

Flu Vaccination in Patients With Acute Coronary Syndromes: Treatment Benefit in Prespecified Subgroups

Ricardo León de la Fuente, Enrique P. Gurfinkel, Diego Toledo and Branco Mautner, on behalf of the group of Estudio FLUVACS

Instituto de Cardiología y Cirugía Cardiovascular, Fundación Favaloro, Buenos Aires, Argentina.

Background. The first prospective clinical Flu Vaccination in Acute Coronary Syndromes (FLUVACS) Trial has provided some evidence that flu vaccination together with standard therapy may be useful during the winter season to reduce the risk of death and major cardiac events in patients with acute myocardial infarction.

Patients and method. Information available in the FLUVACS database was analyzed to evaluate the efficacy of flu vaccination in different subgroups. Logistic regression was used to identify features related with better therapeutic results.

Results. Flu vaccination was effective in reducing the incidence of the composite endpoint (death, nonfatal myocardial reinfarction or recurrent angina prompting urgent revascularization) in most subgroups at 6 months after inclusion. The regression model showed a greater benefit of flu vaccination in patients with no ST-segment elevation or older than 65 years, nonsmokers and patients with a TIMI risk score higher than 6.

Conclusions. Our data suggest that vaccination for secondary prevention of flu during the acute phase of myocardial infarction may be effective in a broad range of patients with acute coronary artery disease, regardless of their initial clinical risk.

Key words: *Myocardial infarction. Infection. Immunology.*

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INTRODUCTION

Data that suggest a clear connection between acute or chronic infectious processes and atherosclerotic disease are widely available.¹ Epidemiological studies

Correspondence: Dr. E.P. Gurfinkel.
Fundación Favaloro.
Avda. Belgrano 1746. (1093) Capital Federal. Argentina.
E-mail: epgurfinkel@ffavaloro.org

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Vacunación antigripal en pacientes con síndromes coronarios agudos: beneficio del tratamiento en diferentes subgrupos

Introducción. El primer ensayo prospectivo sobre vacunación antigripal en pacientes con síndromes coronarios agudos (estudio FLUVACS) demostró que su aplicación durante la época invernal, sumada a la medicación estándar, fue más efectiva para reducir el riesgo de muerte y episodios cardiovasculares mayores en pacientes con infarto agudo de miocardio.

Pacientes y método. Se analizó la información disponible de la base de datos del estudio FLUVACS, para evaluar la eficacia de la vacunación antigripal en diferentes subgrupos de pacientes. Se empleó un método estadístico de regresión logística para determinar qué rasgos estaban relacionados con un mejor resultado terapéutico.

Resultados. La vacunación antigripal fue efectiva para reducir la incidencia del punto final combinado (muerte, infarto no fatal o angina recurrente que requiriera revascularización urgente) en la mayoría de los subgrupos a los 6 meses de seguimiento después de la inclusión. El modelo estadístico de regresión reveló un mayor beneficio con la vacunación antigripal en pacientes sin elevación del segmento ST, en los enfermos mayores de 65 años de edad, en los no fumadores y en pacientes con calificación de riesgo TIMI > 6.

Conclusiones. Los resultados obtenidos en este estudio indican que el uso de la vacunación antigripal como prevención secundaria en pacientes que cursan la fase aguda de un infarto de miocardio podría beneficiar a un amplio grupo de enfermos con este diagnóstico, independientemente del riesgo clínico basal.

Palabras clave: *Infarto de miocardio. Infección. Inmunidad.*

point to an increase in the number of persons who have myocardial infarction and die of cardiovascular disease during the winter season and influenza virus epidemics.^{2,3} Naghavi et al⁴ documented this in a recent observational study of coronary heart disease patients, and Lavallee et al⁵ found a lower incidence of stroke among patients vaccinated against influenza during the winter of 1999-2000 in Paris, France.

Results obtained in the first study of patients treated with antibiotics⁶ strongly suggest that the immune

system may be involved in the development of atherosclerosis, as in any clinical condition involving immunosuppressive therapy. These findings focus attention on B lymphocytes. However, we know there are very few B lymphocytes in atherosclerotic plaques.

