Health Services and Outcomes Research

Influenza Vaccination and Major Adverse Vascular Events in High-Risk Patients

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Background—We sought to determine the association between influenza vaccination and major adverse vascular events because the association remains uncertain.

Methods and Results—A total of 31,546 participants were enrolled from 40 countries. Eligibility included age ≥55 years and known vascular disease. The primary outcome was a composite of death resulting from cardiovascular causes, myocardial infarction, or stroke during 4 influenza seasons (2003–2007). Influenza vaccination was associated with a lower risk of the outcome during 3 influenza seasons (defined using World Health Organization FluNet reports): 2004 to 2005 (adjusted odds ratio [OR], 0.62; 95% confidence interval [CI], 0.50–0.77), 2005 to 2006 (adjusted OR, 0.69; 95% CI, 0.53–0.91), and 2006 to 2007 (adjusted OR, 0.52; 95% CI, 0.42–0.65), the same years that circulating influenza matched the vaccine antigen. In 2003 to 2004, there was an incomplete match between circulating influenza and the vaccine antigen, and there was no association between influenza vaccination and the outcome (adjusted OR, 0.96; 95% CI, 0.73–1.27). However, tests of potential biases in the analyses revealed associations between influenza vaccination and outcome during noninfluenza seasons except 2003 to 2004. The summary ORs in the influenza season (OR, 0.65; 95% CI, 0.58–0.74) and noninfluenza season (OR, 0.66; 95% CI, 0.57–0.76) were almost identical. The reduction in risk of noncardiovascular death associated with the influenza vaccine ranged from 73% to 79%.

Conclusion—Although initial analyses suggest that influenza vaccination was associated with reduced risk of major adverse vascular events during influenza seasons when the influenza vaccine matched the circulating virus, sensitivity analyses revealed that risk of bias remained. A randomized trial is needed to definitively address this question. (Circulation. 2012;126:278-286.)

Key Words: infection ■ myocardial infarction ■ prevention ■ stroke ■ vaccination

It is well established that deaths caused by acute myocardial infarction and stroke mortality increase by ≈10% to 15% in the winter months.1,2 Influenza, which circulates during winter months, may be an important causative factor for this increase in vascular mortality. Several observational studies have established an association between influenza infection and major adverse vascular events.3–6 Mechanisms that have been postulated to explain this increased risk include the precipitation of plaque rupture, endothelial dysfunction, reactivation of other latent infections leading to plaque rupture, fever-associated tachycardia, and metabolic derangements related to infection, including elevation of triglycerides and serum glucose levels.7

Clinical Perspective on p 286

Whether immunizing high-risk patients against influenza reduces major vascular events is uncertain.1 Observational studies that have evaluated the association between influenza vaccination and major adverse vascular events such as myocardial infarction and stroke have had conflicting results.7–17 A meta-analysis of 2 small randomized trials showed no significant difference of immunization in preventing acute
myocardial infarction or cardiac death, although point estimates of effect tended toward protection and a recent small open-label randomized trial showed a reduction in major adverse vascular events in influenza-vaccinated patients with a history of acute coronary syndrome.1,18–21

We sought to determine whether influenza vaccination was associated with a reduction in major adverse vascular events using a large clinical database consisting of prospectively collected data from the Ongoing Telmisartan Alone and in Combination With Ramipril Global EndPoint Trial (ONTARGET) and the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) trials.22–24

Methods

Study Population

Participants in the ONTARGET/TRANSCEND trials were ≥55 years of age and had a history of known vascular disease or diabetes mellitus with documented end-organ damage.22 These 2 double-blind, placebo-controlled randomized trials were conducted from 2002 to 2007 to examine the efficacy of an angiotensin receptor blocker (telmisartan) and an angiotensin-converting enzyme inhibitor (ramipril) alone versus in combination (ONTARGET) and an angiotensin receptor blocker (telmisartan) versus placebo in participants intolerant to angiotensin-converting enzyme inhibitors (TRANSCEND) in reducing cardiovascular outcomes.22–24 Patients with symptomatic congestive heart failure, uncontrolled hypertension, history of a heart transplantation, a major noncardiac illness expected to reduce life expectancy or to interfere with study participation, and a significant disability precluding regular follow-up visits were excluded.22

In total, 31,546 participants were recruited from 733 sites in 40 countries over the study period. Participants were reviewed 6 weeks after enrollment and then every 6 months for up to 5.5 years (median, 56 months). In total, 99.8% of participants were followed up until the primary outcome occurred or the end of study. The study was approved by the ethics review board of local institutions in all countries. All participants provided written informed consent.

