Study Population (MONICA Augsburg Echocardiographic Substudy)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive</th>
<th>Hypertensive</th>
<th>Normotensive</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>346</td>
<td>367</td>
<td>402</td>
<td>282</td>
</tr>
<tr>
<td>Age, years</td>
<td>46.8±13.2</td>
<td>56.7±12.8</td>
<td>45.2±12.4</td>
<td>59.4±10.0</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.0±3.0</td>
<td>28.1±3.7</td>
<td>25.0±4.0</td>
<td>28.8±4.9</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>124.9±9.6</td>
<td>149.6±17.3</td>
<td>118.5±11.0</td>
<td>149.7±16.2</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>77.0±7.6</td>
<td>88.2±12.2</td>
<td>73.8±8.0</td>
<td>85.4±11.6</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>2.9</td>
<td>8.2</td>
<td>1.7</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Mean values ± SD are presented.

TABLE 2. Age and BMI Stratified by T8590C Genotype and the Genotype Distribution in Different Subgroups of the Study Population (MONICA Augsburg Echocardiographic Substudy)

<table>
<thead>
<tr>
<th>Variable</th>
<th>TT</th>
<th>CT</th>
<th>CC</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1055</td>
<td>313</td>
<td>29</td>
</tr>
<tr>
<td>Age, years (mean ± SD)</td>
<td>51.4±13.6</td>
<td>51.9±13.6</td>
<td>49.9±13.2</td>
</tr>
<tr>
<td>BMI, kg/m² (mean ± SD)</td>
<td>26.8±4.17</td>
<td>26.8±4.30</td>
<td>26.6±3.53</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>532 (74.6)</td>
<td>168 (23.6)</td>
<td>13 (1.8)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>523 (76.5)</td>
<td>145 (21.2)</td>
<td>16 (2.3)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>46 (73.0)</td>
<td>16 (25.4)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>No diabetes, n (%)</td>
<td>1009 (75.6)</td>
<td>297 (22.3)</td>
<td>28 (2.1)</td>
</tr>
</tbody>
</table>

TABLE 3. SBP and DBP Measurements According the T8590C Genotype, Assuming a Dominant and a Recessive Effect of the C Allele

<table>
<thead>
<tr>
<th>Genotype</th>
<th>TT</th>
<th>CT</th>
<th>CC</th>
<th>P*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined, n</td>
<td>1055</td>
<td>313</td>
<td>29</td>
<td>0.61</td>
<td>0.026</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>134.3±0.53</td>
<td>134.2±0.97</td>
<td>141.4±3.17</td>
<td>0.16</td>
<td>0.26</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>80.7±0.34</td>
<td>80.3±0.63</td>
<td>85.4±2.06</td>
<td>0.89</td>
<td>0.021</td>
</tr>
<tr>
<td>Men, n</td>
<td>532</td>
<td>168</td>
<td>13</td>
<td>0.66</td>
<td>0.039</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>137.6±0.76</td>
<td>136.1±1.35</td>
<td>147.4±4.88</td>
<td>0.56</td>
<td>0.104</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>82.9±0.50</td>
<td>81.9±0.88</td>
<td>87.9±3.18</td>
<td>0.38</td>
<td>0.086</td>
</tr>
<tr>
<td>Women, n</td>
<td>523</td>
<td>145</td>
<td>16</td>
<td>0.16</td>
<td>0.26</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>130.9±0.71</td>
<td>132.7±1.35</td>
<td>136.0±4.05</td>
<td>0.38</td>
<td>0.086</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>78.4±0.46</td>
<td>78.8±0.88</td>
<td>83.1±2.65</td>
<td>0.38</td>
<td>0.086</td>
</tr>
</tbody>
</table>

Values are least square means ± SE. SBP adjusted for age, BMI, gender (combined group), and antihypertensive medications. DBP adjusted for age, BMI, and gender (combined group). Antihypertensive medications were not significant in the model. In combined group and in men, age was not significant in the model.

*2-tailed descriptive P values from t test for independent data for the dominant model (CC + CT vs TT); †2-tailed descriptive P values from t test for independent data for the recessive model (CC vs CT + TT).

predicted by Hardy–Weinberg equilibrium and were similar to those reported in the study by Gainer et al.10 The baseline characteristics of the study population, stratified by hypertension status and gender, are shown in Table 1. Age and BMI stratified by T8590C genotype and the genotype distribution in different subpopulations are shown in Table 2. In total, 649 probands (46.5%) were hypertensive.

Effect of the T8590C Polymorphism on Blood Pressure Measurements

Compared with individuals with TT or CT genotype, CC carriers had higher SBP and DBP levels with similar trends in both men and women. In contrast, if CC carriers and CT carriers were combined (ie, assuming a dominant mode of action), no significant differences with regard to blood pressure levels were found compared with TT carriers (Table 3). In both genetic models, no interactions between genotype and covariates (age, BMI, gender, and antihypertensive medications) were found.

When assuming a recessive effect of the C allele, the OR of having hypertension attributable to the CC genotype compared with CT and TT genotype was 3.31 (95% CI, 1.38 to 7.96) in the entire study population (Table 4). No significant interaction between T8590C genotype and gender or any other covariate in the model (age, BMI) was found. These findings indicate that there is no significant difference in the effect of the T8590C genotype on the prevalence of hypertension between men and women.

Assuming a dominant effect of the C allele, there was no significant effect of the C allele on the prevalence of hypertension in the entire study group, whereas in women, some indication for an association with the prevalence of hypertension was found (OR, 1.60; 95% CI, 1.03 to 2.47; P = 0.036; Table 5).

Effect of the T8590C Polymorphism on LVM Measurements

In 1122 individuals (559 men and 563 women), echocardiograms of sufficient quality were available. No blood pressure–independent effect of the T8590C polymorphism on LVM measurements could be found regardless of whether a dominant or a recessive effect of the C allele was assumed (Table 6). Analyzing interactions between genotypes (domi-
nant and recessive model) and covariates (age, gender, BMI, SBP, and antihypertensive medications) did not reveal any effects.

**Effect of the T8590C Polymorphism on Creatinine Clearance**

In 1383 individuals, the creatinine clearance was calculated using Cockcroft-Gault formula. No effect of the T8590C polymorphism on creatinine clearance was found regardless of whether a dominant or a recessive effect of the C allele was assumed (Table 7). Furthermore, the genotype distribution was not different between individuals with mildly impaired renal function (creatinine clearance ≤80 mL/min) and individuals with normal renal function (creatinine clearance >80 mL/min; data not shown).

**Discussion**

In the present study, we describe an association between the functional T8590C polymorphism (F434S) of the CYP4A11 gene and hypertension in the MONICA Augsburg echocardiographic substudy. Our results are consistent with a recessive effect of the less frequent C allele resulting in relevant increases of absolute blood pressure values as well as the prevalence of hypertension in our population-based sample. These findings expand the results of the study by Gainer et al, who postulated a significant association with arterial hypertension and the 8590C allele in 2 independent samples (Tennessee Cohort and Framingham Offspring Cohort).10

In contrast to Gainer et al, our findings are consistent with a relatively profound recessive rather than dominant mode of action of this loss-of-function variant. In our analyses, abso-

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**TABLE 4. Genotype Distribution of the T8590C Polymorphism in Men and Women Stratified by Presence or Absence of Hypertension and ORs for Hypertension, Assuming a Recessive Effect of the C Allele**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normotensive</td>
<td>Hypertensive</td>
<td>Normotensive</td>
<td>Hypertensive</td>
</tr>
<tr>
<td>All individuals</td>
<td>346</td>
<td>367</td>
<td>402</td>
<td>282</td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8590 TT, n (%)</td>
<td>258 (74.6)</td>
<td>274 (74.7)</td>
<td>316 (78.6)</td>
<td>207 (73.4)</td>
</tr>
<tr>
<td>8590 CT, n (%)</td>
<td>85 (24.6)</td>
<td>83 (22.6)</td>
<td>79 (19.7)</td>
<td>66 (23.4)</td>
</tr>
<tr>
<td>8590 CC, n (%)</td>
<td>3 (0.9)</td>
<td>10 (2.7)</td>
<td>7 (1.7)</td>
<td>9 (3.2)</td>
</tr>
<tr>
<td>8590 C allele frequency</td>
<td>0.13</td>
<td>0.14</td>
<td>0.12</td>
<td>0.15</td>
</tr>
<tr>
<td>OR (95% CI), P value*</td>
<td>4.30 (1.08–17.15), P=0.039</td>
<td>2.93 (0.88–9.84), P=0.081</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Combined men and women

| OR (95% CI), P value† | 3.31 (1.38–7.96), P=0.016 |

Non-diabetics

| OR (95% CI), P value* | 4.11 (1.02-16.62), P=0.047 | 2.98 (0.89–10.02), P=0.078 |

Combined men and women

| OR (95% CI), P value* | 3.28 (1.36–7.92), P=0.008 |

**TABLE 5. ORs for Hypertension, Assuming a Dominant Effect of the C Allele of the T8590C Polymorphism**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normotensive</td>
<td>Hypertensive</td>
<td>Normotensive</td>
<td>Hypertensive</td>
</tr>
<tr>
<td>All individuals</td>
<td>346</td>
<td>367</td>
<td>402</td>
<td>282</td>
</tr>
<tr>
<td>OR (95% CI), P value*</td>
<td>0.95 (0.66–1.38), P=0.79</td>
<td>1.60 (1.03–2.47), P=0.036</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Combined men and women

| OR (95% CI), P value† | 1.17 (0.89–1.56), P=0.27 |

Non-diabetics

| OR (95% CI), P value* | 0.98 (0.67–1.43), P=0.91 | 1.67 (1.07–2.61), P=0.024 |

Combined men and women

| OR (95% CI), P value* | 1.22 (0.91–1.63), P=0.18 |

*2-tailed descriptive P values from WALD-χ² test; †2-tailed P values from WALD-χ² test adjusted according to Bonferroni-Holm.18
DBP were elevated in homozygous CC allele carriers of the present study is remarkable for the extent by which SBP and focuses on this phenotype for the first time. In this respect, the blood pressure values in relation to the genotype, our analysis by dominant or recessive inheritance. Are required to clarify whether blood pressure is modulated mechanisms affected by the individuals and more detailed knowledge on the molecular allele carriers. Thus, further studies on larger numbers of lute blood pressure values as well as the number of hypertensive individuals were distributed equally in CT and TT allele carriers. Thus, further studies on larger numbers of individuals and more detailed knowledge on the molecular mechanisms affected by the CYP4A11 T8590C allele status are required to clarify whether blood pressure is modulated by dominant or recessive inheritance.

