Influenza vaccination reduces cardiovascular events in patients with acute coronary syndrome

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Aims
Influenza infection has been shown to accentuate the progression of atherosclerosis and precipitate the occurrence of acute coronary syndrome (ACS). However, the protective effects of the influenza vaccine on cardiovascular events are still inconclusive.

Methods and results
The study was a prospective randomized open with blinded endpoint (PROBE) study. The 439 patients who had been admitted due to ACS within 8 weeks were enrolled and randomly allocated to receive inactivated influenza vaccine in the vaccine group and no treatment in the control group. All patients were treated with the standard therapy including revascularization according to primary cardiologists. The primary endpoint, which was the combined major cardiovascular events, including death, hospitalization from ACS, hospitalization from heart failure, and hospitalization from stroke, occurred less frequently in the vaccine group than the control group [9.5 vs. 19.3%, unadjusted HR 0.70 (0.57–0.86), \( P = 0.004 \)]. There was no significant difference in the incidence of cardiovascular death between the vaccine and control groups [2.3 vs. 5.5%, unadjusted HR 0.39 (0.14–1.12), \( P = 0.088 \)].

Conclusion
The influenza vaccine reduced major cardiovascular events in patients with ACS. Therefore, it should be encouraged as a secondary prevention in this group of patients.

Keywords
Influenza • Vaccine • Acute coronary syndrome • Myocardial infarction • Prevention

Introduction
Atherosclerosis is a chronic inflammatory disease of the arteries associated with pro-inflammatory lipid abnormalities. Local inflammation in the arterial intima promotes the initiation, progression, and rupture of atherosclerotic lesions causing coronary thrombosis. There have been studies suggesting the role of chronic indolent infections, such as periodontal infection or persistent Chlamydia pneumoniae infection in the chronic atherosclerotic process. Failure of clinical trials using antibiotics against C. pneumoniae to prevent cardiovascular events in patients who survived acute myocardial infarction (AMI) and in those after coronary stent replacement has led to a decreased interest in the role of infection in cardiovascular disease. However, in contrast to chronic infection, acute infection may trigger more severe and abrupt inflammatory change in atherosclerotic plaque and may result in plaque destabilization and rupture, thus causing acute coronary syndromes (ACSs) over a few days or weeks.

Acute influenza infection has been shown to accentuate the progression of atherosclerosis and precipitate the occurrence of ACS. There have been several case–control studies that demonstrated the association between influenza infection and ACS. Several case–control studies have also demonstrated the beneficial effects of the influenza vaccine in coronary artery disease (CAD) patients. However, previous randomized clinical trials showed the inconclusive effects on cardiovascular death. Therefore, we conducted this study to evaluate the effects of the influenza vaccine on cardiovascular outcomes in ACS patients.

Methods
This was a prospective randomized open with blinded endpoint (PROBE) study. The randomization was 1:1 using a computer-
generated sequence in block randomization size of 4. The study was approved by the Chiang Mai University Ethics Committee and was done in accordance with the Helsinki Declaration and Good Clinical Practice.

Study population and interventions
Patients, who had been admitted due to ACS within 8 weeks during November 2007 to October 2008, were screened and they were recruited into the study if they were older than 50 years old and agreed to participate. Patients with the serum creatinine level >2.5 mg/dL, significant liver disease, haemoglobin level <10 g/dL, cancer or had life expectancy <1 year, had contraindications to or had previous influenza vaccination were excluded. A single-dose intramuscular injection of 0.5 mL of split, inactivated influenza vaccine was given to patients in the vaccine group. All patients were given the standard ACS treatment, including coronary revascularization, according to their primary cardiologists. The study flow is shown in Figure 1.

Outcomes
Study nurses, who were blinded to the subjects’ treatment group, were responsible for data collection which included monthly telephone interview and hospital visit inquiries. The data on symptoms, hospitalization, and treatments were collected. The follow-up duration was 12 months. The primary endpoint was any major adverse cardiovascular events (MACEs), including death, hospitalization for ACS, hospitalization for heart failure, hospitalization for stroke between randomization and 12 months. The secondary endpoint was cardiovascular death at 12 months. The endpoints were verified by cardiologists who were unaware of the patients’ treatment group.