Influenza Vaccination

Annual immunization status with trivalent influenza vaccine was determined by use of a self-reported questionnaire at the study enrollment visit, 2-year follow-up visit, and end of study visit. Self-reported questionnaire has been shown to be a highly accurate method for determining influenza vaccination status in adults.25 Influenza vaccine is reformulated annually to include antigens from influenza strains anticipated to circulate in the ensuing influenza season. We therefore analyzed the ONTARGET/TRANSCEND database as a series of 4 cohorts, each corresponding to an influenza season. For example, the 2003 to 2004 cohort included all patients enrolled in the study by June 1, 2003, and followed up until May 31, 2004. The following cohorts were included: 2003 to 2004, 2004 to 2005, 2005 to 2006, and 2006 to 2007. An important limitation of using self-reported questionnaires is that we were able to determine only whether an individual patient had been vaccinated against influenza for a given season, not the date of vaccination. We did not conduct analyses for the 2002 to 2003 influenza season because too few participants were enrolled. Participants who developed the primary outcome or died (of any cause) were excluded from subsequent analysis.

Primary Outcome

The primary outcome was a composite of major adverse vascular events, including cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. All study outcomes were prospectively adjudicated by a central committee blinded to study medication allocation and influenza vaccination status with the use of standardized criteria.22

Statistical Analysis

Baseline characteristics for each influenza season were stratified according to history of influenza vaccination and compared by use of the χ² test, Fisher exact test, or Student t test as appropriate. Logistic regression models were used to estimate the unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the association between influenza vaccination and the composite primary outcome during each influenza season (2003–2007). Complete cases analysis was performed in the event of missing data because there were far fewer than 10% missing values for all variables; missing influenza vaccination status ranged from 0.36% in the 2006 to 2007 cohort to 1.5% in the 2003 to 2004 cohort. We defined influenza season for the southern hemisphere as June 1 to November 30 and as December 1 to May 31 for the northern hemisphere. The dates encompassed the peak influenza activity for all participating countries; influenza surveillance was gathered with the World Health Organization Global Influenza Surveillance Network, FluNet, retrospectively.

To avoid a lack of independence associated with counting multiple outcomes, only the first outcome was counted. Models were adjusted for potential confounding variables, including history of coronary artery disease, diabetes mellitus, hypertension, stroke, admission to a nursing home, and use of aspirin, β-blockers, lipid-lowering drugs, angiotensin-converting enzyme inhibitors, or angiotensin II inhibitors. We also created a propensity score for influenza vaccine use to reduce the effect of bias on the basis of a tendency for healthier persons to be vaccinated against influenza.27,28 The propensity score included the following variables: age, sex, body mass index, ethnicity, education, vitamin use, smoking history, alcohol use, and history of pneumococcal vaccination. The covariates included in the propensity score were selected a priori. Age, sex, education, and markers of healthy living have been associated with influenza vaccination,29 so these were the covariates chosen for the propensity score. Comorbidities that are risk factors for influenza infection have also been associated with influenza vaccination; however, we did not include them in the propensity score because all patients in the study were at risk of influenza because of comorbidity based on inclusion criteria.

Seven additional sensitivity analyses were conducted to assess the risk of bias in our study. First, we identified the influenza seasons when the antigen in the vaccine was well matched to the predominant influenza isolate circulating in the study regions.30–39 The hypothesis being that a reduction in the primary outcome would be seen only during such well-matched seasons. Second, we conducted analyses during the noninfluenza season, postulating that the influenza vaccine would have less association with the prespecified outcome in the noninfluenza season compared with the influenza season. Noninfluenza seasons were defined as December 1 to May 31 for the southern hemisphere and June 1 to November 30 for the northern hemisphere (all weeks not included in the influenza season for a particular study year).

