Assessing Evidence of Interaction Between Smoking and Warfarin: A Systematic Review and Meta-analysis

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Warfarin, the most commonly used oral anticoagulant worldwide, plays a major role in the treatment and prevention of thromboembolic events in various forms of cardiovascular diseases, such as atrial fibrillation, prosthetic heart valve, DVT, and ischemic stroke. Warfarin is eliminated through hepatic metabolism and the cytochrome P450 (CYP) enzyme system primarily by the 2C9 and, to a minor extent, 2C19, 3A4, and 1A2 subtypes. Several drugs and substances, therefore, can cause significant drug interaction with warfarin by interfering with the activities of these enzymes. Smoking is a well known cause of significant drug interaction in humans. Experiments in human, animal, and tissue models have indicated that chronic smoking is associated with enhanced drug clearance through hepatic microsomal enzyme induction. The primary causal agents in smoking are believed to be the polycyclic aromatic hydrocarbons, a group of chemical compounds consisting of fused aromatic rings formed by incomplete combustion of carbon-containing substances. Because polycyclic aromatic hydrocarbons are known to induce CYP1A1, -1A2, and -2E1 activities, interaction between warfarin and smoking
theoretically can occur.\textsuperscript{4} However, clinical evidence of this interaction remains inconclusive. Previous studies demonstrated that smoking increased warfarin clearance, and smoking cessation was associated with an increased international normalized ratio (INR) value.\textsuperscript{6,7} Conversely, several retrospective studies reported no differences in warfarin dosage requirement among warfarin users with or without smoking history.\textsuperscript{5} Current clinical practice guidelines on smoking cessation and anticoagulation management provide little to no guidance on this controversial issue.\textsuperscript{9,10} With such a high prevalence of smoking in society, information regarding the smoking-warfarin interaction is of significant value to clinical practice. The primary objective of the present study, therefore, was to systematically review all relevant information regarding the smoking-warfarin interaction and to provide overall summary of the evidence.

Materials and Methods

Literature Search

To identify studies that evaluated the interaction between warfarin and smoking, two independent investigators (P. D., T. M.) searched the PubMed, Embase, Cochrane Central Register of Controlled Trials, CINAHL, Allied and Complementary Medicine, PsycINFO, and International Pharmaceutical Abstract databases and ClinicalTrials.gov from 1966 to December 2008. The medical subject heading search terms were “warfarin” with “smoking” or “tobacco” or “cigarette” or “polycyclic aromatic hydrocarbon.” Non-English articles were included if they included an English abstract with sufficient information. The bibliographies of retrieved articles were checked for additional pertinent studies.

Study Selection

An investigation was included in our systematic review if it met each of the following criteria: (1) The study was reported in an original article; (2) the study assessed the effects of smoking on pharmacokinetic parameters, dosage requirement, or clinical effects of warfarin; and (3) the study design was a randomized controlled trial, prospective uncontrolled study, cross-sectional study, cohort study, or case-control study.

Data Extraction

Two investigators independently reviewed the articles. All disagreements between investigators were solved by discussion and consensus. We used a standardized extraction form to obtain data on study design, patient characteristics, numbers of participants, drug regimen, detailed history of smoking, duration of follow-up, intervention (dosage, frequency, and duration of therapy), and relevant results. In the case of observational studies, an attempt was made to qualitatively assess the overall quality of the study.

Data Analysis

Two investigators (P. D., N. C.) independently evaluated both clinical and statistical heterogeneity of all studies that met the inclusion criteria. For clinical heterogeneity, the assessment was performed according to the patient, intervention, comparator, and outcome principle, as described elsewhere.\textsuperscript{11} For statistical heterogeneity, the assessment was performed using Q statistics, which help to determine the degree of variation across studies that resulted from heterogeneity rather than by chance. $P < .10$ was considered evidence of heterogeneity.\textsuperscript{12,13} We also used the $I^2$ statistic to determine the degree of heterogeneity across studies. An $I^2$ of $25\%$, $50\%$, and $75\%$ indicates low, medium, and high heterogeneity, respectively.\textsuperscript{14} A meta-analysis was performed using the random-effects models of DerSimonian and Laird.\textsuperscript{15} For studies with continuous outcomes, the weighted mean difference was used, whereas the overall risk ratio was used for pooling dichotomous outcomes. Publication bias was assessed with Begg test\textsuperscript{15} and Eggers test.\textsuperscript{16} Statistical significance was set at $P < .05$.