Normally, B lymphocytes are activated in the presence of specific antigens, but this seldom occurs spontaneously. This activation highlights the rapid humoral response that follows vaccination. Whether specific or not, this response reflects an immediate migration of subpopulations of those cells capable of responding to the induced stimulus.⁷ In the case of influenza virus antibodies, these cells can be found in peripheral blood one week after vaccination.⁸

Initial results of the Flu Vaccination in Acute Coronary Syndromes (FLUVACS) study were recently published.⁹ These were obtained from a 6-month follow-up after the administration of a single dose of the World Health Organization (WHO) recommended strain for the southern hemisphere winter of 2001.¹⁰ Trial results showed a significant reduction in incidence of the triple endpoint (death, nonfatal myocardial reinfarction and recurrent angina prompting rehospitalization) in patients who received the flu vaccination, compared with those in the control group. Essentially, the benefit was limited to the group with myocardial infarction.¹¹

Patients hospitalized with acute coronary syndromes clearly constitute a heterogeneous group with varied baseline characteristics. Different clinical and biochemical variables and electrocardiographic modifications are associated with different prognoses. Stratification of risk according to baseline characteristics could optimize patient management and help define therapeutic strategies for patients diagnosed as having myocardial infarction,¹² especially for those who would potentially benefit from preventive flu vaccination. We analyzed FLUVACS data to evaluate the prognosis and treatment with flu vaccination in different subgroups of patients with myocardial infarction. These subgroups were defined according to diagnosis on admission of the presence or absence of a range of clinical and electrocardiographic characteristics, some of which are associated with greater clinical risk.

PATIENTS AND METHODS

This was a post-hoc study based on information obtained from the FLUVACS database. Briefly, it was a prospective, multicenter, controlled trial for which patients were randomly recruited during winter 2001. We studied two groups: a clinical group of 200 patients with acute myocardial infarction (AMI), with or without ST-segment elevation, admitted within 72 h of the event. Inclusion criteria were: presenting ECG changes such as ST-segment elevation or depression,

transient ST-segment elevation (15 min) ≥ 0.1 mV, or the sum of T-wave inversion in two contiguous leads from two consecutive measurements with cardiac enzyme elevation (total creatine kinase [CK] above the limit for normal, or CK-MB $> 5\%$ of total CK, or troponin T concentrations > 0.1 $\mu\text{g/mL}$). The angioplasty group consisted of 101 patients with no history of unstable angina, myocardial revascularization surgery, angioplasty or evidence of tissue necrosis, admitted for planned coronary angioplasty (CA) procedures. We excluded patients with symptoms of hepatic or renal insufficiency, congestive heart failure (Killip class IV), terminal illness or any other impediment to follow-up, as well as those likely to suffer adverse reactions to the vaccination.

Each group was randomly divided into two equally sized subgroups. Group A patients received a single intramuscular flu vaccination. Group B was the control group. All patients diagnosed as having AMI received standard therapy. Enrollment began in May 2001 and ended in early September 2001. The prespecified composite endpoint analyzed at 6-month follow-up was the sum of death, nonfatal myocardial reinfarction and angina prompting urgent myocardial revascularization. Baseline patient characteristics recorded on admission included clinical risk indicators such as age, sex, history of smoking, diabetes mellitus, myocardial revascularization history and presence of infarction with or without ST-segment elevation. We used these findings to define the subgroups.

Statistical analysis

Details of the statistical methods used in the FLUVACS study are described elsewhere. Relative risk (RR) with 95% confidence intervals (CI) was calculated for incidence of death as a primary endpoint and for the composite endpoint at 6-month follow-up of death, nonfatal myocardial reinfarction and angina prompting urgent myocardial revascularization. We used chi-squared univariate analysis for each of the risk factors recorded on admission to evaluate the features associated with better evolution. The Mantel-Haenszel test and Breslow-Day method were used to evaluate the variables. We constructed a logistical regression model to analyze all significant factors (Breslow-Day $P < .20$) in terms of interaction by treatment. We based our selection of variables on the biological significance of these factors, administration or non-administration of the vaccine, and endpoint.

We used Kaplan-Meier curves to determine event-free survival in the 2 groups of patients with and without flu vaccination. The 2 curves were compared with the Mantel-Haenszel log rank test, and $P < .05$ was considered significant.

All data were analyzed with SPSS 10.0 software for Windows.

RESULTS

We examined information on the 301 patients included in the FLUVACS database to evaluate the effects of flu vaccination by comparison with a control group. Analysis of the data for age, sex, and cardiovascular history as recorded on admission showed different demographic characteristics between both groups, although these were not statistically significant (Table 1).