Third, the adjusted ORs for each influenza season were combined to create a summary OR. The adjusted ORs were combined to help improve the precision of the estimate and to determine whether there was heterogeneity within the estimate. Our a priori hypothesis to explain possible heterogeneity was differences due to well-matched versus incompletely matched vaccine seasons. A reduction of heterogeneity and a significant test of interaction on the basis of well-matched versus incompletely matched vaccine seasons would increase the confidence in our results. The generalized estimating equation approach was used to account for the correlation between each cohort⁴⁰ because each cohort included similar participants. A summary OR for the noninfluenza seasons was also created. Heterogeneity was tested for the correlated sample. We defined significant heterogeneity as P<0.10.⁴¹

Fourth, we evaluated the effect of influenza vaccination history over several influenza seasons on our primary outcome. We hypothesized that evidence of mounting immunity and/or persistent immunity would increase the confidence in our results. Fifth, because we
did not have information on the date of influenza vaccination for the patients and simply classified patients as influenza vaccinated or not vaccinated for a given season, we could have introduced immortal time bias into the analyses.32 We therefore restricted analyses of the primary outcome to patients who had study visit dates during the 3 months when the vaccine was most likely to have been given (ie, October, November, and December in the northern hemisphere and April, May, and June in the southern hemisphere). We hypothesized that if the point estimates in these analyses were similar to the point estimates from the full analyses, the presence of immortal time bias would be less likely.

Sixth, we examined the association between influenza vaccination and all noncardiovascular deaths. Previous studies of influenza vaccination have demonstrated reductions in all-cause mortality of up to 50%, an implausible reduction given that the proportion of deaths caused by influenza is estimated to be 5%.43 This overestimate of vaccine effectiveness has since been attributed to bias.44 Thus, we hypothesized that any reduction in mortality associated with the influenza vaccine beyond 5% would be due to bias.

Finally, we evaluated the impact of the pneumococcal vaccine on major adverse vascular events. One study found an association between pneumococcal vaccination and risk of cardiovascular outcomes; the authors hypothesized that pneumococcal vaccination may protect against cardiovascular events by reducing the risk of atherosclerosis through the prevention of Streptococcus pneumoniae infection.44 However, this study had several limitations, and others have not confirmed this association.9,12,16,17,45 Thus, we hypothesized that we would not detect an association between pneumococcal vaccination and major adverse vascular events, and if an association was detected, it would likely be due to confounding bias. The model was adjusted for the following covariates: coronary artery disease; diabetes mellitus; hypertension; stroke; admission to a nursing home; use of aspirin, β-blockers, lipid-lowering drugs, angiotensin-converting enzyme inhibitors, or angiotensin II inhibitors; and a propensity score for pneumococcal vaccination that included age, sex, body mass index, ethnicity, education, vitamin use, smoking history, alcohol use, and history of influenza vaccination. Statistical analyses were carried out with SAS version 8.2 (SAS Institute Inc, Cary, NC).

The study sponsor, Boehringer Ingelheim, played no role in the study design, data collection, analysis of the data, interpretation of the data, writing of the report, or decision to submit the paper for publication.

Results

Patient Characteristics

Baseline characteristics of participants in each influenza season, stratified by influenza vaccination status, are presented in Table 1. The proportions of participants receiving the influenza vaccine varied by year, ranging from 28% during the 2005 to 2006 influenza season to 47% during the 2006 to 2007 influenza season. Influenza-vaccinated participants were more likely to be older, to be male, to have known coronary artery disease, to smoke, and to receive the pneumococcal vaccine and were less likely to have diabetes mellitus, hypertension, or history of stroke.

Influenza Vaccination and Risk of Major Adverse Vascular Events

In the unadjusted analysis, influenza vaccination was associated with a reduced risk of the primary outcome during 3 influenza seasons when the circulating viruses were well matched with the vaccine antigen: the 2004 to 2005 influenza season (OR, 0.74; 95% CI 0.61–0.90; P = 0.003), the 2005 to 2006 influenza season (OR, 0.76; 95% CI, 0.58–1.0; P = 0.046), and the 2006 to 2007 influenza season (OR, 0.59; 95% CI, 0.48–0.73; P < 0.0001; Table 2). Influenza vaccination was not associated with a reduced risk of the primary outcome during the incompletely matched influenza season.
The summary OR for the 4 adjusted ORs from the influenza seasons was 0.65 (95% CI, 0.58–0.74; P<0.001), and there was statistically significant heterogeneity (P=0.003). Heterogeneity remained when only the 3 well-matched influenza seasons were combined (summary OR, 0.60; 95% CI, 0.52–0.68; P for heterogeneity=0.09). However, the interaction test with the incompletely matched influenza season (adjusted OR, 0.96; 95% CI, 0.73–1.27) was significant (interaction P=0.003). The summary OR for the 4 adjusted ORs from the noninfluenza seasons was 0.66 (95% CI, 0.57–0.76; P<0.0001; P for heterogeneity=0.11).

