Lack of Association between Pneumococcal Vaccination and Outcomes in Patients Presenting with ST-Elevation Myocardial Infarction

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ABSTRACT

Background: Pneumococcal vaccination has been reported to have conflicting results on preventing adverse cardiovascular events in a myriad of populations. We therefore investigated the effect of pneumococcal vaccination on preventing subsequent adverse cardiovascular events in a group of high-risk patients; those presenting with an ST-elevation myocardial infarction (STEMI). **Methods:** Patients undergoing acute percutaneous coronary intervention (PCI) for a STEMI at a single community referral hospital were prospectively entered into American College of Cardiology (ACC) cardiac catheterization/PCI registry. Information regarding pneumococcal vaccination and outcomes relating to recurrent MI and death were obtained from chart abstraction. **Results:** Four hundred and seventy-three patients underwent PCI for a STEMI from 1/1/2007 to 12/31/2010. The majority of patients were male (64.9%) and Caucasian (99.6%), with a mean age of 63.6 years (±13.8). During a median follow-up of 12.7 months, there were 69 (14.6%) deaths and 22 (4.5%) recurrent MIs. Patients who had received pneumococcal vaccination were at increased risk of mortality (hazard ratio = 2.08; 95% confidence interval 1.34-3.23; $P = 0.001$). However, patients who had received pneumococcal vaccination were older, and more likely to have hypertension and diabetes. After correcting for confounders in a multivariate Cox regression model, there was no significant association of pneumococcal vaccination with increased mortality. There was also no significant difference in recurrent MI. **Conclusion:** Pneumococcal vaccination was not associated with differences in all-cause mortality or recurrent MI, after correcting for major confounding clinical variables. Given the conflicting findings regarding pneumococcal vaccination, a prospective, randomized study will be required to clarify its cardio-protective role, if any.

Keywords: Acute ST-elevation myocardial infarction, outcomes, pneumococcal vaccination

INTRODUCTION

In spite of major advances in treatment, heart disease remains the number one cause of mortality in the United State.[1] The rise in incidence of acute myocardial infarction (MI) in the winter months is a well-documented phenomenon.[2] Risk of MI and strokes have been reported to increase substantially after a diagnosis of systemic respiratory tract infections.[3,4] This risk was highest in the first 3 days after diagnosis and decreased thereafter.[3] The same phenomenon, but to a lesser extent, was also noted with urinary tract infections. As plaque rupture and subsequent destabilization leads to the vast majority of acute coronary syndromes (ACS),[5] inflammation related to an acute infection would be a plausible explanation accounting for increased incidence of MI in the post-infectious period.[6]

In the context of infection destabilizing and preceding an ACS, there has been great interest in reducing ACS by preventing respiratory tract infections, either through influenza vaccination[7,8] or prophylactic use of antibiotics.[9,10] Interestingly pneumococcal vaccination in $Ldlr^{-/-}$ mice reduced extent of atherosclerosis and plasma from these mice given to $Ldlr^{-/-}$ naïve mice transferred the protective benefit.[11] The benefit was shown to be attributable to induction of high levels of anti-oxidized low-density lipoprotein-specific Immunoglobulin M levels, which were

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cross-reactive with pneumococcal determinants. A clinical association of pneumococcal vaccination with reduction in MI was first shown by Lamontagne *et al*.[12] Since the initial report, there has been intense debate regarding the coronary benefits of pneumococcal vaccination with studies reporting conflicting results.[13-17] Our own study in patients with suspected ACS revealed a significantly lower 6-month mortality rate in those who had received pneumococcal vaccination with or without influenza vaccine.[18] However, our study had the limitation of being predominantly male with patients suspected of an ACS, of whom only a subset had bona fide ACS or non-ST-elevation MI (STEMI). In addition, none of the studies targeted high-risk patients such as those presenting with acute STEMI. With this background in mind, our current study explores the association between pneumococcal vaccination and subsequent adverse cardiovascular outcomes in a relatively homogenous population of all patients presenting with a STEMI and undergoing primary coronary intervention at a single, tertiary care referral center.

METHODS

Patients presenting to Westmoreland Regional Hospital of the Excela Health System with a STEMI, eligible for an acute catheterization-based intervention and successfully undergoing the procedure were entered into an American College of Cardiology (ACC)-cath database prospectively. Demographics on the patients and detailed variables such as use of anti-platelet agents and cardiac medications as well as admission parameters and outcomes related to the admission (cardiogenic shock, use of intra-aortic balloon counter-pulsation, death) were all entered into the database prospectively. Pneumococcal vaccination status was determined by chart abstraction from the time of admission related to the STEMI as well as all subsequent admissions. All patients admitted to the hospital are asked routinely about their influenza and pneumococcal vaccination status and offered the vaccination if they meet criteria as part of a quality measure set by the hospital. Hence, this information was available on all patients admitted with a STEMI.