For data analysis, we were able to categorize included studies into different groups, such as multivariate and univariate studies and those using changes in warfarin dosage requirement and INR as main outcomes. We conducted various analyses, including overall analyses and sensitivity analyses, of these groups of trials where possible. For studies using warfarin dose in milligrams as outcome, we expressed warfarin dose as a weekly dose. A sensitivity analysis of the meta-analysis, including only studies adjusting for pharmacogenetic factors, also was performed because these factors were known to strongly influence outcomes in warfarin users. Because changes in warfarin dosage requirement was expressed by either percentage change or change in milligrams for such an analysis, a conversion of data was needed. Because warfarin dosing in clinical practice generally is adjusted using percentage change, we converted change in milligrams to percent change for the purpose of data pooling and data analysis. Such conversion was performed using the following formula: (change in mg/mean warfarin dose in mg) $\times \ 100 = \text{percentage change of warfarin dose}$. The 95% CI was calculated using the following formula: lower interval/upper interval $= \text{mean} \pm 1.96 \times \text{SE}$.

Results

Our search identified 1,240 articles, but only 33 articles met the inclusion criteria (Fig 1). Of the 1,207 excluded articles, 1,175 did not evaluate a
Quality of Included Studies

The quality of study design and reporting was variable with different outcome parameters, reflecting a paucity of good-quality data on this issue. The best available data were from six cross-sectional studies that used multivariate analysis to evaluate effects of smoking on warfarin dosage requirement. Based on some similarity in the reported outcomes, we were able to perform a meta-analysis of these studies. Another source of high-quality information was from the experimental study by Bachmann et al. The rest of the data were mostly from cross-sectional studies using univariate analysis. One of these studies did not specify the authors; however, this work was performed at the University of Illinois at Chicago. Despite the lack of authorship, the article provided adequate data to be included in our systematic review.

Effect of Smoking on Warfarin Pharmacokinetics

Three studies evaluated the effects of smoking on pharmacokinetic parameters of warfarin. Due to major differences in study design, we were unable to perform a meta-analysis of these studies. Therefore, only a descriptive report is summarized here.

Bachmann et al conducted a prospective crossover study among nine chronic smokers (at least 1 pack/d) aged 19 to 60 years who were otherwise healthy. The study was conducted in two phases separated by a 1-month washout period. In the first phase, subjects received an average daily warfarin dose of 0.032 mg/kg for 2 weeks while continuing to smoke. After a 1-month abstinence period from smoking, subjects received a 2-week treatment with warfarin similar to the first phase but without smoking. The measured pharmacokinetic parameters of warfarin were steady-state plasma levels, clearances, half-life, and apparent volume of distribution. Results showed that smoking

Characteristics of Included Studies

Among the 13 included studies, 12 were cross-sectional studies (seven prospective and five retrospective), and one was an experimental study (Table 1). For smoking pattern, 12 studies were conducted in current smokers, whereas one study was conducted after smoking cessation. For outcome measures, three studies reported differences in pharmacokinetic parameters of warfarin, two evaluated differences in INR values, and eight evaluated differences in warfarin dosage requirement (Table 1).

Table 1—Overall Study Design and Description of Intervention or Exposure and Outcomes