Patient’s influenza vaccination history appeared to influence the primary outcome (Table 4). During the 2006 to 2007 influenza season, influenza-vaccinated patients with a history of prior influenza vaccination during the previous 2 influenza seasons appeared to have fewer major adverse vascular events than those without a history of vaccination (ie, evidence of mounting immunity; P for trend=0.0096). Similarly, non–influenza-vaccinated patients with a history of influenza vaccination appeared to have fewer major adverse vascular events than those with no vaccination history during the previous influenza seasons (ie, evidence of persistent immunity; P for trend=0.0085).

### Table 2. Association Between Influenza Vaccination and Risk of Major Adverse Vascular Events During the Influenza Season

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Primary Outcome in Influenza-Vaccinated Subjects, n (%)</th>
<th>Primary Outcome in Non–Influenza-Vaccinated Subjects n (%)</th>
<th>Unadjusted OR (95% CI)</th>
<th>P</th>
<th>Adjusted* OR (95% CI)</th>
<th>P</th>
<th>Matched†</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003–2004</td>
<td>96/8566 (1.1)</td>
<td>142/13 697 (1.0)</td>
<td>1.08 (0.83–1.40)</td>
<td>0.55</td>
<td>0.96 (0.73–1.27)</td>
<td>0.79</td>
<td>H1N1–match</td>
</tr>
<tr>
<td>2004–2005</td>
<td>155/11 624 (1.3)</td>
<td>274/15 253 (1.8)</td>
<td>0.74 (0.61–0.90)</td>
<td>0.003</td>
<td>0.62 (0.50–0.77)</td>
<td>&lt;0.0001</td>
<td>H1N1–match</td>
</tr>
<tr>
<td>2005–2006</td>
<td>70/7499 (0.93)</td>
<td>231/18 876 (1.2)</td>
<td>0.76 (0.58–1.00)</td>
<td>0.046</td>
<td>0.69 (0.53–0.91)</td>
<td>0.009</td>
<td>H1N1–match</td>
</tr>
<tr>
<td>2006–2007</td>
<td>145/12 441 (1.2)</td>
<td>269/13 795 (2.0)</td>
<td>0.59 (0.48–0.73)</td>
<td>&lt;0.0001</td>
<td>0.52 (0.42–0.65)</td>
<td>&lt;0.0001</td>
<td>H1N1–match</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval.

*Adjusted by propensity score for influenza vaccination (body mass index, age, sex, ethnicity, education, vitamin use, smoking history, alcohol use, history of pneumococcal vaccination), history of coronary artery disease, diabetes mellitus, hypertension, stroke, admission to a nursing home, or use of aspirin, β-blocker, lipid lowering drugs, ACE inhibitor or angiotensin II inhibitor.

†A match was as the majority (≥50%) of the circulating influenza virus being antigenically similar to the vaccine strain.

‡The predominant influenza isolate(s) circulating in the study regions.30–39

![Figure 1. Association between influenza vaccination and the risk of the primary outcome during (A) the influenza season and (B) the noninfluenza season.](image_url)
Restricting analyses of the association between influenza vaccination and major adverse vascular events to study visits during the 3 months when influenza vaccination was most likely to occur to evaluate the possible impact of immortal time bias revealed point estimates similar to those in the full analyses: 2004 to 2005 influenza season, 14 of 813 for vaccinated patients versus 44 of 1181 for nonvaccinated patients (OR, 0.45; 95% CI, 0.25–0.83); 2005 to 2006 influenza season, 9 of 673 for vaccinated patients versus 28 of 1397 for nonvaccinated patients (OR, 0.66; 95% CI, 0.31–1.41); and 2006 to 2007 influenza season, 3 of 59 for vaccinated patients versus 24 of 101 for nonvaccinated patients (OR, 0.17; 95% CI, 0.05–0.60).