Patient's demographics, past medical history, smoking history, physical examination findings, coronary imaging, initial and follow-up laboratory results, and admission and discharge medications were obtained from the ACC/cath database. The left ventricle ejection fraction was obtained from left ventriculography performed as part of the cardiac catheterization or from echocardiogram (if ventriculography not done). The primary end-point was a combination of all-cause mortality and recurrent MI during follow-up. Mortality data and data regarding recurrent MI was obtained by chart abstraction of hospital admissions subsequent to the STEMI admission. All study protocols were approved by the Institutional Review Board with waiver of informed consent.

Statistical analysis

Patient demographic characteristics were compared between patients who had received pneumococcal vaccination and those who had not received pneumococcal vaccination prior to the index STEMI using Chi-square statistic for categorical variables and the Student's unpaired *t*-test for continuous variables. A two-tailed $P < 0.05$ was considered as significant. Kaplan-Meir survival curves were generated for the two groups of patients using recurrent MI, all-cause mortality and combined recurrent MI and death as an outcome variable of interest. Cox regression modeling was performed to assess the effect of receipt of pneumococcal vaccination on these outcomes. Multiple patient demographic and presenting variables were entered into a Cox model in a univariate manner to assess which of these were significant. Univariate variables identified to be significant at a $P \leq 0.10$ were entered into a multivariate model Cox regression model along with the addition of receipt of influenza and pneumococcal vaccination to assess any associations with adverse outcomes that may remain after correcting for the multiple significant clinical variables identified in the univariate modeling. All analyses were performed using STATA 12.1 (STATA Corp., College Station, Texas, USA).

RESULTS

Four hundred and seventy-three patients presenting with a STEMI and undergoing percutaneous coronary intervention (PCI) from 01/01/2007 to 12/31/2010 were enrolled in the ACC catheterization/PCI registry. The study population was predominantly Caucasian (99.6%) and male (64.9%) with a mean age of 63.6 years (±13.8). Mean follow-up duration was 68.2 (±64.8) weeks. There were a total of 69 (14.6%) deaths, 22 (4.7%) recurrent MI, with five patients presenting with recurrent MI leading to death during the same hospitalization. Hence, there were a total of 86 (18.2%) patients with composite outcome of death or recurrent MI. 6 (1.3%) patients had a cerebrovascular accident during follow-up and 3 (0.6%) had a documented transient ischemic attack. 165 (34.9%) of patients had received pneumococcal vaccination prior to the index MI, with 28 (5.9%) patients receiving it during follow-up. We analyzed the data with just pneumococcal vaccination being received prior to index MI, as well as including the 5.9% of patients that received pneumococcal vaccination

after the index MI in a separate analysis. The results, with or without these 5.9% of patients, remained unchanged. Hence, here we present the results with the 5.9% of patients being included as immunized in the analysis.

Not surprisingly patients who had received pneumococcal vaccination had more comorbidity as compared to the non-vaccinated group. Patients who had received pneumococcal vaccination were significantly older, female, with history of congestive heart failure (CHF), diabetes mellitus, hypertension, hyperlipidemia, chronic obstructive pulmonary disease as well as prior coronary artery disease, and strokes (Table 1), as compared to the non-vaccinated group. However, the non-vaccinated group was more likely to be smokers. There was no difference in peak troponin-I levels or the medications at time of discharge between the two groups (Table 1).

Patients were more likely to have received influenza vaccination in the season prior to the index MI presentation if they had also received pneumococcal vaccination. There was a significant correlation between the two vaccines ($R = 0.61$, $P < 0.0001$), with 82% of patients who had received pneumococcal vaccination also being vaccinated against influenza. Similar to pneumococcal vaccination, patients who had received influenza vaccination were statistically significantly older, and more likely to have comorbidities such as previous MI, diabetes mellitus, prior stroke and dyslipidemia and less likely to be current smokers (data not shown). This is not surprising as the Center for Disease Control recommendation for pneumococcal vaccination and influenza vaccination are very similar.