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Study Design</th>
<th>Population</th>
<th>Intervention/Exposure Variable</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bachmann et al/1979</td>
<td>Prospective experimental</td>
<td>Healthy volunteers who smoked</td>
<td>Smoking cessation</td>
<td>Warfarin pharmacokinetics</td>
</tr>
<tr>
<td>Whitley et al/2007</td>
<td>Cross-sectional</td>
<td>Patients receiving warfarin</td>
<td>Smoking</td>
<td>Warfarin dose requirement</td>
</tr>
<tr>
<td>Aquilante et al/2006</td>
<td>Cross-sectional</td>
<td>Patients receiving warfarin</td>
<td>Smoking</td>
<td>Warfarin dose requirement</td>
</tr>
<tr>
<td>Gage et al/2008</td>
<td>Cross-sectional</td>
<td>Patients receiving warfarin</td>
<td>Smoking</td>
<td>Warfarin dose requirement</td>
</tr>
<tr>
<td>Lee et al/2005</td>
<td>Cross-sectional</td>
<td>Patients receiving warfarin</td>
<td>Smoking</td>
<td>Warfarin dose requirement</td>
</tr>
<tr>
<td>Lenzini et al/2008</td>
<td>Cross-sectional</td>
<td>Patients receiving warfarin</td>
<td>Smoking</td>
<td>Warfarin dose requirement</td>
</tr>
<tr>
<td>Millikan et al/2007</td>
<td>Cross-sectional</td>
<td>Patients receiving warfarin</td>
<td>Smoking</td>
<td>Warfarin dose requirement</td>
</tr>
<tr>
<td>UIC/1999</td>
<td>Cross-sectional</td>
<td>Patients receiving warfarin</td>
<td>Smoking</td>
<td>Warfarin pharmacokinetics</td>
</tr>
<tr>
<td>Mungall et al/1985</td>
<td>Cross-sectional</td>
<td>Patients receiving warfarin</td>
<td>Smoking</td>
<td>Warfarin pharmacokinetics</td>
</tr>
<tr>
<td>Mitchell/1972</td>
<td>Cross-sectional</td>
<td>Patients receiving warfarin</td>
<td>Smoking</td>
<td>Warfarin dose requirement</td>
</tr>
<tr>
<td>Weiner et al/1984</td>
<td>Cross-sectional</td>
<td>Patients receiving warfarin</td>
<td>Smoking</td>
<td>Warfarin dose requirement</td>
</tr>
<tr>
<td>McGriff-Lee et al/2005</td>
<td>Cross-sectional</td>
<td>Patients receiving warfarin</td>
<td>Smoking</td>
<td>INR</td>
</tr>
<tr>
<td>Pambonkian et al/2008</td>
<td>Cross-sectional</td>
<td>Patients receiving warfarin</td>
<td>Smoking</td>
<td>INR</td>
</tr>
</tbody>
</table>

INR = international normalized ratio; UIC = University of Illinois at Chicago.
cessation led to a 13% increase in steady-state warfarin level, 13% decrease in warfarin clearance, 23% increase in warfarin half-life, and 11% increase in volume of distribution.

Mungall et al\textsuperscript{16} conducted a population pharmacokinetics study using 613 blood samples from 163 warfarin users aged 18 to 77 years to evaluate the influence of various demographic factors, including smoking status, on warfarin clearance. For the pharmacokinetics model, a one-compartment open model with first-order absorption and first-order elimination was used with an assumed extent of availability of 1. Using a linear regression model, the authors found that smoking increase warfarin clearance by 10%, which is consistent with findings from Bachmann et al.\textsuperscript{6}

One study\textsuperscript{22} compared warfarin pharmacokinetic parameters between 18 smokers and 35 nonsmokers who received at least 1 month of stable warfarin dose. Parameters measured were total and unbound plasma concentration and clearance of S- and R-warfarin enantiomers. Results showed no significant differences in warfarin pharmacokinetic parameters between smokers and nonsmokers, a finding that is not in line with the two previously discussed studies.

**Effect of Smoking on Warfarin Dosage Requirement**

Among the eight cross-sectional studies evaluating the effect of smoking on warfarin dosage requirement,\textsuperscript{6,17-21,24,25} six were conducted using multivariate analysis with either percentage of change in warfarin dose in milligrams (three studies),\textsuperscript{8,17,19} or exact warfarin dose in milligrams using univariate analysis.\textsuperscript{8,17,19} The remaining two studies evaluated a relationship between smoking status and warfarin dosage using univariate analysis.\textsuperscript{24,25} Therefore, we were able to perform two meta-analyses: (1) three multivariate studies\textsuperscript{8,17,19} with percentage of change in warfarin dose as an outcome and (2) three multivariate studies\textsuperscript{8,17,19} with exact warfarin dose in milligrams required as an outcome. A sensitivity analysis of multivariate studies that included pharmacogenomic factors was undertaken. In addition, a sensitivity analysis combining two univariate studies\textsuperscript{24,25} with three multivariate studies\textsuperscript{8,17,19} using warfarin dose in milligrams as the same outcome also was performed.