Because Gainer et al’s study lacks an analysis of absolute blood pressure values in relation to the genotype, our analysis focuses on this phenotype for the first time. In this respect, the present study is remarkable for the extent by which SBP and DBP were elevated in homozygous CC allele carriers of the T8590C polymorphism. In fact, the elevation by ~7 mm Hg and 5 mm Hg in SBP and DBP is much larger than that observed with most other hypertension-related polymorphisms.1 Thus, the CYP4A11 polymorphism may be remarkable for a relatively strong effect for a relatively common variant if this association can be confirmed in further studies. Indeed, our findings indicate that >9 million people in the European Union and 5.8 million in the United States carry a genotype that exposes to a 3.3-fold risk for hypertension.

Phenotypic data of the MONICA Augsburg echocardiographic substudy allow the evaluation of the potential impact of the T8590C polymorphism on LV geometry. No effect of this polymorphism on LVM or geometry was found regardless of whether a dominant or recessive mode of action was assumed. Together, these data let us assume that this polymorphism has a significant effect in regulation of blood pressure, but an additional myocardial effect is unlikely. This may be explained by the renal expression of the gene and the localization of the functional active metabolite 20-HETE in the proximal tubules with yet no evidence of cardiac expression of the gene.

To evaluate the potential impact of genetic variation in the CYP4A11 gene on renal function, we calculated the creatinine clearance using Cockcroft–Gault formula and tested its association with the T8590C polymorphism. There was no significant effect regardless of whether a dominant or a recessive effect of the C allele was assumed. Within the complex regulation of renal vascular tone and with respect to different cofactors sensitizing the vasoconstrictor activity of 20-HETE,19 the effect of this polymorphism seems to be strong enough to modulate renal function. This observation may be important because the present study is the first evaluation of the T8590C polymorphism on renal function in a population-based sample. Unfortunately, we have no information on renal sodium and potassium handling in these individuals. Indeed, 20-HETE excretion may be regulated by salt intake.20 Specifically, it has been suggested that salt sensitivity of blood pressure may result from impairment of natriuresis mechanism dependent on 20-HETE.20 Because our large population-based sample lacks phenotypic data about salt intake and salt-sensitive hypertension, our analysis cannot address these important phenotypes.

**Limitations**

Our study lacks functional data that may explain the mechanism that mediates the association between the CYP4A11
polymorphism and arterial blood pressure. In this respect, Gainer et al demonstrated by in vitro experiments that the C allele of the T8590C polymorphism results in a phenylalanine to serine replacement that reduces the 20-HETE synthase activity of CYP4A11 by more than half. In vivo verification of this finding would be of great interest, but in our patient sample, no 24-hour urine was collected. Moreover, more detailed studies on mechanistic implications of the 8590C allele are needed specifically with respect to dietary, preventive, or therapeutic interventions in carriers of this genotype.

Furthermore, association studies require repetitive replication before definitive conclusions can be drawn. In this respect, the CYP4A11 polymorphism is remarkable for consistent findings in several population-based samples, as well as supportive data from a quantitative trait locus for blood pressure on rat chromosome 5 syntenic to human chromosome 1p33-p35, in which CYP4A11 is located, and finally, congruent data from CYP4A14 knockout mice, a gene that is closely related to the human CYP4A11 gene.

Perspectives

The study by Gainer et al and our data nicely demonstrate that candidate gene association studies can give insights into the unraveling of common and multifactorial phenotypes if stringent criteria for the study design are applied (eg, biological plausibility, rigorous phenotypic and genotypic assessment, appropriate statistical analysis, as well as independent replication).

In fact, the consistence of the present findings with the 2 population samples studied by Gainer et al is indicative for a reproducible finding and allows to speculate that the CYP4A11 gene is of importance for blood pressure regulation in the human population. Further replication studies focusing on functional phenotypes and on possible pharmacogenetic interactions are needed for a better understanding of the role of CYP4A11 in the complex regulation of blood pressure.

Acknowledgments

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References

Arterial Aging
Is It an Immutable Cardiovascular Risk Factor?
Samer S. Najjar, Angelo Scuteri, Edward G. Lakatta

Cardiovascular diseases are the leading causes of morbidity, mortality, and disability in industrialized countries, and according to World Health Organization estimates, they are poised to also become, within the next decade, the major causes of mortality in developing nations. This cardiovascular disease epidemic is occurring despite unprecedented advances in the diagnosis and treatment of these conditions. This situation is only expected to worsen because the world population is aging.

Epidemiological studies have unequivocally shown that age is the dominant risk factor for cardiovascular diseases. Indeed, the incidence and prevalence of hypertension, coronary heart disease, congestive heart failure, and stroke all steeply increase with advancing age. However, most of the research efforts have focused on developing interventions that target "traditional" risk factors for coronary heart disease (eg, hypertension, hypercholesterolemia, etc.) or identifying newer ones, whereas little attention has been devoted to aging. This is because age has usually been viewed as a chronological and unmodifiable, hence unpreventable or untreatable, risk factor. Instead, the risky components of aging have been attributed, in part, to an increased time of exposure to other established cardiovascular risk factors, which, in turn, may vary in number and severity with increasing age.

These arguments expose our major shortcoming in understanding why age is such a potent risk factor for cardiovascular diseases, namely our poor insight into the specific elements that constitute the risky components of aging vis a vis the cardiovascular system. In other words, although we have always intuitively accepted age as being a risk factor and have taken this to be a "truism," we did not have, until recently, good mechanistic or molecular explanations as to why this would be the case.

In this article, we briefly review the evidence implicating arterial aging as a cardiovascular risk factor, summarize selected recent advances in vascular biology that provide insights into the mechanisms that may underlie the increased risks conferred by arterial aging, and discuss existing interventions to prevent or retard accelerated arterial aging, as well as potential new ones worthy of investigation.

Arterial Aging in Apparently Healthy Humans
The age-associated changes in arterial structure and function in apparently healthy humans are summarized in the Table...
and have been reviewed recently.\textsuperscript{1} Cross-sectional studies show that elastic arteries, such as the central aorta, on average, dilate with age (Figure 1A), leading to an increase in lumen size.\textsuperscript{2} The thickness of the arterial wall, as indexed by the thickness of the intimal and medial layers, increases in a linear fashion nearly 3-fold between the ages of 20 and 90 years even in the absence of atherosclerotic plaques\textsuperscript{3} (Figure 1B). Postmortem studies show that this age-associated increase in arterial wall thickening is caused mainly by an increase in intimal thickening,\textsuperscript{4} even in populations with low incidence of atherosclerosis. Note in Figure 1B that not only the average intimal medial thickness (IMT) increases with advancing age, but that the range of values for IMT is greater at higher ages, suggesting significant heterogeneity in the magnitude of the age-associated thickening process among older individuals: some exhibit low values of IMT for their age and are termed “successful,” whereas others have “accelerated” alterations.

The age-associated increase in thickness of the central arterial wall is accompanied by an increase in stiffness (Figure 1C).\textsuperscript{5} This has been attributed to the repeated cycles of distensions and elastic recoils of the arterial wall, which are thought to accelerate the fragmentation and depletion of elastin, as well as the deposition of collagen.\textsuperscript{6} Stiffness can be further amplified in the presence of specific gene polymorphisms.\textsuperscript{7} The age-associated increase in central arterial stiffness, in turn, contributes to shifting the return of reflected waves to an earlier time during systole, which leads to an increase in central pressure augmentation (Figure 1D).\textsuperscript{8} Thus, although peripheral systolic blood pressure and pulse pressure increase with age,\textsuperscript{9} for a given brachial blood pressure, central blood pressure is higher in older persons.\textsuperscript{10}

Endothelial cells play a pivotal role in regulating several arterial properties, including vascular tone, vascular permeability, angiogenesis, and the response to inflammation. Endothelial-derived substances (eg, NO, endothelin-1) are determinants of large arterial compliance,\textsuperscript{11} suggesting that endothelial cells may also modulate central arterial stiffness. However, endothelial function in central arteries has not been directly assessed in humans. In the brachial artery, endothelial function, as assessed by agonist- or flow-mediated vasoreactivity, has been shown to decline with advancing age.\textsuperscript{12,13} However, in contrast to central arteries, the stiffness of muscular arteries does not increase with advancing age.\textsuperscript{14} Thus, the manifestations of arterial aging may vary among the different vascular beds, reflecting differences in the structural compositions of the arteries and, perhaps, differences in the age-associated signaling cascades that modulate the arterial properties (see below), or differences in the response to these signals across the arterial tree.