Definition
Acute ST-segment elevation myocardial infarction (STEMI) was defined as chest pain longer than 20 min with the ECG demonstrated ST-segment elevation in at least two consecutive leads. Non ST-segment elevation myocardial infarction (NSTEMI) was defined as chest pain longer than 20 min and rising of cardiac troponin or CK-MB without ST-segment elevation. Unstable angina (UA) was defined as chest pain at rest without evidence of rising of cardiac troponin or CK-MB. NSTEMI and UA were defined as non-ST segment elevation acute coronary syndrome (NSTEACS).

Hospitalization for ACS was defined as hospitalization for acute STEMI, NSTEMI, or UA. Hospitalization for heart failure was defined as hospitalization from clinical signs or symptoms of heart failure requiring intravenous diuretics. Hospitalization for stroke was defined as hospitalization of sudden onset of neurological deficit and confirmed by imaging. Cardiovascular death was defined as death due to ACS, sudden death, heart failure, or stroke.

Statistical analysis
All analyses were done on intention to treat basis. Results were presented as mean ± SD for continuous variables and as percentage for categorical data. Continuous data were compared (all tests two-sided) by unpaired t-test. Categorical data were compared using χ² or Fisher’s exact test, where appropriate. Survival curves were assessed by the Kaplan–Meier method and compared using a log-rank test. Hazard ratios (HRs) and 95% CI were calculated by the Cox proportional hazards model. The variables included in the adjusted model predicting MACE were age, sex, serum creatinine, medication, and coronary revascularization. We assessed interaction terms between the influenza vaccination and variables including age, sex, diabetes, serum creatinine, type of ACS, and coronary revascularization to determine if there was a different effect of vaccination between groups. All statistical analyses were performed using SPSS (SPSS Statistic 17.0, SPSS, Inc., Chicago, IL, USA). A two-sided test was used to indicate statistical significance at a P-value of < 0.05.

The sample size calculation was based on 1-year MACE incidence from the Flu Vaccination for Acute Coronary Syndrome (FLUVACS) study. Under the assumption of frequency of events of 37% in the controls, and of 22% in the active arm, we estimated the sample size of each group to 200 patients [for significant level of <5% and power (1−b) of 80%]. The rate of loss to follow-up was estimated at 5%, and we therefore planned to enroll at least 210 patients per group.

Results
A total of 641 ACS patients were screened and 442 patients were recruited into the study but 3 of them were excluded due to screening error (diagnosis of ACS was not confirmed). The 159 patients with STEMI, 206 with NSTEMI, and 74 with UA were
included in the study. The 221 patients were randomized to the vaccine group and 218 patients were randomized to the control group. The median time of follow-up was 360 (range 3–365) days. One patient in each group was lost to follow-up.

The baseline characteristics were not significantly different between the two groups regarding to age, sex, underlying disease, type of ACS, and coronary revascularization (Table 1). The mean age was 66 ± 9 year old. Patients were predominantly male. About one-third had STEMI, of which 75% had received reperfusion therapy. For patients with NSTEACS, 33.3% of them underwent revascularization during admission, 15.7% underwent revascularization after index admission, and 48.9% did not receive revascularization. The left ventricular ejection fraction was comparable between groups. Majority of the patients received standard medications, including aspirin, β-blocker, and statin (97.3, 74, and 84.2%, respectively). Patients in the vaccine group received angiotensin-converting enzyme inhibitor (ACE-I) more often than those in control group (64.2 vs. 52.8% for the vaccine vs. control group, respectively, \( P = 0.02 \) (Table 1). Patients who received ACE-I had lower levels of serum creatinine than patients who did not receive ACE-I (1.1 ± 0.3 vs. 1.3 ± 0.4 mg/dL, \( P < 0.001 \)). There was no hospitalization related to side effects of the influenza vaccine.

