Nonnarcotic Analgesic Use and the Risk of Hypertension in US Women

Brent M. Egan

“Nonnarcotic Analgesic Use and the Risk of Hypertension in US Women” presents epidemiological observations that are intriguing and have potentially important public health and clinical implications. The high prevalence and incidence of hypertension in this comparatively healthy (nurses) cohort of middle-aged and older women 44 to 69 years of age was substantial. The prevalence of hypertension at baseline was 32%. The incidence of hypertension among the women who were normotensive in 1990 and followed an average of 7.4 years (381,078 person yr/51,630 persons) was an impressive 20.5% (51,630/25,579) or ~2.8% annually. The relatively high incidence of hypertension occurred despite the fact that 50% of these women had a reported body mass index of ≤24 kg/m², whereas ~60% of Americans in this age range have a body mass index >25 kg/m².

The high rate of analgesic use was also noteworthy. Eighty-five percent of women provided information on their use of 1 of 3 analgesics, including aspirin, acetaminophen, and nonsteroidal anti-inflammatory drugs (NSAIDs). Seventy percent of the sample reported using at least 1 of these 3 analgesics 1 or more days monthly. Self-reported use on a monthly basis was of similar magnitude for aspirin (44%), acetaminophen (43%), and NSAIDs (37%).

A striking and novel observation in this report is the positive and consistent association between the frequency of use for all 3 classes of analgesics and the relative risk of hypertension after controlling for multiple confounders in the multivariate model. The Table represents one clinician’s attempt to put the risks in simple quantitative terms for the individual, as well as for the population of women in this age range. The multivariate relative risks, taken from Table 2 of the authors’ original paper, and the calculated absolute risks (per 1000) to the individual associated with a given frequency of use for each analgesic are shown in the third column of the Table in this commentary. The population-attributable risk (PAR/1000) of developing hypertension among middle-aged women associated with analgesic use is shown in the fourth column.

In the absence of analgesic use, ~25.5 women/1000 (2.55%) in this cohort developed hypertension annually. Given the prevalence and frequency of analgesic use reported and the risk of incident hypertension associated with that use, ~4.5 additional women/1000 (0.45%) develop hypertension annually, ie, the sum of the PARs for the 3 analgesics. These data suggest that ~15% (4.5/[25.5 + 4.5]) of the hypertension developing in middle-aged women is associated with analgesic use.

Epidemiological association between frequency of analgesic use and incident hypertension does not establish a pathogenetic relationship. Therefore, it may be useful to examine the implications of the report from various perspectives.

Epidemiological Validity

The Nurses’ Health Study is a well-known cohort of 121,700 women that began in 1976. Although the data are based on self-reports from questionnaires, nurses are credible historians. One additional point is that this cohort of nurses was healthier than the average US woman as reflected in the lower reported body mass indices and prevalence of diabetes. Nevertheless, the Nurses’ Health Study has been a rich and invaluable resource during the past quarter century for assessing various factors related to women’s health.

The observation associating analgesic use with incident hypertension is strengthened by persistence after adjustment for several potential confounders. These include age, body mass index, physical activity, smoking status, diabetes mellitus, alcohol intake, sodium consumption, family history of hypertension, and concurrent use of other analgesics. Moreover, the reported association between analgesic use and incident hypertension is consistent with reports from 4 other large studies (Dedier et al references 4, 10, 24, and 25). Of note, the association between the frequency of acetaminophen use and incident hypertension was even stronger in a younger cohort of 80,000 nurses 31 to 50 years old (Dedier et al reference 10).

Limitations

One potential limitation noted by the authors is that women who use analgesics may be seen more often by physicians than women who do not use analgesics. Consequently, there may be an ascertainment bias in self-reports on the incidence of physician-diagnosed hypertension. Although women who did not have at least one physical examination during the baseline and follow-up period were excluded from the analysis, bias related to differential ascertainment may not have been completely eliminated. Another limitation of the data set is that, although information on frequency of analgesic use was obtained, quantity was not.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

From the Medical University of South Carolina, Departments of Medicine and Pharmacology, Charleston, SC.