<table>
<thead>
<tr>
<th>Arterial Parameter</th>
<th>Humans &gt;65 Years</th>
<th>Monkeys 15–20 Years</th>
<th>Rats 24–30 Months</th>
<th>Rabbits 3–6 Years</th>
<th>Hypertension</th>
<th>Atherosclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumenal dilation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>?</td>
</tr>
<tr>
<td>↑ Stiffness</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>↑ Collagen</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>?</td>
</tr>
<tr>
<td>↓ Elastic</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>±</td>
<td>?</td>
</tr>
<tr>
<td>Endothelial dysfunction</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Diffuse intimal thickening</td>
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<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
</tr>
<tr>
<td>Lipid involvement</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>±</td>
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<td>↑ VSMC number</td>
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<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>↑ Matrix</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>↑ Local Ang II-ACE</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
<td>+</td>
</tr>
<tr>
<td>MMP dysregulation</td>
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<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
</tr>
<tr>
<td>↑ MCP-1/CCR2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>↑ ICAM</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>↑ TGFβ</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>↑ NADPH oxidase</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>↓ VEGF</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>↓ NO bioavailability</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</tr>
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<td>+</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Hypertension</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>±</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>±</td>
<td>+</td>
</tr>
</tbody>
</table>

? indicates unknown.

Table adapted from Wang and Lakatta.\textsuperscript{62}
There is growing recognition that telomere length may be construed as a tissue-specific marker of biological, as opposed to chronological, age. Telomeres are specialized structures located at the end of chromosomes, which shorten with each replication, unless they are rescued by the enzyme telomerase reverse transcriptase. When telomere length reaches a critical size, reflecting numerous cycles of attrition, no further cellular replication is possible and the cell becomes senescent. Telomere length has been shown to be inversely associated with chronological age in endothelial cells from human abdominal aorta, iliac arteries, and iliac veins. The impact of telomere-induced vascular senescence may be accentuated in older individuals, in whom recent studies indicate that the number and activity of endothelial progenitor cells is reduced, suggesting an age-associated diminution in regenerative capacity, which may contribute to the age-associated impairment in angiogenesis.

Arterial Aging in Cardiovascular Diseases

Although the aforementioned changes in arterial structure and function with aging were thought previously to be part of normative aging, this concept was challenged when data emerged showing that these changes are accelerated in the presence of cardiovascular diseases.

Patients with hypertension exhibit greater carotid wall thickness, central arterial stiffness, and central pressure augmentation than normotensive subjects, even after adjusting for age. They are thought to have higher central arterial diameters, although this is presently debated. Hypertensive individuals exhibit endothelial dysfunction, and the mechanisms underlying their endothelial dysfunction are similar to the ones that occur with normotensive aging, albeit they appear at an earlier age. The normotensive offspring of hypertensives also exhibit endothelial dysfunction, suggesting that endothelial dysfunction may precede the development of clinical hypertension. Among hypertensive men, shorter telomere length of circulating white blood cells is associated with greater arterial stiffness.

The metabolic syndrome, which is quite prevalent among older individuals, is associated with elevated carotid arterial thickness and stiffness. Diabetics also exhibit higher carotid IMT than nondiabetics, and they have accelerated progression of their IMT. Although their central arterial stiffness is increased, this is not accompanied by an increase in the central pressure augmentation. Diabetics also exhibit endothelial dysfunction, which can be found in their first-degree relatives who have insulin resistance. The circulating white blood cells of insulin-dependent diabetics have shorter telomere lengths than those from normoglycemic controls or noninsulin-dependent diabetics.

Patients with atherosclerosis have increased thickness and stiffness of their central arterial walls, greater central pressure augmentation, and shorter telomere lengths on their circulating white blood cells. They also exhibit endothelial dysfunction, which has been implicated in the pathogenesis of atherosclerosis and is one of its earliest pathologic manifestations.
Accelerated Arterial Aging Is Risky

Increased IMT is associated with silent ischemia among asymptomatic older individuals and is an independent predictor of stroke and future myocardial infarction (Figure 2A). The strength of IMT as a risk factor for cardiovascular diseases equals or exceeds that of most other traditional risk factors. Over and above IMT, arterial geometry, which is derived from the interplay between IMT and lumen diameter, is also an independent predictor of coronary or cerebrovascular events. Furthermore, increased central arterial stiffness is an independent predictor of stroke and future myocardial infarction (Figure 2C). Increased central arterial pressure augmentation is an independent predictor of all-cause and cardiovascular mortality in patients with end-stage renal disease (Figure 2B). Increased central arterial pressure augmentation is an independent predictor of all-cause and cardiovascular mortality in patients with end-stage renal disease (Figure 2C). Several studies have now demonstrated that impaired endothelial vasoreactivity, in both the coronary and peripheral arterial beds, is an independent predictor of future cardiovascular events (Figure 2D).

Age-Associated Arterial Remodeling Under the Microscope

Further insights into the mechanisms that may underlie the increased cardiovascular risks associated with accelerated arterial aging can be gleaned from animal studies because they allow us to probe the cellular and molecular determinants of the macroscopic changes observed in humans, and because in many species, arterial diseases do not accompany vascular aging, thus allowing us to distinguish between effects attributable to aging and those attributable to superimposed disease. As shown in the Table, the patterns of age-associated changes in arterial structure and function in rodents, rabbits, and nonhuman primates are quite similar to those in humans.

Aging of the Arterial Intima

In rodent and nonhuman primate models of aging, diffuse intimal thickening is observed with advancing age, even though these animals do not develop atherosclerosis. The diffusely thickened aging intima (Figure 3A) contains matrix proteins, collagen, glycosaminoglycans, vascular smooth muscle cells (VSMCs) that are thought to have migrated from the media, increased expression of aortic intimal adhesion molecules (Figure 3B), and increased adherence of monocytes to the endothelial surface. Within the thickened intima, the levels of the inflammatory chemokine monocyte chemoattractant protein-1 (MCP-1) and its receptor, which have been implicated in the pathogenesis of atherosclerosis, are also elevated. Of note, in aged rats and monkeys, there is no evidence that “traditional” inflammatory cells (ie, leukocytes) infiltrate the aortic wall; instead, inflammatory...
molecules, including MCP-1, are produced and secreted by endothelial cells and VSMCs.

The expression and activity of transforming growth factor-β1 (TGF-β1), a multifunctional growth factor that regulates cell replication, synthesis of extracellular matrix components, and the response to injury, are also increased in the aged intima. Furthermore, the bioavailability of NO is decreased with aging, whereas the activity of NAD(P)H oxidase and the production of reactive oxygen species are increased, which can lead to peroxidation of lipids and oxidative modifications of proteins.

Thus, increased intimal thickening should not be construed as “subclinical atherosclerosis” but as a marker of arterial aging. However, the 2 are linked because the biochemical, enzymatic, metabolic, inflammatory, and cellular changes within the diffusely thickened intima that accompanies advancing age are the very same ones that are implicated in the pathogenesis and pathophysiology of arterial diseases such as atherosclerosis. Indeed, in mice, rabbits, and nonhuman primates, experimental atherogenesis is more severe in older versus younger animals, even when the intensity or duration of the exposure to risk factors (eg, elevated plasma lipids) is equivalent (Figure 3C).

Aging of Endothelial Cells

Important alterations in the structure and function of endothelial cells accompany advancing age, including a higher prevalence of cells with polyploid nuclei, increased endothelial permeability, alterations in the arrangement and integrity of the cytoskeleton, the appearance of senescence-associated β-galactosidase staining, and the expression of several inhibitors of the cell cycle. Endothelial cells of aged arteries secrete more plasminogen activator inhibitor-1, favoring thrombosis formation. Furthermore, with aging endothelial cell production of vasoconstricting growth factors such as angiotensin II (Ang II) and endothelin increases, and that of vasodilatory factors (eg, NO, prostacyclin, and endothelium-derived hyperpolarizing factor) is reduced. These age-associated alterations in the arterial wall create a metabolically and enzymatically active milieu that is conducive for the initiation or progression of superimposed vascular diseases (eg, atherosclerosis).

Endothelial cells exhibit shorter telomere lengths with aging and suppressed activity of telomerase reverse transcriptase. Senescence-like phenotypic changes in endothelial cells can also be induced in the absence of telomere length changes through glycation of collagen. Advanced glycation end products, which accumulate with aging, increase the production of superoxide anion through the activation of NAD(P)H oxidase. The coupling of advanced glycation end products to their receptors on endothelial cells also triggers inflammatory cell recruitment and activation and enhances thrombogenesis by stimulating platelet aggregation.