**Meta-analysis of Multivariate Studies Using Changes in Milligrams of Warfarin Dose as Outcome**

Studies by Lee et al,\textsuperscript{19} Aquilante et al,\textsuperscript{17} and Whitley et al\textsuperscript{8} were conducted among 544 patients (range, 63-350 patients) and evaluated the effect of smoking on warfarin dose requirement using multivariate analysis (Table 2). Mean age and mean warfarin dose in both the Aquilante et al\textsuperscript{17} and the Whitley et al\textsuperscript{8} studies ranged from 59.0 ± 14.0 years to 69.0 ± 11.0 years and 36.61 ± 16.03 mg/week to 37.1 ± 16.0 mg/week, respectively. Lee et al\textsuperscript{19} studied an Asian population with an age range of 45 to 73 years and a mean warfarin dose of 3.30 ± 2.23 mg/d, which translated into 23.1 ± 15.61 mg/week. Pharmacogenomic factors were included in the regression model only in Aquilante et al,\textsuperscript{17} whereas clinical factors were used in Lee et al,\textsuperscript{19} and Whitley et al\textsuperscript{8}. When pooled and analyzed together using a random effects model, we found that smokers require 2.26 mg more of warfarin per week compared with nonsmokers (Fig 3), but this finding was not statistically significant (95% CI, 2.53-7.04; \( P = .355 \)). Additionally, we found significant heterogeneity among these three studies (Q statistic, 7.69; \( P = .021 \); \( I^2 = 74.0\% \)).

**Sensitivity Analysis of Multivariate Studies That Included Pharmacogenomic Factors**

A sensitivity analysis that included all studies with pharmacogenomic factors was performed. This analysis was done by converting the results of the Aquilante et al\textsuperscript{17} study from extra milligrams of warfarin required to percent change in warfarin dose as described earlier. After the conversion, the Aquilante et al\textsuperscript{17} study was pooled with Millican et al,\textsuperscript{21} Lenzini et al,\textsuperscript{20} and Gage et al,\textsuperscript{18} for a total study population of 2,133 patients. Results of this analysis showed that smoking was significantly associated with a 13.21% (95% CI, 8.59-17.83; \( P < .001 \)) increase in warfarin dosage requirement compared with nonsmoking. We found no heterogeneity among these
Stop smoking for at least 1 year), light smokers (defined as smoking 20 cigarettes/d), and heavy smokers (defined as smoking 20 cigarettes/d). For the Mitchell et al. study, the mean doses for nonsmokers, light smokers, and heavy smokers were 7.46 ± 0.37 mg/d, 7.86 ± 0.35 mg/d, and 7.57 ± 0.50 mg/d, respectively. For the Weiner et al. study, the mean doses for nonsmokers, light smokers, and heavy smokers were 5.0 ± 4.3 mg/d, 5.1 ± 2.7 mg/d, and 3.9 ± 2.1 mg/d, respectively. Both studies reported no significant relationship between smoking status and warfarin dose.

Because these two univariate studies used warfarin dosage in milligrams as an outcome, which was similar to the three multivariate studies, we pooled the data and conducted a sensitivity analysis on these five studies. For this purpose, because there were four studies (Q statistic, 2.47; P = .481; I², 0%) (Fig 4). Begg and Egger tests indicated no publication bias in this analysis (P = .497 and P = .740, respectively).

**Sensitivity Analysis of Both Multivariate and Univariate Studies**

Univariate studies by Mitchell et al. and Weiner et al. assessed the relationship between smoking status and mean warfarin dose among 404 patients (range, 174-230 patients) (Table 3). The mean age in the Weiner et al. study ranged from 56.7 ± 11.4 years to 60.7 ± 12.1 years, although no information on age was available in the Mitchell et al. study. These studies classified their populations into three subgroups: nonsmokers (defined as patients who had never smoked or had