Influenza Vaccination and Risk of Noncardiovascular Deaths
In adjusted analysis, noncardiovascular death was associated with the influenza vaccine; associated reductions in risk ranged from 73% to 79% (Table 5). Adjusted analysis could not be performed for the 2003 to 2004 influenza season because of too few deaths during this time period.

Pneumococcal Vaccination and Risk of Major Adverse Vascular Events
There was no association between pneumococcal vaccination and the primary outcome during any of the influenza seasons (Figure 2).

Table 3. Association Between Influenza Vaccination and Risk of the Major Adverse Vascular Events During the Noninfluenza Season

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Primary Outcome in Influenza-Vaccinated Subjects, n (%)</th>
<th>Primary Outcome in Non–Influenza-Vaccinated Subjects, n (%)</th>
<th>Unadjusted OR (95% CI) P</th>
<th>Adjusted* OR (95% CI) P</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003–2004</td>
<td>80/8550 (0.94)</td>
<td>144/13 699 (1.05)</td>
<td>0.89 (0.68–1.17) 0.40</td>
<td>0.81 (0.61–1.09) 0.16</td>
</tr>
<tr>
<td>2004–2005</td>
<td>112/11 581 (0.97)</td>
<td>208/15 187 (1.4)</td>
<td>0.70 (0.56–0.89) 0.003</td>
<td>0.64 (0.50–0.83) 0.0005</td>
</tr>
<tr>
<td>2005–2006</td>
<td>66/7495 (0.88)</td>
<td>214/18 859 (1.1)</td>
<td>0.77 (0.59–1.0) 0.07</td>
<td>0.74 (0.56–0.98) 0.04</td>
</tr>
<tr>
<td>2006–2007</td>
<td>87/12 383 (0.70)</td>
<td>165/13 691 (1.2)</td>
<td>0.58 (0.45–0.75) &lt;0.0001</td>
<td>0.50 (0.38–0.67) &lt;0.0001</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval.

*Adjusted by propensity score for influenza vaccination (body mass index, age, sex, ethnicity, education, vitamin use, smoking history, alcohol use, history of pneumococcal vaccination), history of coronary artery disease, diabetes mellitus, hypertension, stroke, admission to a nursing home, or use of aspirin, β-blocker, lipid-lowering drug, angiotensin-converting enzyme inhibitor, or angiotensin II inhibitor.

Influenza Vaccination History on Major Adverse Vascular Events in Influenza-Vaccinated and Nonvaccinated Patients

<table>
<thead>
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<tr>
<td>Effect of mounting immunity</td>
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<tr>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>2006–2007 influenza season, n (%)</td>
<td>11 093 (98.23)</td>
<td>200 (1.77)</td>
</tr>
<tr>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td></td>
<td>1877 (99.05)</td>
<td>18 (0.95)</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>1247 (99.05)</td>
<td>12 (0.95)</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>5211 (98.8)</td>
<td>64 (1.2)</td>
</tr>
<tr>
<td>−</td>
<td>−</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>13 111 (98.79)</td>
<td>161 (1.21)</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>1637 (98.73)</td>
<td>21 (1.27)</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>5786 (99.16)</td>
<td>49 (0.84)</td>
</tr>
<tr>
<td>Effect of persistent immunity</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>2006–2007 influenza season, n (%)</td>
<td>11 093 (98.23)</td>
<td>200 (1.77)</td>
</tr>
<tr>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td></td>
<td>1462 (96.31)</td>
<td>56 (3.69)</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>544 (98.91)</td>
<td>6 (1.09)</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>5211 (98.8)</td>
<td>64 (1.2)</td>
</tr>
<tr>
<td>−</td>
<td>−</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>13 111 (98.79)</td>
<td>161 (1.21)</td>
</tr>
<tr>
<td>+</td>
<td>−</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>5506 (98.74)</td>
<td>70 (1.26)</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td>5786 (99.16)</td>
<td>49 (0.84)</td>
</tr>
</tbody>
</table>
In this large, prospective, multinational study, on initial analyses, we found influenza vaccination to be associated with a reduced risk of major adverse vascular events during the influenza season compared with no influenza vaccination when the predominant circulating influenza virus was well matched to the influenza antigen contained in the influenza vaccine. These findings support the results of a meta-analysis of 2 small clinical trials and a recent small open-label trial that have attempted to address whether influenza vaccination reduces major adverse vascular events.\(^1,18\)\textendash{}21 Although the meta-analysis of the 2 trials, in which there were very few events, showed no statistically significant difference in acute myocardial infarction (16 of 476 versus 19 of 483 for nonvaccinated participants; risk ratio, 0.84; 95% CI, 0.44\textendash{}1.64) or cardiac death (11 of 476 versus 26 of 483 for nonvaccinated participants; risk ratio, 0.51; 95% CI, 0.15\textendash{}1.76), the point estimates tended to show protection.\(^1,20\) A recent randomized trial evaluated whether the influenza vaccine prevented major adverse vascular events in patients with a history of acute coronary syndromes. In this study, there were fewer events in the vaccinated group (21 of 221) compared with nonvaccinated patients (42 of 218) 1 year after enrollment (unadjusted hazard ratio, 0.70; 95% CI, 0.57\textendash{}0.86); however, the small size and open-label design may have introduced bias into the results. Indeed, the vaccinated group tended to be younger and were more likely to receive timely revascularization for their initial acute coronary syndrome and to be on an angiotensin-converting enzyme inhibitor, or angiotensin II inhibitor.\(^21\)