Aging of the Arterial Media

Salient features of the age-associated changes in the media include the deposition of extracellular matrix proteins such as fibronectin and type-2 matrix metalloprotease (MMP-
which promotes matrix protein degradation and facilitates VSMC migration.67

Aortic medial VSMCs from older rats are larger in size and fewer in number than those in the aorta from young adult rats.68 Some of these cells appear to have undergone an age-associated phenotypic modulation toward a dedifferentiated and synthetic state. VSMC migration from the medial to the intimal compartment is a plausible mechanism for the increased number of VSMC within the diffusely thickened intima of central arteries as they age. Furthermore, after arterial injury, they undergo, in part, the muscle cell growth that accompanies the exaggerated neointimal formation in older versus younger rats69 and the accelerated remodeling response in older versus adult rats.70 This exaggerated response is attributable to factors intrinsic to the vessel wall because the excessive intimal hyperplasia is still observed when aortae from old animals are transplanted into younger ones.69

The aged media are also characterized by alterations in the content and integrity of the structural matrix proteins that are implicated in arterial stiffening, namely elastin and collagen, as well as their linkages to other matrix constituents or each other. Elastin content decreases with advancing age because of a deficiency in the synthesis of elastin, which is attributed, in part, to repression of elastin gene expression by B-Myb, a critical factor in the pathogenesis and promotion of arterial diseases such as hypertension and atherosclerosis. Thus, it is likely that the imbalance among the various growth factor signaling cascades in the aged arterial wall not only accounts for age-associated arterial remodeling but also provides a pleiotropic role of Ang II on arterial remodeling that may influence arterial aging. An age-associated increase in Ang II is observed in the thickened intima.66 Several factors such as sympathetic activity and hemodynamic factors (eg, shear and circumferential stress) likely contribute to the age-associated increase in Ang II within the arterial wall. Ang II signaling increases collagen production within the arterial wall, promotes NADPH oxidase activity, and enhances the migration of VSMCs. Infusion of Ang II to young rats in concentrations that elicit a modest increase in arterial pressure imparts to their central arteries some of the structural and molecular characteristics of arterial aging.

Ang II Signaling

Arterial components of the Ang II–signaling cascade increase with aging in rats, nonhuman primates, and humans. The highest expression of Ang II is observed in the thickened intima.66 Several factors such as sympathetic activity and hemodynamic factors (eg, shear and circumferential stress) likely contribute to the age-associated increase in Ang II within the arterial wall. Ang II signaling increases collagen production within the arterial wall, promotes NADPH oxidase activity, and enhances the migration of VSMCs. Infusion of Ang II to young rats in concentrations that elicit a modest increase in arterial pressure imparts to their central arteries some of the structural and molecular characteristics of arterial aging.

Thus, Ang II signaling appears to play a critical role in modulating many of the stimuli and signals that govern arterial aging and regulate its structural and functional response and adaptation (Figure 4). Importantly, many of the same metabolic, enzymatic and cellular factors that are activated or suppressed by Ang II signaling and by other signaling cascades (eg, NO, bradykinin, endothelin, norepinephrine, prostanoids, etc.) are increasingly recognized as critical factors in the pathogenesis and promotion of arterial diseases such as hypertension and atherosclerosis. Thus, it is likely that the imbalance among the various growth factor signaling cascades in the aged arterial wall not only accounts for age-associated arterial remodeling but also provides a...
mechanistic link between arterial aging and arterial diseases and provides insight into why accelerated vascular aging is a risk factor for these diseases.

**Interventions to Retard or Prevent Accelerated Arterial Aging**

As with other cardiovascular risk factors, lifestyle modifications, including the prescription of aerobic exercise, dietary modifications, caloric restriction, and weight loss, can prevent or retard the progression of intimal medial thickening\(^74-76\) and arterial stiffening\(^77\) and improve endothelial function.\(^78-80\)

A detailed discussion of pharmaceutical interventions that can modulate the elements of arterial aging is beyond the scope of this article. It is worth noting that inhibiting angiotensin receptor signaling beginning at an early age markedly delays the age-associated increase in collagen content and intimal medial thickening in rodents,\(^81,82\) and that breaking nonenzymatic collagen cross-links with a novel thiazolium agent reduces arterial stiffness in nonhuman pri-mates\(^83\) and in humans,\(^84\) although its blood pressure-lowering effects have been less impressive.\(^85\)

The aforementioned insights from animal models and human studies indicate that the components of arterial aging are modifiable, so the traditional view of arterial aging, which attributes the age-associated changes solely to passive sequelae of wear and tear from repetitive cycles of distension and recoil of central arteries,\(^6\) is no longer tenable. These insights also provide us with a growing list of putative factors that could be targeted by specific interventions aimed at retarding or preventing accelerated arterial aging. For example, strategies to attenuate the effects of molecules or signaling cascades involved in accelerated intimal thickening (eg, TGF-β), stiffening (eg, NO bioavailability, deficits in elastin synthesis), protein degradation (eg, MMP-2), arterial wall inflammation (eg, MCP-1), fibrosis (eg, Ang II), or injury (eg, reactive oxygen species) are deserving of further investigation.

**Summary and Perspectives**

Age is the dominant risk factor for cardiovascular diseases, and the aforementioned age-associated changes in vascular structure and function are the likely culprits that underlie, in large part, the increased cardiovascular risks associated with aging. Insights from animal studies suggest that the links between vascular aging and vascular diseases stem from the fact that many of the biochemical, enzymatic, and cellular alterations that are operative in accelerated vascular aging, as well as the signals that modulate them, are also involved in the pathogenesis and progression of arterial diseases such as hypertension and atherosclerosis. This establishes the interaction between arterial aging and these diseases and provides a basis for the epidemiological observations that aging confers increased risks for the occurrence of these diseases, lowers the threshold for their appearance, and influences the severity of their manifestation.

An important corollary of this is that age should no longer be viewed as an immutable cardiovascular risk factor. It is our hope that a greater appreciation of the link between arterial aging and cardiovascular diseases will stimulate further investigation into strategies aimed at preventing or retarding arterial aging, with the hopes that this would attenuate the appearance or the severity of cardiovascular diseases. As a first step, there is a critical need to improve and standardize the methodologies used in the noninvasive measurement of the elements of arterial aging in humans, to develop age- and sex-specific normative values, and to devise guidelines for the appropriate timing and interpretation of these tests. This, in turn, will require the recruitment of, and intercollaboration among, a consortium of vascular biologists, translational researchers, and clinicians to catalyze a significant maturation in the field of arterial aging and bring it to the bedside.

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**References**

Arterial Aging and Cardiovascular Risk

37


Short- and Long-Term Incidence of Stroke in White-Coat Hypertension

Paolo Verdecchia, Gian Paolo Reboldi, Fabio Angeli, Giuseppe Schillaci, Joseph E. Schwartz, Thomas G. Pickering, Yutaka Imai, Takayoshi Ohkubo, Kazuomi Kario

Methods

The International Collaborative Study of the Prognostic Utility of ABPM was initiated to examine the relationship between ambulatory BP and the risks of cardiovascular disease using individual data from a pooled sample of large observational cohorts that contain ambulatory BP measurements. The aims of the study, the structure of the database, and all analytic and publication aspects were discussed and agreed upon in advance. The study from the United States was the New York Prognostic Effects of ABPM (NYPEAP) study; the study from Italy was the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study; and the studies from Japan were the Ohasama study and the Jichi Medical School (JMS)-ABPM Study, Wave I. Details regarding inclusion and exclusion criteria in the single studies have been published previously. The majority of subjects in the NYPEAP (83%), PIUMA (88%), and JMS-ABPM (88%) cohorts had a clinic BP ≥140 mm Hg systolic BP (SBP) or 90 mm Hg diastolic BP (DBP) at entry compared with only 27% in the Ohasama community sample. Subjects on antihypertensive medications in NYPEAP, PIUMA, and JMS-ABPM, clinically normotensive subjects (ie, those with office BP <140 mm Hg SBP and 90 mm Hg DBP) were generally healthy volunteers recruited from the hospital staff or asymptomatic subjects without medical problems referred to the hospital facility for various reasons.

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Hypertension is available at http://www.hypertensionaha.org

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Subjects with overt cardiac or cerebrovascular disease, cancer, or hepatic or renal disease at enrollment were excluded. Subjects with diabetes, defined by a fasting glucose of 7.8 mmol/L or use of an oral hypoglycemic agent or insulin, were included. All subjects provided informed consent to be included in each of the 4 studies, which were approved by local ethical committees.

**BP Measurement**
Details regarding the procedures for clinic BP and ABPM in the NYPEAP, PIUMA, Ohasama, and JMS-ABPM cohorts have been published previously. Clinic BP was taken at the time of enrollment into the study. In the NYPEAP study, a BP taken by the physician was available for 85% of participants. When missing, the clinic BP taken by a nurse was substituted.

In all 4 studies, ABPM was carried out at entry. In the PIUMA study, the monitor (SpaceLabs 5200, 90202, or 90207; SpaceLabs) was set to measure BP every 15 minutes during the entire 24-hour period. In the NYPEAP study, readings were taken either: (1) every 15 minutes between 6 AM and 12 PM and at 30-minute intervals between 12 PM and 6 AM using either a Del Mar Avionics P2 or P3 or a SpaceLabs 5200 (first 672 subjects); or (2) every 15 minutes between 8 AM and 10 PM and at 30-minute intervals between 10 PM and 8 AM using a SpaceLabs 90202 monitor (last 341 subjects).

In the Ohasama study, readings were taken at 30-minute intervals. Well-trained public health nurses visited each participant on a weekday morning to attach the ABPM device and to detach it the next morning. The participants kept a diary to record daily activities. A physician was available for 85% of participants. When missing, the clinic BP taken by a nurse was substituted.