### The effects of the influenza vaccine on cardiovascular outcome

The patients in the vaccine group had lower rate of MACE than those in the control group [9.5 vs. 19.3%, unadjusted HR 0.70 (0.57–0.86), \( P = 0.004 \)] (Table 2). The rate of hospitalization for ACS was significantly lower in the vaccine group than in the control group [4.5 vs. 10.6%, unadjusted HR 0.73 (0.55–0.91), \( P = 0.032 \)]. Of 36 patients whom had been hospitalized from ACS, 21 were diagnosed NSTEMI (15 in the control group and 6 in the vaccine group) and the others were diagnosed UA (8 in the control group and 4 in the vaccine group). The rate of hospitalization for heart failure was not significantly different between the control and vaccine group [1.8 vs. 4.6%, unadjusted RR 0.9 (0.49–1.01), \( P = 0.111 \)]. The total mortality also did not differ between two groups [2.7 vs. 5.5% in the vaccine vs. control group, unadjusted HR 0.73 (0.50 to 1.03), \( P = 0.156 \)]. Among 14 patients who died during follow-up, 13 of them died from cardiovascular diseases and 1 patient in the vaccine group died from bladder carcinoma. There was no significant difference in the incidence of cardiovascular death between the vaccine and control groups [2.3 vs. 5.5%, unadjusted HR 0.39 (0.14–1.12), \( P = 0.088 \)]. The Kaplan–Meier curves of cumulative event-free survival for MACE are shown in Figure 2. The effects of vaccination on MACE were adjusted with age, sex, serum creatinine, ACE-I treatment, and coronary revascularization. Patients in the vaccine group had significantly lower incidence of MACE and hospitalization for ACS than patients in the control group after adjusting with the above parameters [adjusted HR 0.67 (0.51–0.86), \( P = 0.005 \) and adjusted HR 0.68 (0.47–0.98), \( P = 0.039 \) for MACE and hospitalization for ACS, respectively] (Table 2). The effects of vaccination on MACE were consistent across all subgroups of the patients (Figure 3).

### Discussion

The association between influenza infection and ACS has been demonstrated in several studies. This study demonstrated a significant reduction in MACE in ACS patients receiving the influenza vaccine compared with controls with an HR of 0.70 (0.57–0.86), \( P = 0.004 \). The beneficial effects of the influenza vaccine persisted after adjustment for variables affecting MACE and also remained in every subgroup of the patients.

Influenza infection may be a very important precipitating factor of ACS via several potential mechanisms. Acute severe inflammation during acute influenza infection can precipitate plaque rupture and trigger coagulation cascade which are the
principal pathophysiology of ACS. In addition, the association of influenza virus and progression of atherosclerosis have been demonstrated in the animal model.10

The seasonal patterns of influenza infection in tropical regions are different from temperate zones. Despite the difference in seasonality, the association between influenza infection and ACS has been demonstrated from recent studies.12,24 Kuanprasert et al.24 have demonstrated a high prevalence of influenza infection proceeding the occurrence of ACS using clinical and serological criteria.

Immune response to the influenza vaccine in CAD patients has been shown to be comparable with healthy control.25 Therefore the influenza vaccine should be able to prevent influenza infection in these patients and consequently be able to prevent the occurrence of ACS. There have been two randomized-controlled studies regarding the effects of the influenza vaccine in CAD patients.19,20 The FLUVACS recruited 200 AMI patients and 101 planned percutaneous coronary intervention (PCI) patients.20 The study demonstrated the significant reduction in cardiovascular mortality and MACEs but the subgroup analysis showed that the benefit was confined to AMI patients, but did not extend to the planned PCI patients. Another study, the FLUCAD study recruited the CAD patients with optimal treatment, in which 25.5% of them were ACS patients and 44.6% of the patients received PCI. The FLUCAD study demonstrated that the influenza vaccine had no effects on cardiovascular death although the patients receiving influenza vaccine had a significantly lower rate of coronary ischaemic events than the control group.19 The disparity between the FLUVACS and the FLUCAD study may be contributed by the difference in study population. The FLUVACS recruited 200 AMI patients and 101 planned percutaneous coronary intervention (PCI) patients.20 The study demonstrated the significant reduction in cardiovascular mortality and MACEs but the subgroup analysis showed that the benefit was confined to AMI patients, but did not extend to the planned PCI patients. Another study, the FLUCAD study recruited the CAD patients with optimal treatment, in which 25.5% of them were ACS patients and 44.6% of the patients received PCI. The FLUCAD study demonstrated that the influenza vaccine had no effects on cardiovascular death although the patients receiving influenza vaccine had a significantly lower rate of coronary ischaemic events than the control group.19 The disparity between the FLUVACS and the FLUCAD study may be contributed by the difference in study population. The FLUVACS study comprised a higher proportion of ACS patients than the FLUCAD study, therefore the patients in the control group had higher cardiovascular mortality rate than the control group in the FLUCAD study and the patients in the FLUVACS study had more beneficial effects from the influenza vaccine. Our study population was the ACS patients with lower cardiovascular event rate than the FLUVACS study but higher than the FLUCAD study. In this population, influenza vaccination significantly decreased the MACE rate and non-significantly decreased cardiovascular mortality. These findings from the FLUVACS, the FLUCAD and our study might imply that with the higher risk of the patients, the greater the benefits from the influenza vaccine were to be expected.