We were able to evaluate outcomes over 4 influenza and noninfluenza seasons. Indeed, the fact that we found an association between influenza vaccination and major adverse vascular events during well-matched influenza seasons and not for the incompletely matched year (2003\textendash{}2004 influenza season; adjusted OR, 0.96; 95% CI, 0.73\textendash{}1.27; \(P=0.79\)) increased the confidence in our results. It should be noted that there is evidence that incompletely matched influenza vaccine still provides protection against laboratory-confirmed influenza in the elderly;\(^44\) thus, some reduction in vaccine effectiveness against laboratory-confirmed influenza during the incompletely matched 2003 to 2004 influenza season has been observed in patients with high-risk medical conditions, including diabetes mellitus and known vascular disease.\(^47\) This could explain why there was no association between the influenza vaccine and our primary outcome during the incompletely matched influenza season.

### Table 5. Association Between Influenza Vaccination and Risk of Noncardiovascular Death During the Influenza Season

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Outcome in Influenza-Vaccinated Subjects, n (%)</th>
<th>Outcome in Non–Influenza-Vaccinated Subjects, n (%)</th>
<th>Unadjusted OR (95% CI)</th>
<th>(P)</th>
<th>Adjusted* OR (95% CI)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003\textendash{}2004</td>
<td>Noncardiovascular deaths 1/9210 (0.01)</td>
<td>12/15 015 (0.08)</td>
<td>0.14 (0.02\textendash{}1.04)</td>
<td>0.06</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Cancer deaths 0/9377 (0)</td>
<td>5/15 271 (0.03)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Deaths resulting from other causes 1/9407 (0.05)</td>
<td>7/15 292 (0.01)</td>
<td>0.23 (0.03\textendash{}1.89)</td>
<td>0.17</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>2004\textendash{}2005</td>
<td>Noncardiovascular deaths 28/12 443 (0.23)</td>
<td>89/16 562 (0.54)</td>
<td>0.42 (0.27\textendash{}0.64)</td>
<td>0.0001</td>
<td>0.26 (0.16\textendash{}0.40)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Cancer deaths 12/16 606 (0.10)</td>
<td>46/16 742 (0.27)</td>
<td>0.35 (0.18\textendash{}0.65)</td>
<td>0.001</td>
<td>0.20 (0.10\textendash{}0.39)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Deaths resulting from other causes 16/16 656 (0.13)</td>
<td>43/16 757 (0.26)</td>
<td>0.49 (0.28\textendash{}0.87)</td>
<td>0.015</td>
<td>0.33 (0.18\textendash{}0.60)</td>
<td>0.0004</td>
</tr>
<tr>
<td>2005\textendash{}2006</td>
<td>Noncardiovascular deaths 7/8051 (0.09)</td>
<td>75/20 313 (0.37)</td>
<td>0.23 (0.11\textendash{}0.51)</td>
<td>0.0002</td>
<td>0.21 (0.10\textendash{}0.46)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>Cancer deaths 5/8087 (0.06)</td>
<td>40/20 419 (0.20)</td>
<td>0.32 (0.12\textendash{}0.80)</td>
<td>0.015</td>
<td>0.27 (0.10\textendash{}0.69)</td>
<td>0.0065</td>
</tr>
<tr>
<td></td>
<td>Deaths resulting from other causes 2/8094 (0.02)</td>
<td>35/20 457 (0.17)</td>
<td>0.14 (0.03\textendash{}0.60)</td>
<td>0.008</td>
<td>0.14 (0.03\textendash{}0.58)</td>
<td>0.0070</td>
</tr>
<tr>
<td>2006\textendash{}2007</td>
<td>Noncardiovascular deaths 34/13286 (0.26)</td>
<td>99/14724 (0.67)</td>
<td>0.38 (0.26\textendash{}0.56)</td>
<td>&lt;0.0001</td>
<td>0.27 (0.18\textendash{}0.41)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Cancer deaths 16/13294 (0.12)</td>
<td>60/14723 (0.41)</td>
<td>0.29 (0.17\textendash{}0.51)</td>
<td>&lt;0.0001</td>
<td>0.17 (0.10\textendash{}0.31)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Deaths resulting from other causes 18/13307 (0.14)</td>
<td>39/14716 (0.27)</td>
<td>0.51 (0.29\textendash{}0.89)</td>
<td>0.018</td>
<td>0.47 (0.25\textendash{}0.86)</td>
<td>0.0137</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval.