**White-Coat Hypertension**
WCH was defined by an average awake ambulatory BP $<130$ mm Hg SBP and $80$ mm Hg DBP. We also determined the risk of stroke associated with a definition of WCH based on an awake ambulatory BP $<135/85$ mm Hg.

**Follow-Up**
Follow-up was based on telephone contacts or periodical clinical visits at the referring facility or through the Regional Stroke Registration System. Stroke was defined as a focal central nervous system lesion considered vascular in origin and having clinical sequelae lasting $\geq 24$ hours. Fatal and nonfatal strokes were included. Transient ischemic attacks were excluded from the present analysis.

**Data Analysis**
Statistical analysis was performed using SPSS (SPSS) and SAS-Stat (SAS Institute). One-way ANOVA and multiple comparisons with the Tukey test when appropriate were performed to compare the study sites and the 3 groups with clinical normotension, WCH, and ambulatory hypertension. We report the number of strokes that were recorded in each study, the total number of person years of follow-up for that event, and the unadjusted incidence rate. For survival analyses, event-free curves were estimated using Kaplan–Meier product-limit method and compared by the Mantel (log-rank) test. For subjects who experienced multiple events, analysis was restricted to the first event. The independent effect of several prognostic factors on survival was tested by stepwise Cox model.

**TABLE 1. Main Characteristics in the Study Population**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Cohort (n=5955)</th>
<th>NYPEAP (n=1296)</th>
<th>PIUMA (n=2620)</th>
<th>Ohasama (n=1277)</th>
<th>JMS-ABPM (n=762)</th>
<th>Overall P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>56 (14)</td>
<td>50 (13)</td>
<td>51 (12)</td>
<td>61 (10)</td>
<td>72 (10)</td>
<td>$0.0001$</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$&lt;0.0001$</td>
</tr>
<tr>
<td>White, %</td>
<td>64.1</td>
<td>92.2</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>$0.0001$</td>
</tr>
<tr>
<td>Black, %</td>
<td>1.4</td>
<td>6.4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>$0.0001$</td>
</tr>
<tr>
<td>Asian, %</td>
<td>34.2</td>
<td>0</td>
<td>0</td>
<td>100</td>
<td>100</td>
<td>$0.0001$</td>
</tr>
<tr>
<td>Other, %</td>
<td>0.3</td>
<td>1.4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Sex, % men</td>
<td>50</td>
<td>65</td>
<td>53</td>
<td>34</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>68.2 (16)</td>
<td>75.1 (14)</td>
<td>75.1 (14)</td>
<td>54.0 (9)</td>
<td>56.0 (10)</td>
<td>$0.0001$</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.3 (5.3)</td>
<td>25.1 (3.5)</td>
<td>26.8 (3.9)</td>
<td>23.4 (3.0)</td>
<td>24.0 (3.5)</td>
<td>$0.0001$</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>11.0</td>
<td>not available</td>
<td>7.6</td>
<td>17.5</td>
<td>11.9</td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking, %</td>
<td>19.7</td>
<td>10.7</td>
<td>23.6</td>
<td>19.3</td>
<td>20.9</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.43 (1.08)</td>
<td>5.85 (1.11)</td>
<td>5.54 (1.09)</td>
<td>4.98 (0.93)</td>
<td>5.17 (0.88)</td>
<td>$0.0001$</td>
</tr>
<tr>
<td>Serum creatinine, mmol/L</td>
<td>87.5 (22)</td>
<td>95.5 (23)</td>
<td>87.5 (21)</td>
<td>not available</td>
<td>79.6 (19)</td>
<td>$0.0001$</td>
</tr>
<tr>
<td>Serum glucose, mmol/L</td>
<td>5.50 (1.35)</td>
<td>5.81 (1.18)</td>
<td>5.63 (1.38)</td>
<td>not available</td>
<td>5.33 (1.39)</td>
<td>$0.0001$</td>
</tr>
<tr>
<td>Office SBP, mm Hg</td>
<td>149 (23)</td>
<td>150 (21)</td>
<td>154 (20)</td>
<td>131 (18)</td>
<td>160 (22)</td>
<td>$0.0001$</td>
</tr>
<tr>
<td>Office DBP, mm Hg</td>
<td>90 (14)</td>
<td>94 (11)</td>
<td>95 (11)</td>
<td>74 (11)</td>
<td>91 (14)</td>
<td>$0.0001$</td>
</tr>
<tr>
<td>Office PP, mm Hg</td>
<td>59 (17)</td>
<td>56 (18)</td>
<td>58 (17)</td>
<td>57 (14)</td>
<td>69 (16)</td>
<td>$0.0001$</td>
</tr>
<tr>
<td>Awake SBP, mm Hg</td>
<td>139 (17)</td>
<td>141 (17)</td>
<td>141 (16)</td>
<td>129 (14)</td>
<td>145 (18)</td>
<td>$0.0001$</td>
</tr>
<tr>
<td>Awake DBP, mm Hg</td>
<td>87 (15)</td>
<td>91 (10)</td>
<td>91 (11)</td>
<td>76 (8)</td>
<td>82 (29)</td>
<td>$0.0001$</td>
</tr>
<tr>
<td>Awake PP, mm Hg</td>
<td>52 (15)</td>
<td>49 (13)</td>
<td>50 (11)</td>
<td>53 (8)</td>
<td>62 (29)</td>
<td>$0.0001$</td>
</tr>
<tr>
<td>Sleep SBP, mm Hg</td>
<td>121 (18)</td>
<td>122 (18)</td>
<td>124 (17)</td>
<td>112 (15)</td>
<td>127 (18)</td>
<td>$0.0001$</td>
</tr>
<tr>
<td>Sleep DBP, mm Hg</td>
<td>72 (11)</td>
<td>76 (11)</td>
<td>75 (11)</td>
<td>64 (8)</td>
<td>72 (11)</td>
<td>$0.0001$</td>
</tr>
<tr>
<td>Sleep PP, mm Hg</td>
<td>49 (11)</td>
<td>46 (13)</td>
<td>49 (11)</td>
<td>48 (8)</td>
<td>55 (11)</td>
<td>$0.0001$</td>
</tr>
</tbody>
</table>

Using self-reports of the times participants went to sleep and woke up, ambulatory BP readings were aggregated to create a mean of all readings taken while awake and the mean of all readings taken during sleep. This was done separately for SBP and DBP and for pulse pressure (PP), the difference between SBP and DBP.
Analyses were stratified by study site because of expected differences in stroke rate between the different groups. Several potential confounding variables assessed at entry were considered in the analysis: current smoking status, weight, height, body mass index, total cholesterol, and use of antihypertensive medication, including those titrated off before ABPM. In 2-tailed tests, \( P \) values < 0.05 were considered statistically significant.

**Results**

**Cohort Features**

As shown in Table 1, age of the subjects was higher in the JMS-ABPM cohort than in the other cohorts (all \( P < 0.01 \)). Diabetes was more frequent in the Ohasama sample (\( P < 0.001 \)) compared with each of the others, but information was not available from the NYPEAP cohort. Office SBP and PP were highest in the JMS-ABPM cohort (\( P < 0.01 \) versus the other cohorts), whereas office DBP was highest in the PIUMA cohort (\( P < 0.01 \) versus the other cohorts). Comparable differences between the cohorts were found for awake and asleep ambulatory BP.

**Differences Between Groups**

Age of the subjects (Table 2) was higher in the WCH group than in the other groups. Subjects with WCH tended to be women more frequently, smokers less frequently, and diabetics more frequently when compared with those with ambulatory hypertension (all \( P < 0.01 \)). In the WCH group, office BP was intermediate between the normotensive group and that with ambulatory hypertension. In contrast, awake SBP and DBP were lower in the group with WCH than in the normotensive group (both \( P < 0.01 \)), whereas sleep SBP and DBP were comparable between the 2 group. Prevalence of subjects treated with antihypertensive drugs resulting from the last telephone contact or clinical visit during follow-up is reported in Figure 1. A similar proportion of subjects included in the normotensive control group or the WCH group at entry were receiving the 5 classes of antihypertensive drugs (all \( P < \text{NS} \)). In contrast, a greater proportion of subjects belonging to the AH group were receiving diuretics, \( \beta \)-blockers, angiotensin-converting enzyme inhibitors or calcium antagonists (\( P < 0.01 \) versus each of the other groups). Frequency of treatment with angiotensin II antagonists did not differ between the groups.