There were a total 69 deaths in our study, the majority of whom had received the pneumococcal vaccination (22.4% vs. 9.3%, $P < 0.001$; (Figure 1a)). There was no difference in the recurrent MI rate ($P = 0.462$; (Figure 1b)). There were 86 (18.2%) cases with death or recurrent MI, with higher rates of the combined end-point among patients with pneumococcal vaccination compared to the non-vaccinated ones ($P = 0.001$; (Figure 1c)). However, this difference was driven entirely by differences in mortality rate.

We entered various clinical variables into a univariate Cox regression model using a joint outcome variable of all-cause mortality and recurrent MI. The univariate analyses identified age >65 yrs, smoking within 1 year, history of stroke, CHF, pulmonary edema on presentation, cardiogenic shock, chronic renal insufficiency, body mass index >25, influenza, and pneumococcal vaccination parameters to be significantly associated with the outcome (Table 2). In a univariate Cox regression model, pneumococcal vaccination was associated with an increased hazard ratio (HR) of 2.08 (95% confidence interval [CI]: 1.34-3.23,

Table 1 Patient characteristics by pneumococcal vaccination status

Patient characteristics	Pneumococcal vaccination (*n*=473)		*P* value
	Yes (*n*=192)	No (*n*=281)	
Demographics (%)			
Age	71.5 years±11.2	58.2 years±12.8	<0.001
Male	106 (55.2)	201 (71.5)	<0.001
Caucasian	191 (99.5)	281 (99.6)	ns*
Tobacco use within 1 year	53 (29.3)	122 (46.2)	<0.001
Previous MI	22 (11.5)	20 (7.1)	0.106
Previous CHF	8 (4.2)	2 (0.7)	0.018
Diabetes mellitus	62 (32.3)	49 (17.5)	<0.001
Hypertension	117 (60.9)	118 (42.1)	<0.001
Chronic obstructive pulmonary disease	28 (14.6)	15 (5.4)	0.001
CVA	16 (8.3)	4 (1.4)	<0.001
Dyslipidemia	101 (52.6)	86 (30.7)	<0.001
Peripheral vascular disease	8 (4.2)	9 (3.2)	ns
Prior percutaneous intervention	31 (16.2)	26 (9.3)	0.025
Prior coronary artery bypass grafting	23 (12.0)	10 (3.6)	<0.001
Positive family history	36 (18.8)	80 (28.6)	0.015
Presentation on admission			
Pulmonary edema (%)	11 (5.9)	22 (8.6)	ns
Cardiogenic shock (%)	34 (17.9)	41 (15.8)	ns
Hematocrit on admission %	40.7 (±9.3)	43.3 (±5.1)	<0.001
WBC on admission	10.7 (±4.4)	11.6 (±4.5)	0.040
Serum creatinine on admission	1.15 (±0.84)	0.97 (±0.39)	0.003
Left ventricular ejection fraction %	45.2 (±12.5)	47.5 (±10.6)	0.090
Peak CPK-MB	155 (±157)	193 (±199)	0.040
Peak troponin-T	3.8 (±6.2)	3.7 (±5.6)	ns
Time to reperfusion	81.1 min (±127.0)	79.7 min (±118.4)	ns
Medications on discharge (%)			
Aspirin	177 (99.4)	263 (98.9)	ns
Clopidogrel	169 (94.9)	246 (92.8)	ns
Beta-blockers	159 (89.3)	243 (91.7)	ns
Ace-inhibitors/ angiotensin receptor blockers	103 (53.7)	128 (45.6)	ns
Statins	158 (88.8)	236 (89.1)	ns
Outcomes (%)			
Recurrent MI	7 (3.7)	15 (5.3)	ns
Death	43 (22.4)	26 (9.3)	<0.001
Stroke	6 (3.1)	3 (1.1)	ns
Recurrent MI or death	48 (25.0)	38 (13.5)	0.001

*Non-significant. MI: Myocardial infarction, WBC: White blood cell, CPK: Creatine phosphokinase, CHF: Congestive heart failure, CVA: Cerebrovascular accident