At 6-month follow-up, incidence of the primary endpoint (death) and composite endpoint (death, nonfatal myocardial reinfarction and severe recurrent angina) was 2% and 11% respectively, in Group A (vaccinated patients) and 8% and 23% respectively, in Group B (control group). Relative risk for death in Group A vs Group B was 0.25; 95% CI; 0.07-0.86; $P=0.01$. Relative risk for the composite endpoint in Group A vs Group B was 0.51; 95% CI, 0.30-0.86; $P=0.009$ (Figure 1).

In the trial, the benefit of vaccination was limited to patients with AMI as no differences appeared for planned CA patients. However, at 6 months there was a consistent reduction in triple endpoint incidence among AMI patients associated with flu vaccination in the majority of the subgroups studied.

Relative risk reduction associated with flu vaccination was significantly greater in the following patient subgroups: men, age >65, with non-ST segment elevation AMI, with elevated enzyme levels on admission, non-diabetic patients, non-smokers, patients with no history of previous revascularization, and those with a TIMI risk score >6.

Flu vaccination favored a greater reduction in incidence of the composite endpoint among subgroups with a higher baseline risk (age >65, diabetic patients, TIMI risk score ≥ 6). However, the benefits of flu vaccination were also seen in those who a priori were not at high risk (non-diabetic patients, non-smokers, patients with no history of revascularization). Significantly, risk reduction was greater among those diagnosed as having non-ST segment elevation AMI (RR reduction 0.13; 95% CI, 0.03-0.52) when compared to patients with ST-segment elevation AMI (RR reduction 1.0; 95% CI, 0.42-0.38) (Figure 2).

DISCUSSION

In most of the subgroups in this trial, patients diagnosed as having myocardial infarction benefited consistently from flu vaccination. We are aware that the trial involved a limited number of patients and that random factors may well be involved. However, we believe that independent non-specific activation of B lymphocytes may be due to the existence of a clearly unstable clinical condition probably involving endothelial damage in circumstances in which, *a priori*, the

TABLE 1. Baseline characteristics of patients. Myocardial infarction group

Characteristics	Group A (vaccination) n=100	Group B (control) n=100
Age, average in years	64	66
Men	65	73
STEMI	47	37
Previous infarction	21 (45%)	20 (54%)
History of thrombolysis	13 (27%)	12 (32%)
Primary angioplasty	6 (13%)	5 (14%)
Neither lysis nor primary TCA	28 (60%)	20 (54%)
NSTEMI	53	63
Hypertension	56	33
Diabetes	20	19
Previous myocardial infarction	14	14
Smoking habit	42	30
MRS or previous angioplasty	14	23

TCA indicates transluminal coronary angioplasty; MRS, myocardial revascularization surgery; CK, creatine kinase; CK-MB, creatine kinase, MB fraction; NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; TnT, troponin T.

absence of clinical instability would suggest a different immune status, such as occurs in the context of planned transluminal CA in apparently stable patients.

Earlier epidemiological studies showed a reduction in cardiovascular events in association with flu vaccine administration in patients diagnosed as having myocardial infarction, and also found evidence that flu vaccine reduced the risk of stroke.^{4,5} However, because this is the first controlled prospective study of flu vaccination in patients with myocardial infarction, no data are available from similar studies with which we could compare our results.

Subgroup analysis

In well-known case studies of antithrombosis therapy, analysis of the data obtained from particularly positive trials generally shows consistent benefits in subgroups of patients with clinical characteristics remarkably similar to those of the FLUVACS population.⁹ This is the case for the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group (ESSENCE)¹³ and in the Thrombolysis In Myocardial Infarction (TIMI) 11B study,¹⁴ for example. In both cases, enoxaparin¹⁵ was significantly more effective in patients with ST-segment depression, aged >65, non-smokers, and in those with a history of previous myocardial revascularization.