TABLE 2. Main Characteristics in the Normotensive Group and in the Groups With WCH and Ambulatory Hypertension

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive Group (n=1549)</th>
<th>WCH (n=398)</th>
<th>Ambulatory Hypertension (n=4008)</th>
<th>Overall P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>55 (14)</td>
<td>61 (14)*†</td>
<td>55 (14)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sex, % women</td>
<td>60</td>
<td>63†</td>
<td>45</td>
<td>0.0001</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>60.7 (15)†</td>
<td>63.2 (14)*†</td>
<td>71.5 (15)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.1 (3.4)†</td>
<td>24.9 (3.8)*†</td>
<td>25.9 (3.9)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>14.3†</td>
<td>11.7†</td>
<td>9.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cigarette smoking, %</td>
<td>19.9</td>
<td>13.9†</td>
<td>20.2</td>
<td>0.010</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.11 (1.01)†</td>
<td>5.42 (1.07)*‡</td>
<td>5.55 (1.08)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Serum creatinine, mmol/L</td>
<td>86.0 (19)</td>
<td>82.4 (17)†</td>
<td>87.6 (23)</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum glucose, mmol/L</td>
<td>5.59 (1.40)†</td>
<td>5.42 (1.12)‡</td>
<td>5.50 (1.36)</td>
<td>0.23</td>
</tr>
<tr>
<td>Office SBP, mm Hg</td>
<td>124 (11)†</td>
<td>150 (12)*†</td>
<td>158 (19)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Office DBP, mm Hg</td>
<td>74 (9)†</td>
<td>86 (11)*†</td>
<td>96 (11)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Office PP, mm Hg</td>
<td>50 (10)†</td>
<td>65 (16)*†</td>
<td>62 (18)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Awake SBP, mm Hg</td>
<td>126 (12)†</td>
<td>121 (6)*†</td>
<td>146 (15)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Awake DBP, mm Hg</td>
<td>78 (21)†</td>
<td>73 (5)*†</td>
<td>92 (10)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Awake PP, mm Hg</td>
<td>48 (20)†</td>
<td>49 (6)*†</td>
<td>54 (12)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sleep SBP, mm Hg</td>
<td>110 (13)†</td>
<td>110 (11)*†</td>
<td>127 (17)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sleep DBP, mm Hg</td>
<td>64 (9)†</td>
<td>63 (7)*†</td>
<td>76 (11)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sleep PP, mm Hg</td>
<td>45 (8)†</td>
<td>47 (8)*†</td>
<td>51 (12)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

\*\( P < 0.01 \) vs normotensive group; †\( P < 0.01 \) vs ambulatory hypertension; ‡\( P < 0.05 \) vs ambulatory hypertension.

Figure 1. Percentage of subjects treated with antihypertensive drugs resulting from the last telephone contact or clinical visit during follow-up. ACE indicates angiotensin-converting enzyme.
TABLE 3. Entry Characteristics of Subjects With and Without Future Stroke

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Future Stroke</th>
<th>Future Stroke</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>55 (14)</td>
<td>68 (12)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sex, % men</td>
<td>49.3</td>
<td>56.3</td>
<td>0.04</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>68 (16)</td>
<td>64 (16)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.3 (3.8)</td>
<td>25.0 (4.0)</td>
<td>0.19</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>10.5</td>
<td>23.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Asian ethnic group, %</td>
<td>33.5</td>
<td>53.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cigarette smoking, %</td>
<td>19.3</td>
<td>29.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.43 (1.08)</td>
<td>5.35 (1.06)</td>
<td>0.293</td>
</tr>
<tr>
<td>Serum creatinine, mmol/L</td>
<td>86.9 (22)</td>
<td>91.1 (20)</td>
<td>0.028</td>
</tr>
<tr>
<td>Serum glucose, mmol/L</td>
<td>5.50 (1.3)</td>
<td>5.78 (1.8)</td>
<td>0.021</td>
</tr>
<tr>
<td>Office SBP, mm Hg</td>
<td>148 (22)</td>
<td>159 (24)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Office DBP, mm Hg</td>
<td>90 (14)</td>
<td>90 (14)</td>
<td>0.95</td>
</tr>
<tr>
<td>Office PP, mm Hg</td>
<td>59 (16)</td>
<td>69 (19)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Awake SBP, mm Hg</td>
<td>139 (17)</td>
<td>149 (19)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Awake DBP, mm Hg</td>
<td>87 (15)</td>
<td>87 (12)</td>
<td>0.657</td>
</tr>
<tr>
<td>Awake PP, mm Hg</td>
<td>52 (15)</td>
<td>61 (14)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sleep SBP, mm Hg</td>
<td>121 (17)</td>
<td>134 (21)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sleep DBP, mm Hg</td>
<td>72 (11)</td>
<td>76 (12)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sleep PP, mm Hg</td>
<td>49 (11)</td>
<td>58 (14)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Incidence of Stroke

There were 213 new cases of stroke. Overall, the JMS-ABPM cohort showed the highest rate of stroke (6.09/100 person years) followed by the Ohasama cohort (2.12/100 person years), and the PIUMA cohort (0.59/100 person years), and the NYPEAP cohort (0.19/100 person years).

At entry (Table 3), subjects with future stroke were older, leaner, and more frequently smokers, diabetics, and of Asian ethnic origin than the subjects without future stroke (all P<0.01). Office and awake SBP and PP, but not DBP, were higher in the group with future stroke than in that without future stroke (all P<0.001). Sleep SBP, DBP, and PP were higher in the group with future stroke (all P<0.001).

The cumulative hazard for stroke (Figure 2) differed between the normotensive group, the group with WCH, and the group with ambulatory hypertension. In a Cox analysis (Table 4) stratified by center, WCH was associated with a nonsignificant 1.15 hazard ratio for stroke compared with the normotensive group (P=0.658). The no-interaction assumption of the stratified model was evaluated according to Kleinbaum17 and found acceptable at the <0.01 level. The no-interaction assumption implies that the variables being stratified (ie, center) do not interact with the covariates in the model. When office SBP and awake SBP were forced in the same model, office BP did not yield statistical significance (P=0.322), and the risk of stroke increased by 2% for any 1 mm Hg increase in the awake SBP (95% CI, 1% to 3%; P=0.0001). The 6-year risk factor-adjusted probability of stroke in clinically normotensive individuals and in hypertensive subjects with WCH and ambulatory hypertension is depicted in Figure 4. Estimates have been made in smokers and nonsmokers for either sex.

**Discussion**

This study is the first to investigate the short- and long-term risk of stroke in subjects with WCH, ambulatory hypertension, and clinical normotension in a large multinational and multiethnic population. WCH was defined by an average daytime ambulatory BP <130 mm Hg SBP and <80 mm Hg DBP because in a previous analysis, the risk of cardiovascular events increased in association with higher ambulatory BP levels. Average daytime levels of BP <130/80 mm Hg have been defined as definitely normotensive.14

During the entire follow-up period, the incidence of stroke did not differ between the WCH and the normotensive control groups. However, stroke rate showed a trend to increase after the sixth year of follow-up in the group with WCH, and the corresponding hazard curve crossed that of the ambulatory hypertension group by the ninth year of observation. Results were consistent among the different cohorts and were independent of age, sex, cigarette smoking, and previous antihypertensive medications.
Clinical Relevance and Prognostic Value of WCH

ABPM has been approved by the US Centers for Medicare and Medicaid Services\(^1\) for reimbursement in patients with suspected WCH. Although some outcome-based studies suggested that WCH is associated with a risk of events apparently comparable to that of clinically normotensive subjects and inferior to that of subjects with elevated daytime BP,\(^5\)–\(^9\) other studies focused on target organ damage suggested that patients with WCH may be at intermediate risk between the clinically normotensive individuals and those with ambulatory hypertension.\(^7\),\(^8\),\(^19\)–\(^21\) Therefore, the important issue of whether WCH should be considered an innocent condition remains open and unresolved.\(^4\),\(^22\) Unfortunately, only a few data are available on the long-term natural history of WCH. In a longitudinal study, such condition evolved into ambulatory hypertension in 37% of subjects, with an accompanying rise in left ventricular mass.\(^23\) In a study, a comparable proportion of subjects with clinical normotension and WCH evolved toward ambulatory hypertension (15% and 22%, respectively).\(^24\)

In this study, based on 38 100 person years of observation, the highest stroke rate was noted in the clinical-based JMS-ABPM cohort, which included elderly Japanese subjects with hypertension, followed by the Ohasama cohort, which included a general Japanese population, and the PIUMA cohort, which included Italian subjects with essential hypertension. The lowest stroke rate was observed in the NYPEAP cohort, recruited in the New York area. In the absence of a significant center-covariate interaction, our findings can be reliably assumed as consistent across the different cohorts.

An unexpected finding in our study was a distinct trend toward an increased incidence of stroke in the WCH group after the sixth year of follow-up. Although substantiated only by a small number of events, these findings raise some concerns about the long-term safety of WCH. Clearly, further long-term studies are needed to clarify this aspect. In this context, it has been noted that the degree of BP rise during mental stress is a predictor of the long-term growth of atherosclerotic plaque independently of age and initial plaque area.\(^25\) Thus, it could be speculated that frequent BP peaks triggered by alerting reactions to stress may contribute to the rise in long-term risk of carotid atherosclerosis and ultimately of stroke in subjects with WCH.

Study Limitations

Because office and ambulatory BP measurements have been obtained only at entry, no information is available on the prognostic impact of serial changes in these parameters over time. In the Office versus Ambulatory Blood Pressure (OvA) study, in-treatment ambulatory BP predicted cardiovascular events independently of traditional risk factors in treated hypertensive patients.\(^26\) However, the OvA study could not compare the predictive value of pretreatment versus in-treatment BP. In the PIUMA study, in-treatment ambulatory BP was more potent.