Patients with ACS had a high recurrent cardiovascular event rate and several treatment modalities have been demonstrated to prevent such recurrence, including antiplatelet, β-blocker, ACE-I, and statin. Our study demonstrated that in patients with optimal medical therapy, the influenza vaccination can prevent 1 MACE in every 10 vaccinated patients. Previous studies have shown that the cost-benefit and cost-saving of the influenza vaccine was comparable with β-blocker and statin for secondary prevention.26 The safety profile of the influenza vaccine has been shown to be excellent in several studies including our study. The beneficial effects of the influenza vaccine, the cost-effectiveness, and cost-saving have led to the recommendation of annual influenza vaccination as a secondary prevention in patients with CAD. Nevertheless, the vaccine

### Table 2: Effects of the influenza vaccine on major adverse cardiovascular events

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Vaccine (n = 221)</th>
<th>Control (n = 218)</th>
<th>Unadjusted HR (95% CI)</th>
<th>P-value (unadjusted HR)</th>
<th>Adjusted HR (95% CI)</th>
<th>P-value (adjusted HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE, n (%)</td>
<td>21 (9.5)</td>
<td>42 (19.3)</td>
<td>0.70 (0.57–0.86)</td>
<td>0.004</td>
<td>0.67 (0.51–0.86)</td>
<td>0.005</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>6 (2.7)</td>
<td>12 (5.5)</td>
<td>0.73 (0.50–1.03)</td>
<td>0.156</td>
<td>0.62 (0.34–1.12)</td>
<td>0.113</td>
</tr>
<tr>
<td>Hospitalization for ACS, n (%)</td>
<td>10 (4.5)</td>
<td>23 (10.6)</td>
<td>0.73 (0.55–0.91)</td>
<td>0.032</td>
<td>0.68 (0.47–0.98)</td>
<td>0.039</td>
</tr>
<tr>
<td>Hospitalization for HF, n (%)</td>
<td>4 (1.8)</td>
<td>10 (4.6)</td>
<td>0.69 (0.49–1.01)</td>
<td>0.111</td>
<td>0.62 (0.19–2.04)</td>
<td>0.136</td>
</tr>
<tr>
<td>Hospitalization for stroke, n (%)</td>
<td>1 (0.5)</td>
<td>0</td>
<td>—</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Adjusted hazard ratios were adjusted with age, sex, serum creatinine, treatment with angiotensin-converting enzyme inhibitors, and coronary revascularization. Hospitalization for ACS, hospitalization for acute coronary syndrome; hospitalization for HF, hospitalization for heart failure.

![Figure 2](https://academic.oup.com/eurheartj/article-abstract/32/14/1730/527838/261471730527838)
coverage rate is still low. There are many barriers causing low coverage of vaccine including, lack of awareness among patients and physicians, fear of side effects, and availability of the vaccine. Extensive educational programmes and improved accessibility of vaccine should help maximize the benefit of the influenza vaccine for high-risk patients.

There are some limitations in this study. The open-label design of the study may have compromised the validity of the study by crossing-over to the vaccination group from the control group or the bias of the physicians towards more invasive strategies treatment of ACS in the control group. However, there was no cross-over occurring in any patients during the study and none of the patients received additional vaccine. The treatment strategies for ACS were planned before the patient recruitment into the study, therefore, they were not interfered by the assigned treatment. Although the baseline characteristics of the patients may have favoured the vaccine group, the risk reduction in the influenza vaccine persisted after multivariate analysis and adjustment with variables that could have effects on the outcomes. In addition, we did not actively survey for occult influenza infection. However, only one patient in the treatment group, but none in the control group, was admitted due to respiratory tract infection without the evidence of concurrent ACS.

**Conclusion**

The influenza vaccine reduced major cardiovascular events in patients with ACS, therefore should be encouraged as a secondary prevention in this group of patients.

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**Conflicts of interest:** None declared.

**References**