We should stress, however, that this benefit was limited to the first 43 days of treatment and that it tended to weaken during follow-up. In the FLUVACS trial, the rate of events continued to diminish during follow-up in each of the groups, which suggests an additional benefit in comparison with conventional treat-

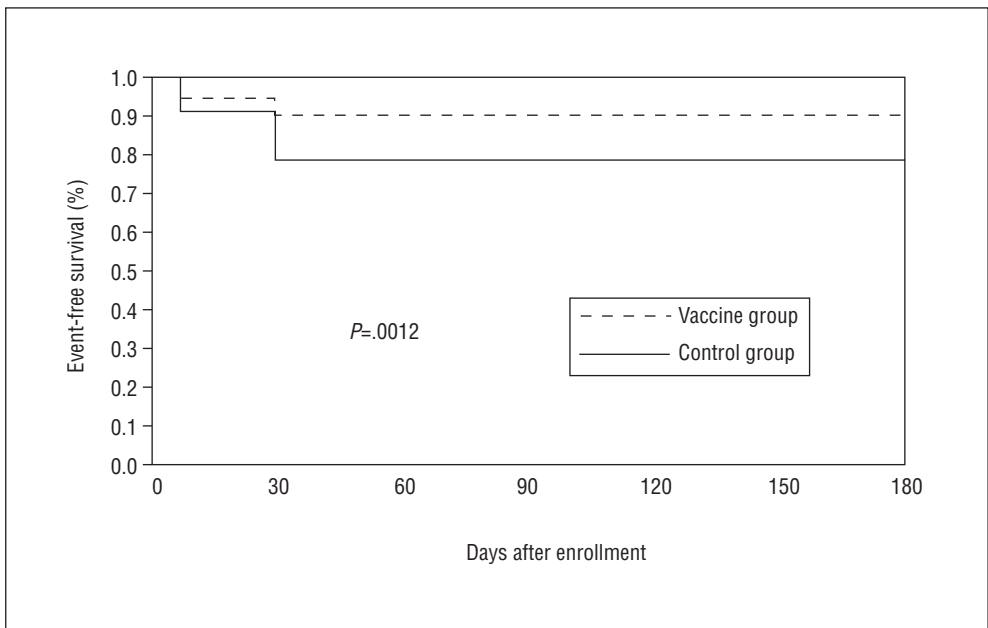


Fig. 1. Kaplan-Meier curve. Event-free evolution (death, nonfatal myocardial reinfarction, recurrent angina prompting urgent myocardial revascularization) at 6-month follow-up.

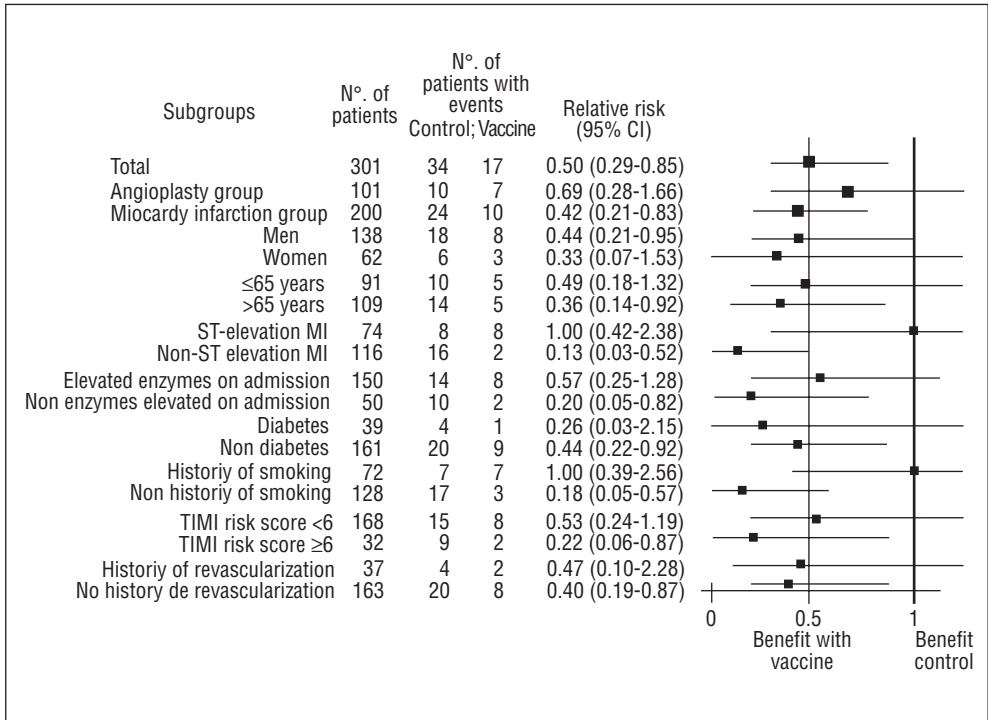


Fig. 2. Rate of events and relative risk (RR) with 95% confidence interval (CI) for composite endpoint (death, nonfatal myocardial reinfarction, recurrent angina prompting urgent myocardial revascularization) in the different subgroups.

ment beyond the pro-thrombotic risk window that follows an acute coronary accident.