### Table 4. Independent Predictors of Stroke

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Comparison</th>
<th>Hazard Ratio</th>
<th>P-Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1 year</td>
<td>1.08</td>
<td>0.000</td>
<td>1.07–1.10</td>
</tr>
<tr>
<td>Sex</td>
<td>Men vs women</td>
<td>1.57</td>
<td>0.003</td>
<td>1.17–2.12</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Yes vs no</td>
<td>1.71</td>
<td>0.001</td>
<td>1.24–2.37</td>
</tr>
<tr>
<td>Previous antihypertensive</td>
<td>treatment</td>
<td>Yes vs no</td>
<td>1.63</td>
<td>0.001 1.23–2.18</td>
</tr>
<tr>
<td>Ambulatory BP category</td>
<td></td>
<td>Normotensive group</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>WCH</td>
<td>1.15</td>
<td>0.658 0.61–2.16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ambulatory hypertension</td>
<td>2.01</td>
<td>0.001 1.31–3.08</td>
</tr>
</tbody>
</table>

Analysis stratified by center. WCH was defined by an average awake BP $<130$ mm Hg SBP and $<80$ mm Hg DBP.
than pretreatment ambulatory BP for cardiovascular risk stratification.\textsuperscript{27} In the present study, a comparable number of subjects who were clinically normotensive or white-coat hypertensives at entry were receiving antihypertensive drugs during follow-up. These data suggest a comparable evolution toward the need of antihypertensive treatment in subjects with WCH and clinically normotensive controls. Finally, because data on mortality shortly after stroke were not available from all cohorts, no separate analysis could be performed on fatal and nonfatal stroke. Similarly, analyses on the different types of stroke (ie, lacunar, embolic, hemorrhagic, etc) were not possible because of insufficient standardization across the different cohorts. A substantial proportion of strokes in hypertensive subjects are attributable to lacunar infarction at the base of the brain, where short straight arteries transmit a substantial BP load from the large arteries to small resistance arteries over a very short distance.\textsuperscript{28}

**Perspectives**

The long-term prognostic impact of WCH remains uncertain. In this multinational outcome-based study, we failed to detect differences in the risk of stroke between subjects with WCH and clinically normotensive controls. The risk of stroke remained consistently higher among subjects with ambulatory hypertension. However, the incidence of stroke showed a trend to increase in the long run in the group with WCH, with the corresponding hazard curve crossing that of the ambulatory hypertension group by the ninth year of follow-up. These data raise the hypothesis, to be tested in future studies, that WCH might not be a benign condition for stroke in the long term.

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**References**


Vascular Development, Pulse Pressure, and the Mechanisms of Hypertension

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Abstract—No caso de uma função cardíaca específica, a curva da pressão arterial (PA) cíclica resulta de 2 fenótipos diferentes: a pressão arterial média (PAM), um componente regular que reflete a resistência da rede microvascular, e a pressão no pulso (PP), um outro componente que corresponde à rigidez e reflexos de onda das artérias de grande calibre. No momento do nascimento, a sobrevivência cardiovascular (CV) é influenciada de forma decisiva pela ligação entre o coração e a aorta torácica e, consequentemente, a adequação da função de Windkessel, a magnitude da acúmulo aórtica de elastina e o nível de PP. A maturation do tronco da aorta e as ramificações resulta dos mecanismos de adaptação que envolvem stress por esforço e tensão, com consequências potenciais importantes no controlo da frequência cardíaca, trânsito dos reflexos de onda e perfusão coronária. Uma optimização adequada da função de Windkessel e, logo, da PP, da perfusão coronária diastólica e da sobrevivência CV implica que, no decorrer do período pós-natal, cada bebê alcance um nível decisivo de PAM. Para se alcançar este nível de PAM, é necessário o desenvolvimento de múltiplos segmentos de resistência da rede microvascular, sobretudo nos rins. Na população adulta, este processo fisiopatológico leva a uma distribuição Gaussiana da PA, com as pessoas a permanecerem no mesmo percentil de PA desde o nascimento (seguido da PA). Sugerimos que a hipertensão resulta de mecanismos vasculares precoce desenvolvidos que orientam a PA para percentis mais altos da curva de distribuição de Gauss. (Hypertension. 2005;46:205-209.)

Key Words: hypertension, arterial pulse

Many experimental models have been developed to investigate the pathophysiological mechanisms of hypertension in humans. Strong similarities have been observed between spontaneously hypertensive rats and patients with essential hypertension. Both involve a progressive increase of vascular resistance responsible for a parallel increase of systolic blood pressure (BP), diastolic BP, and mean arterial pressure (MAP). However, spontaneously hypertensive rats and hypertensive humans differ substantially by 2 particularities. First, in humans, the BP distribution is Gaussian and unimodal, unlike the 2 distinct populations of genetically normotensive and hypertensive rats. Second, the phenomenon known as BP tracking (ie, that individuals remain in the same BP percentile throughout life), noted previously in hypertensive humans, has not been documented in animal models. Research on the influence of intrauterine conditions on the later development of hypertension has pointed to an important role of early developmental processes.

In this article, we describe some of the early phases of development of the arterial system and delineate under what conditions their investigation may contribute to a better understanding of the natural history and the complications of hypertensive vascular disease.

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45
Wave reflections are the common denominator of the cross-talk between the pulsatile and the steady compartments of the arterial tree.\textsuperscript{13,18}

Arterial BP increases and also stimulates growth of blood vessels, but wall thickness rather than vessel diameter is involved.\textsuperscript{12,13} Because hemodynamic factors provide signals that modulate arterial growth, major changes in blood vessels and hemodynamic function are expected around birth. The particular sensitivity of several CV risk factors such as hypertension to intrauterine conditions may be caused by the major changes taking place in blood vessels in the perinatal period.

The description of mechanical forces within the CV system requires distinguishing between those that are pulsatile and those that are predominantly steady and continuous\textsuperscript{13} (Figure). Physiological studies indicate that for a given cardiac function, pulse pressure (PP) is mainly determined by the stiffness of large arteries and the pattern of wave reflections, whereas MAP, the steady component of BP, is influenced by the resistance of smaller arteries and the microvascular network. During the early phase of vascular development, the pulsatile component of BP, which represents a direct continuation of heartbeats, is the predominant module of hemodynamic forces. Through the storage capacities of the aorta, it determines the adequate level of oxygen supply to the tissues. On the other hand, MAP still increases during later phases of development, mainly during completion of the development of microvascular networks at the distal part of the arterial tree.

To understand the role of large arteries in this hemodynamic process, it is important to note that the mechanical forces derived from aortic elasticity are traditionally described on the basis of 2 different mathematical models: one in the time domain (called Windkessel), and the other in the frequency domain, which involves wave reflections.\textsuperscript{13} The former simply advances that the elastic recoil of the aorta enables the cyclic flow coming from the heart to be changed into a continuous flow at the arteriolar (resistant) level. According to Poiseuille’s law, vascular resistance, which predominates in the microvascular network, is an important component of this Windkessel model, in which the time constant of the diastolic decay is, by definition, equal to the product of vascular resistance times compliance (elasticity). The frequency-domain model implies that after ventricular ejection and the resulting shock wave initiated at the origin of the thoracic aorta, a forward pressure wave travels along the arterial tree at a given pulse wave velocity. At any structural (eg, elastin or collagen accumulation affecting stiffness) or geometric (vessel branching) discontinuity of the arterial wall, this wave is reflected backward to return toward the heart. Hence, models issued from the frequency domain imply, like the Windkessel model, the presence of a resistance component as a major trigger for wave reflections.

Finally, it appears from these considerations that: (1) an adequate coupling between the heart and the thoracic aorta, and hence an efficient aortic Windkessel function, needs that an optimal level of vascular resistance, and hence MAP should be achieved; and (2) this critical value of MAP results, at the postnatal period, from the development and the specific location of a given number of resistant segments of the microvascular network.

**Functional Coupling of the Heart and the Thoracic Aorta Around Birth**

Parturition signals an abrupt change in the growth pattern of large arteries. The most dramatic event results from the cessation of placental blood flow and the initiation of pulmonary gas exchange, leading to independent control of systemic and pulmonary arterial pressures. Another important event is the functional coupling of the heart and the thoracic aorta. At the cessation of placental blood flow, perfusion of many arteries, for example, the carotids and iliacs are approximately halved. This probably reflects the decreased demands for perfusion because arterial Po\textsubscript{2} doubles after lung ventilation starts. However, the largest change seen in a major vessel is a >90% decrease of blood flow in the subrenal abdominal aorta.\textsuperscript{14–16} In sheep, this dramatically decreased blood flow is accompanied by a marked reduction of the diameter of the abdominal aorta and a near arrest of wall tissue accumulation that lasts \(\approx\)3 weeks.\textsuperscript{15}

Between 1 and 5 weeks postpartum, stroke volume increases in lambs and other species by \(\geq\)2-fold.\textsuperscript{16,17} This increased stroke volume would place an increased load on the thoracic aorta, especially in its proximal region, if this vessel did not act as a buffering chamber, storing part of the ventricular stroke volume during systole. During diastole, elastic recoil of the aortic wall propels this volume to the periphery, thereby creating continuous peripheral blood flow and the most adequate oxygen supply. It is worth noting that the Windkessel function of the aorta relies heavily on the low
stiffness and reversible extensibility of this vessel. Low stiffness results in a small PP in the ascending aorta, with average pressure during systole being only slightly greater (10 mm Hg) than the mean cycle pressure and pressure during diastole only slightly less (≈5 mm Hg). Thus, an optimal design of the arterial tree is such that the pressure rise during systole is minimized (so that myocardial oxygen demands are minimized) and pressure is maintained as high as possible during diastole (to assure coronary flow). Finally, a rapid perinatal accumulation of elastin is necessary to modulate the Windkessel function of the aorta and accommodate the dramatic postpartum stroke volume increase. This process requires the contribution of vascular smooth muscle (VSM) cells with predominant secretory properties. As shown previously, VSM cells of ectodermal origin and mainly issued from the neural crest are essential for the formation and organization of elastic laminae as well as tenso-receptors of the great vessels. Neural crest usually participates in the central control of the autonomic nervous system and of the renin-angiotensin system. Chronic hypoxia of the near-term chick embryo is accompanied by aortic hypertrophy, ventricular dysfunction, and sympathetic hyperinnervation.