*Adjusted by propensity score for influenza vaccination (body mass index, age, sex, ethnicity, education, vitamin use, smoking history, alcohol use, history of pneumococcal vaccination), history of coronary artery disease, diabetes mellitus, hypertension, stroke, admission to a nursing home, or use of aspirin, \(\beta\)-blocker, lipid-lowering drugs, angiotensin-converting enzyme inhibitor, or angiotensin II inhibitor.

### Figure 2. Association between pneumococcal vaccination and risk of the primary outcome during the influenza season.
The findings of an association between influenza vaccination and reduced major adverse vascular events must be tempered by the facts that the effect sizes during the influenza and noninfluenza seasons were similar and that the summary ORs in the influenza and noninfluenza seasons were almost identical. One possible explanation is that influenza vaccination protects against major adverse vascular during the noninfluenza season because of a carryover effect; influenza infection may precipitate a cascade of events that could lead to eventual, but not immediate, vascular events, particularly cardiovascular death. An alternative and more likely explanation for these results is bias. To the best of our knowledge, no other study has described the association between influenza vaccination and risk of vascular events during nonmatched influenza seasons. In fact, only 1 other study stratified the effect of the influenza vaccine on vascular outcomes over multiple years. This study, based in the United States, found an association between influenza vaccination and hospitalization for cardiac disease during the 1998 to 1999 influenza season (adjusted OR, 0.81; 95% CI, 0.73–0.89) and 1999 to 2000 influenza season (adjusted OR, 0.81; 95% CI, 0.73–0.89). In both influenza seasons, the circulating influenza viruses were well matched with the corresponding vaccine. The association between vaccination and cardiac events outside the influenza seasons was not reported.

Prior observational studies investigating the association between influenza vaccination and major adverse vascular events have been conflicting. These discrepant results are likely explained by bias; studies of influenza vaccination are at high risk of bias because of fundamental differences between individuals who are vaccinated and those who are not. This bias is sometimes referred to as health vaccinee bias or healthy user bias because vaccinated individuals tend to be healthier than nonvaccinated individuals. Recommended strategies to reduce bias in studies of influenza vaccination include adjusting for confounders not typically found in large databases; exploring the unique seasonality of influenza, which enables the detection of changing effect size over matched and unmatched seasons and when influenza is and is not circulating; and avoiding the use of all-cause mortality as an outcome.