In the Randomised Trial of Roxithromycin in Non-Q-Wave Coronary Syndromes: Roxis Pilot Study (ROXIS),⁶ the initial benefit, achieved through an unconventional pharmacological strategy in patients with acute coronary syndrome, was diminished at 90 days of follow-up,¹⁶ and no special benefits or adverse effects were detected in the subgroups of patients enrolled. The same can be said of the Azithromycin in

Acute Coronary Syndrome (AZACS) study,¹⁷ which was based on a population with characteristics similar to those of the ROXIS study participants. Although ANZACS patients were treated with antibiotics for a shorter period than ROXIS patients, the curves representing adverse events diverged during early stages of follow-up but tended to converge in the longer term. This may indicate that the suppressive therapy administered in these studies was insufficient, or perhaps that other little known immunological mediators play

an active role after the first months following an acute coronary event.¹⁸

Dimayuga et al¹⁹ investigated the effect of B cell reconstitution in immunodeficient mice with induced endothelial damage, and found that these cells successfully modulate tissular aggression. In Sweden, Caligiuri and Hansson²⁰ found that splenectomy in apo E-deficient hypercholesterolemic mice aggravated the development of atherosclerosis. They later transferred spleen cells to the same mice, which significantly reduced the progress of the disease.

Clearly, bacterial and viral infections can stimulate immune reaction through specific and non-specific mechanisms that recall and simulate molecular structures known for maintaining chronic illness with a significant inflammatory component, as is the case of atherosclerosis.²¹ The conditions that determine how the innate and acquired immune systems ultimately contribute to the pathogenesis of these entities remain unclear.

This study is a post-hoc analysis of a previously published trial showing that the benefit of administering flu vaccine as a concomitant treatment in patients with myocardial infarction is consistent in most of the subgroups analyzed. In patients with high baseline risk, such as those >65 years, with diabetes and with a TIMI risk score ≥ 6 , we found a statistically significant reduction in composite endpoint incidence at 6-month follow-up. Smokers and patients with ST-segment elevation myocardial infarction did not benefit from the administration of flu vaccination, probably because of the size of the sample (72 and 74 patients, respectively). These results are consistent with those of Nichol et al,²² who consistently found a significant benefit in the use of flu vaccine in all subgroups of patients analyzed whether they were at low, intermediate or high clinical risk, regardless of age group. These results, which are neutral in terms of the benefits to the population with ST-segment elevation AMI, agree with those recently published by Zahn et al,²³ who found that combining roxithromycin had no benefit in patients with ST-segment elevation AMI. Similarly, patients in the planned percutaneous coronary procedures group did not benefit either, probably because of the limited number of patients in the sample.

REFERENCES

1. Chierchia SL. Inflamación y síndrome coronario agudo. *Rev Esp Cardiol* 2001;54:1135-40.
2. Woodhouse PR, Khaw KT, Plummer M, Foley A, Meade TW. Seasonal variations of plasma fibrinogen and factor