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>No.</th>
<th>Age, y ± SD</th>
<th>Sex (% Male)</th>
<th>Dose, mg/d</th>
<th>Method</th>
<th>Results</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Millican et al. 2007</td>
<td>92</td>
<td>58.2 ± 15.5</td>
<td>48 (52.17)</td>
<td>4.9 ± 2.5</td>
<td>Multiple regression model</td>
<td>20.1 (6.0-36.2)-</td>
<td>.002</td>
</tr>
<tr>
<td>Lenzini et al. 2008</td>
<td>676</td>
<td>57 ± 12 to 60 ± 14</td>
<td>325 (48.08)</td>
<td>4.8 ± 2.3 to 5.1 ± 2.5</td>
<td>Multiple regression model</td>
<td>13.7 (4.1-24.2)-</td>
<td>.005</td>
</tr>
<tr>
<td>Gage et al. 2008</td>
<td>1,015</td>
<td>65 ± 14</td>
<td>653 (64.33)</td>
<td>4.8 ± 1.6</td>
<td>Multiple regression model</td>
<td>10 (3-16)-</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Lee et al. 2005</td>
<td>63</td>
<td>59 ± 14</td>
<td>25 (39.7)</td>
<td>3.30 ± 2.23</td>
<td>Multiple regression model</td>
<td>1.53 (-0.43-2.49)-</td>
<td>.126</td>
</tr>
<tr>
<td>Aquilante et al. 2006</td>
<td>350</td>
<td>69 ± 11</td>
<td>306 (87.4)</td>
<td>36.61 ± 16.03×</td>
<td>Multiple regression model</td>
<td>6.6 (2.68-10.52)-</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Whitley et al. 2007</td>
<td>131</td>
<td>66.9 ± 13.1</td>
<td>59 (45.04)</td>
<td>37.1 ± 16×</td>
<td>Multiple regression model</td>
<td>-5.17 (-14.76-3.82)-</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>McGriff-Lee et al. 2005</td>
<td>350</td>
<td>56 ± 16 to 60 ± 13</td>
<td>210 (60.0)</td>
<td>4.9 ± 2.5</td>
<td>Fisher exact test</td>
<td>The percentage of smokers among those below, within, and above INR range were 5%, 10%, and 5%, respectively. No significant differences were detected.</td>
<td>NS</td>
</tr>
<tr>
<td>Pamboukian et al. 2008</td>
<td>80</td>
<td>52.8 ± 13.1</td>
<td>59 (73.7)</td>
<td>NR</td>
<td>Pearson correlation coefficients to assess the relationship of smoking and target INR</td>
<td>r = -0.17</td>
<td>.13</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or No. (%), unless otherwise indicated. NR = not reported. NS = not significant. See Table 1 legend for expansion of other abbreviation.

×Percentage dose change (95% CI).

×Dose in mg/wk

×Extra mg warfarin required (95% CI).

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Effect of Smoking on INR

There were two cross-sectional studies that reported on the effect of smoking on INR. However, we were unable to pool and analyze the data of these studies because one expressed INR as continuous data, and the other expressed it as categorical data.

McGriff-Lee et al conducted a retrospective observational study among 350 patients receiving a stable dose of warfarin for at least 2 weeks. The primary

<table>
<thead>
<tr>
<th>Outcome: Percentage Change of Warfarin Dose</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study (year)</td>
<td>Change (95% CI)</td>
</tr>
<tr>
<td>Millican (2007)</td>
<td>20.10 (6.00, 36.20)</td>
</tr>
<tr>
<td>Gage (2008)</td>
<td>10.00 (3.00, 16.00)</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.455)</td>
<td>12.13 (7.00, 17.27)</td>
</tr>
</tbody>
</table>

**Figure 2.** Pooled estimate of percentage change in warfarin dose.

<table>
<thead>
<tr>
<th>Outcome: Additional Milligrams of Warfarin Dose Required</th>
<th>Additional Milligrams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study (year)</td>
<td>Required (95% CI)</td>
</tr>
<tr>
<td>Lee (2005)</td>
<td>1.53 (-0.43, 3.50)</td>
</tr>
<tr>
<td>Aquilante (2006)</td>
<td>6.60 (2.68, 10.52)</td>
</tr>
<tr>
<td>Whitley (2007)</td>
<td>-5.17 (-14.46, 4.12)</td>
</tr>
<tr>
<td>Overall (I-squared = 74.0%, p = 0.021)</td>
<td>2.26 (-2.53, 7.04)</td>
</tr>
</tbody>
</table>

**Figure 3.** Pooled estimate of additional milligrams of warfarin required.

three subgroups in the univariate studies, we used the data of only nonsmokers and heavy smokers for this analysis. Results showed that smoking was associated with a 2.05 mg/week (95% CI, 1.05-5.15) increase in warfarin dosage requirement compared with nonsmokers. However, this finding was not statistically significant. In addition, we found significant heterogeneity among these five studies (Q statistic, 20.03; P < .001; I², 80.0%) (Fig 5).
prevalence of smoking among patients with cardiovascular diseases requiring anticoagulation therapy, there is a clear need to formally and systematically evaluate the available evidence on this important issue.