In the weeks after birth, arterial growth, and specifically elastin accumulation, correlates with blood flow changes, but a concomitant intriguing flow-independent modulation of arterial growth is seen. This period involves a very rapid aortic elastin and collagen accumulation, independent of blood flow changes. The stimulus that drives this rapid connective tissue synthesis is unknown but serves to preadapt arteries to the large increases of pressure and flow that follow birth. Arterial pressures in near-term fetuses are ≈45 mm Hg, whereas pressure has risen to 65 mm Hg at 3 weeks of age.

The protein product of the elastin gene is synthesized by VSM cells and secreted as a monomer, tropoelastin. After post-translational modification, tropoelastin is cross-linked and organized into elastin polymers that form concentric rings of elastic fenestrated lamellae around the arterial lumen. Elastin-deficient mice die from an occlusive fibrocellular pathology caused by subendothelial proliferation and accumulation of VSM cells in early neonatal life. Elastin bears much of the wall tension generated by BP and constitutes a major determinant of resting vessel diameter. Any alteration of genetic origin may be exacerbated by corresponding wall stress and produces, over the long term, arterial wall defects. Experimental reductions of blood flow rates inhibit elastin accumulation in immature arteries. Perinatal elastin accumulation in arteries of lambs correlates with large vessel-specific changes in blood flow rates at birth. Therefore, reorganization of elastin and its net accumulation continue to be important in arterial remodeling. New elastin is incorporated randomly into lamellae except from some targeting to fenestrae. Thus, the development of the buffering function of the thoracic aorta, and hence the accumulation of elastin, are critical points for CV survival around the birth.

Under normal conditions, only 40% to 50% of blood ejected from the left ventricle is stored in capacitive arteries during systole. A decrease of the capacitive properties of the aorta has a well-established negative impact on left ventricular function and coronary perfusion. This process, mainly noted in the elderly, is observed in several other conditions, as in young subjects with diabetes mellitus. On the other hand, an abnormal increase of the capacitive properties of the aorta can also have negative effects on CV function. It may be responsible for exaggerated arterial blood pooling during systole, worsening vascular impedance through an increase of the inertial component of cardiac workload, eventually leading to CV death. Such complications may arise very early in life but also are able to develop progressively with time, in association with fatigue of the arterial wall. Two different examples may be given. First, the deleterious accelerations of aging or atherosclerosis are predominantly expressed in central arteries, at the site of heart–vessel coupling and of the thoracoabdominal aorta, whereas distal muscular arteries are much less sensitive to aging. Second, early alterations of the placenta and birth weight may be predictors of future hypertension and atherosclerotic complications during life. Together, these findings indicate that: (1) the degree of aortic elastin accumulation at birth influences Windkessel efficiency and thereby the level of aortic PP; (2) the modalities of the Windkessel function require in turn an optimal MAP level, and therefore specific characteristics for the development of small arteries; and (3) such alterations of small arteries, and of microvascular network, are not fully developed at birth and require a maturation of microvessels, which results in a given value of systemic MAP. On the basis of this approach, it is remarkable to observe that adult normotensive and hypertensive populations have exactly the same buffering functions of central arteries under isobaric conditions. These observations explain why it has been proposed that disturbed aortic elasticity may induce the development of chronically elevated BP.

Development of the Aorta and Its Branching

Arterial Tree at the Postnatal Period

The aorta is a nonuniform tube that supplies a branched system in which the elastic modulus increases toward the periphery as individual vessel diameters become smaller. During development, this branching process requires significant changes in the cross-sectional area, the wall thickness, and mostly the aortic length, which play an important role in the heart rate control. During late development and in adults, chronic changes in blood flow rates cause corresponding changes in arterial diameters, whereas pressure increases cause wall thickening. By these means, the vessel structure continually adapts to changing hemodynamic loads. This remodeling is regulated by direct sensitivity of vascular tissues to fluid shear stress in the case of flow and to tensile stress in the case of pressure. The roles of shear and tensile stress in vascular development have been extensively reviewed previously.

The postnatal increase of collagen, and especially collagen cross-linking, principally affects the abdominal aorta and its branching system. During postpartum, collagen enables tissue adaptation to the increased tensile stress. It is remarkably well suited to carry out this role because of the extraordinary tensile strength and stiffness of its fibrils, properties that are...
largely attributable to strong axial and lateral bonding afforded by intermolecular and intramolecular cross-links. These links are important stabilizers of the fibrils. They prevent slippage of adjacent molecules under applied tensile stress and contribute to the yield stress and ultimate tensile stress (strength) of the collagen matrix. Strong correlations between intermolecular cross-linking and tensile strength have been demonstrated in skin, tendon, and bone. A postnatal increase of intermolecular collagen cross-linking serves to resist the concomitant 143% increase of physiological aortic wall stress. In contrast, a progressive or acute reduction in cross-linking might precipitate CV complications.

Aortic length follows the dimensions of contiguous tissues during development and, within some limits, remains constant in adults. During childhood, such arteries are normally subjected to considerable lengthwise stretch in vivo. If newly synthesized tissue is produced in the longitudinal direction at any site along the vessel length, then the remainder of the vessel can retract slightly under the elastic forces that impose longitudinal stretch. Because vascular tissues are incompressible, the retraction must be isovolumic. As a result, the thickness or circumference of the artery wall will increase. With the development of the branched system, the increased vascular resistance is more and more determined by vessel caliber and therefore involves more and more arterial wall discontinuities, an important aspect for the development of wave reflections and therefore for the adequation of coronary perfusion.

Through the branching of the arterial tree, the in vivo hemodynamic status is progressively composed of a complex network of small arteries and arterioles that characterize the resistance vasculature. According to Poiseuille’s law, a higher minimum vascular resistance could result from a combination of reduced lumen diameter of individual vessels, vessels growing longer, or their rarefaction (a decreased number of vessels connected in parallel). Traditional experiments have shown that minimum vascular resistance is increased by 37% in established hypertension. Vascular resistance changes abruptly over the short length of the vessel pathway between arteries and veins, and this has important consequences. First, the very high resistance over a short distance causes MAP to fall precipitously over this short length. Second, suddenly high resistance impedes pulsatile phenomena and steady flow so that theoretically, the amplitude of PP falls concomitantly with MAP, resulting in steady flow through these resistance vessels. Third, and most important, arterial pulsations that cannot enter the high-resistance vessels are reflected and join with pressure waves approaching the high-resistance vessels. Finally, resistance vessels not only contribute to control the capillary pressure but also participate to the occurrence of wave reflections.

An important aspect of these observations is to elucidate under which conditions the development of the microvascular network may affect the resistance properties of the vascular system and hence may determine exactly the MAP level. We learned from the Poiseuille’s law that the length, the radius (to the fourth power), and the thickness of the arteries are the most important geometric factors determining the individual resistance of a given vessel. However, for a tree-like network, the number of blood vessels connected in parallel is another important factor to consider. Computer studies have shown that elimination of a number of small arterioles from a vascular bed (rarefaction) causes an increase of total vascular resistance. The more complex situation to elucidate is that of arcade-like networks, which contain in-series– and in-parallel–coupled arteriolar branches. In these networks, the lengths and diameters of individual arterioles, their branching angles, the location of the branching points, and the number of branches all contribute to resistance. This situation implies that the nature of the change of the network must be defined in addition to the absolute number of blood vessels. Finally, a given degree of microvascular development corresponds to a given level of vascular resistance and hence a given level of MAP, which will contribute to an optimal oxygen supply to the tissues and to an adequate aortic buffering function. Finally, throughout vascular development, it is conceivable that apoptosis or hypertrophy of VSM cells could be independently at work in various vascular territories to maintain optimal levels of vascular resistance and MAP during adulthood. Furthermore, some organs, such as the kidney, might be particularly specialized in all these processes. Accepting this hypothesis, it seems likely that rarefaction of the microvascular network, particularly regarding the nephrons number, may be a major mechanism initiating hypertension.

**Prospective Views and Conclusion**

Structural modifications of small arteries or rarefaction of microvessels are strongly associated with hypertension and traditionally considered to be responsible for high MAP. Throughout this review, we proposed another possibility: a given level of MAP, and hence a given degree of microvascular network development, is required to optimize aortic Windkessel function. This approach may explain why, in a large population with a given genetic and environmental background, a Gaussian BP distribution is observed and therefore concords with the phenomenon of BP tracking, which is commonly observed in human populations. This pathophysiological mechanism, which fits with the predictive value of PP and arterial stiffness on CV morbidity and mortality, is strengthened by recent published findings. First, structural alterations of small artery walls are a significant CV risk factor in hypertensive subjects but in association with increased PP. Second, early wave reflections and increased aortic stiffness, the 2 main determinants of PP, are also significant independent CV risk factors, more prominent than PP itself. Finally, central PP is a stronger CV risk factor than brachial PP, particularly for the prediction of myocardial infarction. Such epidemiological findings strongly suggest that disturbed heart–vessel coupling and Windkessel function, 2 major events of CV development at birth, are important and independent determinants of future CV, and mainly coronary, complications.

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