- VII activity in the elderly: winter infections and death from cardiovascular disease. *Lancet* 1994;343:435-9.
3. Tillet HE, Smith JWG, Gooch CD. Excess death attributable to influenza in England and Wales: age at death and certified cause. *Int J Epidemiol* 1983;12:344-52.
4. Naghavi M, Barlas Z, Siadaty S, Naguib S, Madjid M, Casscells W. Association of Influenza vaccination and reduced risk of recurrent myocardial infarction. *Circulation* 2000;102:3039-45.
5. Lavallee P, Perchaud V, Gauier-Bertrand M, Grabli D, Amarenco P. Association between Influenza vaccination and reduced risk of brain infarction. *Stroke* 2002;33:513-8.
6. Gurfinkel E, Bozovich G, Daroca A, Beck E, Mautner B. Randomised trial of roxithromycin in non-Q-wave coronary syndromes: ROXIS Pilot Study. ROXIS Study Group. *Lancet* 1997; 350:404-7.
7. Cox RJ, Brokstad KA, Zuckerman MA, Wood JM, Haaheim LR, Oxford JS. An early humoral response in peripheral blood following parenteral inactivated Influenza vaccination. *Vaccine* 1994;12:993-9.
8. Brokstad KA, Cox RJ, Olofsson J, Jonsson R, Haaheim LR. Parenteral Influenza vaccination induces a rapid systemic and local immune response. *J Infect Dis* 1995;171:198-203.
9. Gurfinkel E, León de la Fuente R, Mendiz O, Mautner B. Influenza vaccine pilot study in acute myocardial infarction and planned percutaneous coronary intervention. The Flu Vaccination Acute Coronary Syndromes (FLUVACS) Study Group. *Circulation* 2002;105:2143-8.
10. World Health Organization. Communication Disease Surveillance and Response (CRL). Weekly Epidemiological Record. 2000; 75:41 [consultado el 18/03/2002]. Disponible en: www.who.int/disease/flu/index.html
11. Gurfinkel E, Mautner B. Prevención secundaria de la cardiopatía isquémica con la vacuna antigripal. Nueva evidencia sobre el papel de la infección y los síndromes coronarios agudos. *Rev Esp Cardiol* 2002;55:1009-12.
12. Kaski JC, Cruz-Fernández JM, Fernández-Bergés D, García-Moll X, Martín Jadraque L, Mostaza J, et al. Marcadores de inflamación y estratificación de riesgo en pacientes con síndrome coronario agudo: diseño del estudio SIESTA (Systemic Inflammation Evaluation in patients with non-ST segment elevation Acute coronary syndrome). *Rev Esp Cardiol* 2003;56:389-95.
13. Cohen M, Demers C, Gurfinkel EP, Turpie AG, Fromell GJ, Goodman S, et al, for the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. A comparison of low molecular weight heparin with unfractionated heparin for unstable coronary artery disease. *N Engl J Med* 1997;337:447-52.
14. Antman EM, McCabe CH, Gurfinkel EP, Turpie AG, Bernink PJ, Salein D, et al, for the TIMI 11B Investigators. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction: results of the Thrombolysis In Myocardial Infarction (TIMI) 11B trial. *Circulation* 1999;100: 1593-601.
15. Cohen M, Antman EM, Gurfinkel E, Radley D. Enoxaparin in unstable angina/non-ST-segment elevation myocardial infarction: treatment benefits in prespecified subgroups. *J Thromb Thrombolysis* 2001;12:199-206.
16. Gurfinkel E, Bozovich G, Beck E, Testa E, Livellara B, Mautner B. Treatment with the antibiotic roxithromycin in patients with acute non-Q-wave coronary syndromes. The final report of the ROXIS Study. *Eur Heart J* 1999;20:121-7.
17. Cercek B, Shah PK, Noc M, Zahger D, Zeymer U, Matetzky S, et al, for AZACS Investigators. Effect of short-term treatment with azithromycin on recurrent ischa-

- emic events in patients with acute coronary syndrome in the Azithromycin in Acute Coronary Syndrome (AZACS) trial: a randomised controlled trial. *Lancet* 2003;361:809-13.
18. Ramires JAF, Higuchi ML. *Mycoplasma pneumoniae* y *Chlamydia pneumoniae* se asocian con la inflamación y la rotura de las placas coronarias ateroscleróticas. *Rev Esp Cardiol* 2002;55(Supl 1):2-9.
 19. Dimayuga P, Cercek B, Oguchi S, Fredikson GN, Yano J, Shah PK, et al. Inhibitory effect on arterial injury-induced neointimal formation by adoptive b-cell transfer in rag-1 knockout mice. *Arterioscler Thromb Vasc Biol* 2002;22:644-9.
 20. Caliguri G, Nicoletti A, Poirier B, Hansson GK. Protective immunity against atherosclerosis carried by B cell of hypercholesterolemic mice. *J Clin Invest* 2002;109:721-4.
 21. Bachmaier K, Neu N, de la Maza LM, Pal S, Hessel A, Penninger JM. Chlamydia infections and heart disease linked through antigenic mimicry. *Science* 1999;283:1238-9.
 22. Nichol KL, Nordin J, Mullooly J, Lask R, Fillbrandt K, Iwane M. Influenza vaccination and reduction in hospitalization for cardiac disease and stroke among the elderly. *N Engl J Med* 2003;348:1322-32.
 23. Zahn R, Schneider S, Frilling B, Seidl K, Tebbe U, Weber M, et al. Antibiotic therapy after acute myocardial infarction: a prospective randomized study. *Circulation* 2003;107:1253-9.