In our study, we prospectively collected covariates and were therefore able to obtain information on variables seldom found in databases. This is in contrast to most other studies that either collected data from administrative and clinical databases or collected few covariates beyond age, sex, comorbidities, and medications. Confidence in our ability to adjust for important confounders increased when we did not detect an association between pneumococcal vaccination and major adverse vascular events. We hypothesized that if an association were detected, it would likely be due to confounding bias given the general lack of effectiveness of the polysaccharide pneumococcal vaccine against other outcomes such as pneumonia; the majority of studies investigating this issue have not found an association. Our primary outcome was focused and relevant to our study. Furthermore, our primary outcome was prospectively obtained and adjudicated blindly by a central committee. This is in contrast to many of the other studies that depended on databases for measurement of outcomes. However, to critically evaluate our study for risk of bias, we looked at the associated effect of influenza vaccination on noncardiovascular death, a very nonspecific outcome. Influenza mortality is thought cause ~5% of all deaths in the elderly during the winter months. Thus, we hypothesized that the effect size should not be >5%. In fact, the effect size in our study was far greater than 5% and ranged from 73% to 79%, which raises questions about confounding bias despite all efforts to control for bias in our study design.

We were also unable to confirm vaccination history with medical records, and some participants may have been misclassified, although vaccination history ascertained by self-report in adults has a high sensitivity and specificity. We also did not know the date of influenza vaccination, which could lead to immortal time bias. Sensitivity analyses restricting the sample to study visits when influenza vaccination was most likely to occur showed point estimates consistent with the full analyses assessing the association between influenza vaccination and major adverse vascular events, making immortal time bias less likely. We have also assumed that the influenza vaccine administered for a given season contained the antigens recommended by the World Health Organization. We did not perform active surveillance for influenza throughout the study period and therefore did not have individual-level influenza infection data on participants, an important limitation of all the similar studies that have been conducted. Although our definition of influenza season captured the peak influenza activity for all participating countries, sporadic influenza activity can occur year round. We defined matching as either well matched or incompletely matched between the vaccine and the predominant circulating influenza virus worldwide, although there were likely regional differences in the circulating strain. For example, during the 2004 to 2005 influenza season, the predominant globally circulating H3N2 virus matched the vaccine virus (A/Fujian/411/2002-like H3N2); however, the majority of H3N2 isolates circulating in the United States were A/California/7/2004, which did not match the vaccine virus, biasing the results toward the null hypothesis. In addition, although the external validity of this study is high because of the multicountry enrollment and follow-up over multiple influenza seasons, its generalizability may be limited by the fact that the data were obtained in a trial setting.

Despite the many strengths of our study, it remains uncertain whether the influenza vaccine reduces the risk of major adverse vascular events. It seems unlikely that any observational study will be able to overcome the many potential areas of bias associated with this clinical question, and this question will be definitively answered only with a trial design. Definitively addressing whether the influenza vaccine reduces the risk of major adverse vascular events is essential; <50% of patients in this study were vaccinated despite clear guideline recommendations to vaccinate this at-risk group, and large amounts of resources are necessary to significantly increase vaccine coverage. The question is particularly important to address because the efficacy and effectiveness of the influenza vaccine for other clinically
important outcomes in people ≥65 years of age are also uncertain according to a recent Cochrane review. Thus, a large randomized placebo-controlled trial is needed to definitively address whether influenza vaccination reduces the risk of major adverse vascular events.

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Disclosures
None.

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CLINICAL PERSPECTIVE
It remains uncertain whether the influenza vaccine is associated with a reduced risk of vascular events, despite at least 10 observational studies and 3 small randomized controlled trials investigating this association. The existing observational studies were limited by small size, involved only a single influenza season, and/or were at risk of significant bias resulting from study design and the presence of confounding. The 3 randomized controlled trials were small with few event rates, precluding any definitive conclusions. We therefore performed an observational study using data from a large multinational trial of patients at high risk for vascular events involving 31 546 participants from 733 centers in 40 countries. Although initial analyses suggest that influenza vaccination was associated with a reduced risk of major adverse vascular events during influenza seasons when the influenza vaccine matched the circulating virus, detailed sensitivity analyses revealed that evidence of risk of confounding bias remained. A randomized trial is needed to definitively address this question.
Influenza Vaccination and Major Adverse Vascular Events in High-Risk Patients
Jennie Johnstone, Mark Loeb, Koon K. Teo, Peggy Gao, Leanne Dyal, Lisheng Liu, Alvaro Avezum, Ernesto Cardona-Munoz, Peter Sleight, Robert Fagard and Salim Yusuf
on behalf of the Ongoing Telmisartan Alone and in Combination With Ramipril Global EndPoint Trial (ONTARGET) and Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease (TRANSCEND) Investigators

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