Correspondence to Brent M. Egan, MD, Department of Medicine, Medical University of South Carolina, 96 Jonathan Lucas Street, Charleston, SC 29425. E-mail eganbm@musc.edu

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**Biological Plausibility**

The association between analgesic use and incident hypertension appears biologically plausible. As the authors noted, all 3 classes of analgesics can interfere with the genesis of vasodilator and natriuretic prostaglandins. Because the threshold and slope of the renal pressure–natriuresis curve are major determinants of average blood pressure, any adverse effects of the various analgesics on pressure natriuresis or renal function could increase the probability for developing hypertension. Overt analgesic nephropathy is associated with hypertension, but this is an unlikely explanation for the association between acetaminophen, in particular, and hypertension, especially among those with relatively infrequent use.²,³

Perhaps the least expected of the associations is the link of acetaminophen use with incident hypertension. Although acetaminophen has effects on prostaglandin metabolism, the global effects are less than those seen with aspirin and NSAIDs.⁴,⁵ The fact that the linkage between the frequency of acetaminophen use and incident hypertension is comparable to that of aspirin and NSAIDs raises alternative possibilities.

Although acetaminophen has significantly less overall effect on eicosanoid metabolism than aspirin, one might speculate that it affects prostaglandins at target sites that are critical in blood pressure regulation. Another possibility is that acetaminophen augments the risk of hypertension by other actions, eg, reduction in glutathione, which has antioxidant and protein kinase C antagonist properties.⁶ Because oxidative stress and protein kinase C are implicated in the pathogenesis of hypertension,⁷,⁸ the effects of acetaminophen on these key signal transduction pathways could conceivably contribute to a greater risk of hypertension.

Yet another possibility is that the association of acetaminophen use and incident hypertension is indirect via linkage with another variable, eg, headache, which was not included in the analysis. Indirect linkage could also account for the

### Frequency of Use of Analgesic, Relative Risk and Annual Incidence of Hypertension, and the Annual Population-Attributable Risk of Hypertension in Middle-Aged Women*

<table>
<thead>
<tr>
<th>Days/Mo</th>
<th>% Using</th>
<th>% RRₘ</th>
<th>IHTN/1000/yr</th>
<th>PAR/1000/yr ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>40.8</td>
<td>1.00</td>
<td>25.2</td>
<td>0.00</td>
</tr>
<tr>
<td>1–4</td>
<td>22.8</td>
<td>1.08</td>
<td>27.2</td>
<td>0.46*</td>
</tr>
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<td>8.8</td>
<td>1.13</td>
<td>28.5</td>
<td>0.29</td>
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<tr>
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<td>34.8</td>
<td>0.33</td>
</tr>
<tr>
<td>&gt;22</td>
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<td>1.21</td>
<td>30.4</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.55 (PAR for ASA/yr)†</td>
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</table>

**Acetaminophen**

<table>
<thead>
<tr>
<th>Days/Mo</th>
<th>% Using</th>
<th>% RRₘ</th>
<th>IHTN/1000/yr</th>
<th>PAR/1000/yr ASA</th>
</tr>
</thead>
<tbody>
<tr>
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<td>40.8</td>
<td>1.00</td>
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<td>29.0</td>
<td>1.07</td>
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<td>8.6</td>
<td>1.22</td>
<td>31.5</td>
<td>0.49</td>
</tr>
<tr>
<td>15–21</td>
<td>2.4</td>
<td>1.31</td>
<td>33.8</td>
<td>0.19</td>
</tr>
<tr>
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<td>1.20</td>
<td>31.0</td>
<td>0.19</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.39 (PAR for Actm/yr)</td>
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**NSAIDs**