Based on the results of our systematic search, it is clear that there is a paucity of high-quality data on the interaction between smoking and warfarin therapy. Some studies were conducted 20 years ago when certain measures, such as evaluation of warfarin pharmacokinetics and warfarin effects, were not standardized. In addition, some studies evaluated the effect of smoking on warfarin therapy but were not specifically and properly designed, making it difficult to draw a firm conclusion on this matter.

From our analyses, we found conflicting evidence of a smoking-warfarin interaction. Meta-analyses of trials assessing the effect of smoking on warfarin dosage requirement produced mixed results. Although some suggested a significant 12% increase in percentage of warfarin dosage requirement, others

**Discussion**

Although there were reports that suggested possible interaction between smoking and warfarin, data appeared inconclusive and conflicting. With a high prevalence of smoking among patients with cardiovascular diseases requiring anticoagulation therapy, there is a clear need to formally and systematically evaluate the available evidence on this important issue.

Based on the results of our systematic search, it is clear that there is a paucity of high-quality data on the interaction between smoking and warfarin therapy. Some studies were conducted > 20 years ago when certain measures, such as evaluation of warfarin pharmacokinetics and warfarin effects, were not standardized. In addition, some studies evaluated the effect of smoking on warfarin therapy but were not specifically and properly designed, making it difficult to draw a firm conclusion on this matter.

From our analyses, we found conflicting evidence of a smoking-warfarin interaction. Meta-analyses of trials assessing the effect of smoking on warfarin dosage requirement produced mixed results. Although some suggested a significant 12% increase in percentage of warfarin dosage requirement, others

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Age, y</th>
<th>Male, %</th>
<th>Nonsmoker</th>
<th>Light Smoker</th>
<th>Heavy Smoker</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitchell et al.</td>
<td>230</td>
<td>NR</td>
<td>NR</td>
<td>7.46 ± 0.37</td>
<td>7.86 ± 0.35</td>
<td>7.57 ± 0.50</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Weiner et al.</td>
<td>174</td>
<td>17-85</td>
<td>NR</td>
<td>5.0 ± 4.3</td>
<td>5.1 ± 2.7</td>
<td>3.9 ± 2.1</td>
<td>&gt;.05</td>
</tr>
</tbody>
</table>

Data are reported as mean ± SD, unless otherwise indicated. See Table 2 legend for expansion of abbreviation.
additional support that a smoking-warfarin interaction may exist, especially after adjustment in the most comprehensive way available.

For studies evaluating the effects of smoking on warfarin pharmacokinetic parameters, two suggested a 10% to 13% increase in warfarin clearance, whereas one suggested no differences in any parameters.\textsuperscript{6,22,23} However, the latter study was not properly designed to address this issue and was confounded with multiple factors.\textsuperscript{22} As a result, the consistent findings of the first two\textsuperscript{6,23} appear more credible.

Studies by McGriff-Lee et al\textsuperscript{26} and Pamboukian et al\textsuperscript{27} aimed to identify factors associated with nontherapeutic INRs. Although smoking was included in the analysis, the number of smokers in the McGriff-Lee et al\textsuperscript{26} study was too low to have any meaningful statistical power to find a smoking-warfarin effect. For the Pamboukian et al\textsuperscript{27} study, the primary objective was to find factors associated with nonadherence to therapy without any specific detail of their analysis on the effects of smoking on warfarin therapy. Therefore, both studies were not specifically and properly designed to address the issue of interaction between smoking and warfarin therapy.

Case reports were excluded from our main analysis because of inherent bias of reporting only positive findings and lack of a control. Nevertheless, we found three case reports during a literature search and evaluated them.\textsuperscript{7,28,29} The patient age range was 34 to

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Sensitivity analysis of additional milligrams of warfarin required after including univariate studies.}
\end{figure}

suggested otherwise.\textsuperscript{8,17,19} However, it should be noted that the pooled analysis of the former (n = 1,783) may represent a data set with better quality than the latter (n = 544). The three times larger sample size in the first meta-analysis may have helped to increase the power of detecting small differences in warfarin dosage. In addition, these three studies included highly powerful factors that influence the effect of warfarin—CYP2C9 and vitamin K epoxide reductase complex 1 polymorphisms—into their multivariate analyses. For the pooled analysis of the second set of studies,\textsuperscript{8,17,19} two did not take pharmacogenomic factors into consideration. Additionally, there was no heterogeneity among studies in the first meta-analysis, whereas significant heterogeneity was found among the studies in the second meta-analysis.

A sensitivity analysis combining the three multivariate studies\textsuperscript{8,17,19} and two univariate studies\textsuperscript{24,25} showed that smoking did not significantly affect warfarin dosage requirement. However, this result should be interpreted with caution because inclusion of univariate studies may introduce significant bias into a meta-analysis.

Based on the importance of pharmacogenomic factors, we conducted an additional analysis by pooling four multivariate studies\textsuperscript{17,18,20,21} with adjustment for both clinical and pharmacogenomic factors and found that smoking was associated with a 13.21\% increase of warfarin dosage requirement. This analysis lends additional support that a smoking-warfarin interaction may exist, especially after adjustment in the most comprehensive way available.

For studies evaluating the effects of smoking on warfarin pharmacokinetic parameters, two suggested a 10\% to 13\% increase in warfarin clearance, whereas one suggested no differences in any parameters.\textsuperscript{6,22,23} However, the latter study was not properly designed to address this issue and was confounded with multiple factors.\textsuperscript{22} As a result, the consistent findings of the first two\textsuperscript{6,23} appear more credible.

Studies by McGriff-Lee et al\textsuperscript{26} and Pamboukian et al\textsuperscript{27} aimed to identify factors associated with nontherapeutic INRs. Although smoking was included in the analysis, the number of smokers in the McGriff-Lee et al\textsuperscript{26} study was too low to have any meaningful statistical power to find a smoking-warfarin effect. For the Pamboukian et al\textsuperscript{27} study, the primary objective was to find factors associated with nonadherence to therapy without any specific detail of their analysis on the effects of smoking on warfarin therapy. Therefore, both studies were not specifically and properly designed to address the issue of interaction between smoking and warfarin therapy.

Case reports were excluded from our main analysis because of inherent bias of reporting only positive findings and lack of a control. Nevertheless, we found three case reports during a literature search and evaluated them.\textsuperscript{7,28,29} The patient age range was 34 to
80 years, and their smoking history was 39 to 50 packs per year. After smoking cessation without changes in any other factors, all cases experienced a clinically significant increase in INR, ranging from 1.2 to 3.5. All cases required warfarin dosage reduction in the range of 14% to 23%. It is important to note that such an interaction occurred within 6 days to 3 months, which indicates a delayed nature of interaction. Based on this finding, it is prudent to monitor INR closely when a chronic smoker is undergoing a smoking cessation program. The monitoring program may start at 1 week, with close follow-up for up to 3 months.

It is important to note that the investigations included in this review were mostly observational studies and both studies with multivariate analysis and studies using univariate analysis. For studies with multivariate analysis, despite statistical adjustment, residual confounding factors or bias may still exist. For example, smokers may tend to pay less attention to diet, alcohol, vegetables, herbal products, or other environmental factors that may alter warfarin response. Studies lacking adjustment for pharmacogenomic factors, especially vitamin K epoxide reductase complex 1 and CYP2C9, may be affected considerably by a large effect of such genes on warfarin response. Racial differences both within and across studies may influence warfarin response by both genetic polymorphisms and environmental issues, such as vitamin K intake or usage pattern of alternative medicines. In addition to the aforementioned limitations, studies using univariate analysis may be affected by a significant presence of unadjusted confounding factors and bias due to the nature of study design and data analysis. Despite a concern of its internal validity, the consistency of findings across all study designs is indirectly indicative of reliable evidence to support the overall validity of our findings.

In conclusion, current evidence suggests that smoking may potentially cause a significant interaction with warfarin by increasing warfarin clearance, which leads to reduced warfarin effects. Therefore, smokers may require slightly higher doses than non-smokers. On the other hand, smoking cessation may enhance warfarin effects in previous chronic smokers. Based on these findings, close monitoring of warfarin therapy should be instituted when there is a change in smoking status of patients requiring warfarin therapy.

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