<table>
<thead>
<tr>
<th>Days/Mo</th>
<th>% Using</th>
<th>% RRₘ</th>
<th>IHTN/1000/yr</th>
<th>PAR/1000/yr ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>46.8</td>
<td>1.00</td>
<td>25.3</td>
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<td>1.32</td>
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<tr>
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<td>34.2</td>
<td>0.67</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>1.52 (PAR NSAIDs/yr)</td>
</tr>
</tbody>
</table>

ASA indicates acetylsalicylic acid; NSAIDs, nonsteroidal anti-inflammatory drugs; RRₘ, relative risk in multivariate analysis; IHTN/1000/yr, annual incidence of hypertension per thousand middle age women; PAR/1000/yr, population-attributable risk of hypertension per thousand middle-age women (in the entire population) annually associated with use of the analgesic at the frequency indicated; Actm, acetaminophen.

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*Calculation of PAR for each level of analgesic use: The excess risk of hypertension annually in women taking ASA 1–4 days/mo was 2/1000, ie, 27.2 vs 25.2 in those who took no ASA. However, only 22.8% of women took ASA 1–4 days/mo. Therefore, the population-attributable risk of hypertension associated with taking ASA 1–4 days/mo was 2.0 × 0.228 or 0.46/1000 annually.

†PAR of developing hypertension annually associated with each analgesic: The PAR for developing hypertension each year was calculated as the sum of risks for each level of use within a given analgesic category. Of note, in the multivariate analysis the authors controlled for the confounding effects of simultaneous use of other analgesic(s).
similar strengths of association between the 3 classes of analgesics and incident hypertension.

Clinical Correlations
As the authors note, one short-term study in treated hypertensive patients given 1 gram of paracetamol every 8 hours documented a 4 mm Hg increase in supine and standing blood pressures. However, in another well-designed study of hypertensive patients, this adverse effect on blood pressure of acetaminophen at the same dose was not observed. Moreover, in hypertensive patients sensitive to the pressor effect of pseudoephedrine, the combination of chlorpheniramine and acetaminophen did not adversely affect blood pressure. The Joint National Committees Sixth Report on Hypertension indicates that NSAIDs have an adverse effect on blood pressure and limit the effectiveness of several classes of antihypertensive medications. Acetaminophen is not mentioned. In a study of critically ill patients, a single 1-gram dose of paracetamol did not raise, but rather lowered, blood pressure more than 30%.

Limitations of Editorial Estimates of Absolute and Population-Attributable Risk
The calculations of absolute individual risk and population-attributable risk derived from the study data by this clinician may overestimate the potential deleterious effects of these analgesics on incident hypertension. More specifically, the incidence of hypertension in women not taking analgesics was approximately 2.55% per year (25.5/1000). The population-attributable risk of hypertension related to the use of all 3 analgesics was estimated at 0.45% annually (Table). The sum of these 2 risks (2.55% + 0.45%) is 3.0% per year, which exceeds the observed annual incidence of hypertension in the overall sample of slightly under 2.8%. Part of the discrepancy may be explained by the declining denominator of normotensive women each year, which began at 51,630 and declined by the 10,579 new hypertensives to 41,051 in the eighth year.

In summary, the epidemiological association between analgesic use and incident hypertension in the Nurses’ Health Study has important public health and clinical implications. The report raises the possibility that approximately 15% of hypertension developing in middle-aged women is associated with analgesic use. Despite the relative paucity of clinical evidence for a significant adverse blood pressure effect of acetaminophen, the implied population-attributable risk and biological plausibility for hypertension are sufficient to merit further investigative attention. In the absence of further information, it appears that use of any of these 3 analgesics <5 times monthly in otherwise healthy middle-aged and older women has a minimal effect on incident hypertension. For those who use analgesics more frequently, it would seem preferable to have a clear rationale, eg, control of significant pain or prevention of myocardial infarction (aspirin) in at-risk individuals, to justify the various potential adverse effects, including the association with incident hypertension. In treated hypertensive patients requiring analgesics, from a blood pressure perspective, the available evidence favors use of acetaminophen over NSAIDs.

References
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