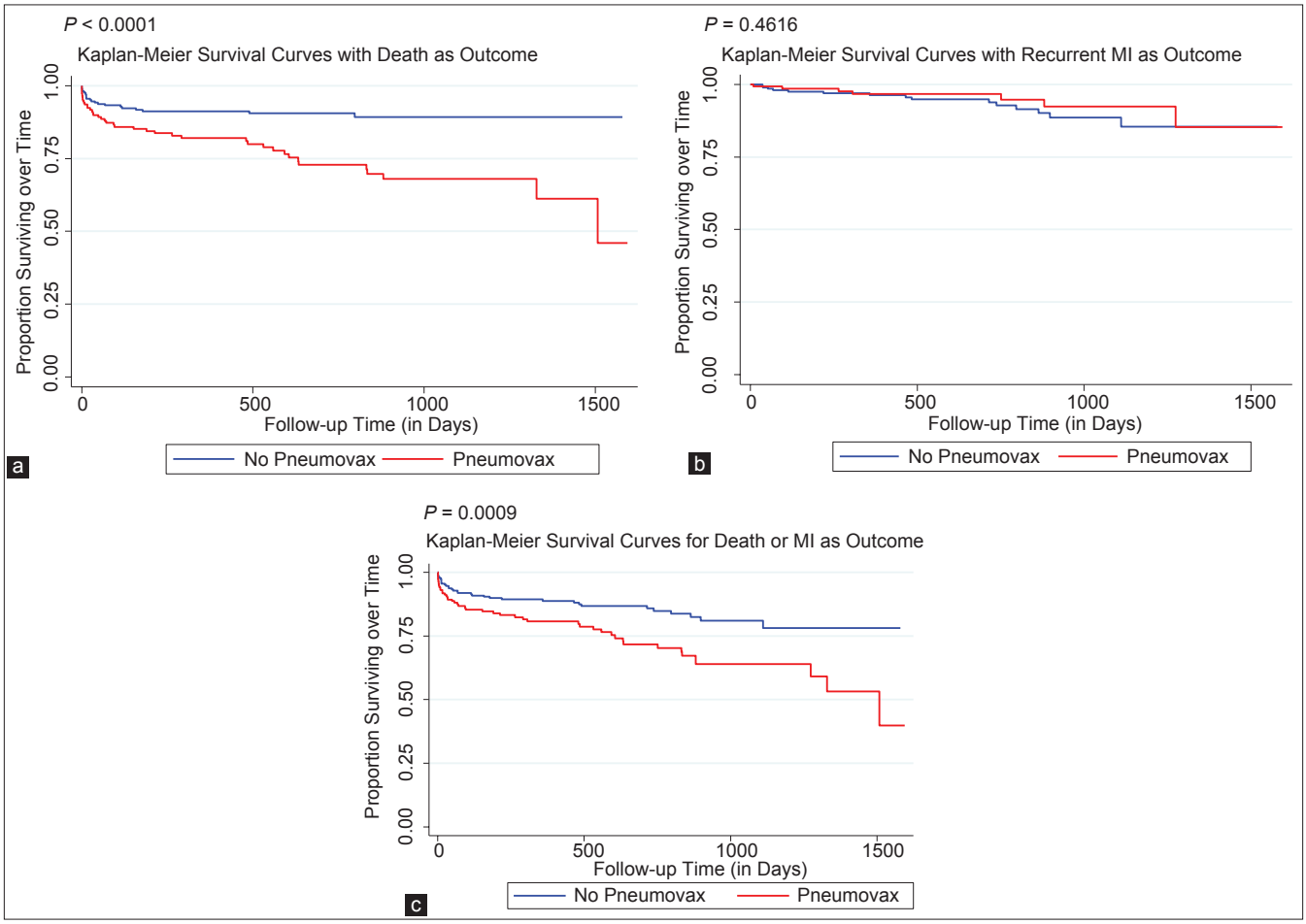

Figure 1. Kaplan-Meier survival curves by pneumococcal vaccination status and (a) death, (b) recurrent myocardial infarction (MI), or (c) death or recurrent MI.

Table 2 Univariate predictors of death or recurrent MI

Patient characteristic	HR	95% CI	*P* value
Age>65 years	3.02	1.88-4.84	<0.001
Smoking within 1 year	0.51	0.30-0.86	0.012
History of CVA	2.27	0.99-5.23	0.053
History of CHF	2.80	0.88-8.93	0.082
Pulmonary edema on presentation	1.32	1.11-1.56	0.002
Cardiogenic shock on presentation	3.76	2.31-6.11	<0.001
Serum creatinine >1.0	2.28	1.47-3.55	<0.001
Body mass index >25	0.63	0.40-1.00	0.049
Influenza vaccination	1.92	1.18-3.11	0.009
Pneumococcal vaccination	2.08	1.34-3.23	0.001

CHF: Congestive heart failure, CVA: Cerebrovascular accident, MI: Myocardial infarction, HR: Hazard ratio, CI: Confidence interval

$P = 0.001$) of all-cause mortality and recurrent MI. These results remained unchanged whether patients, who had received pneumococcal vaccination after the index MI, albeit a minority, were treated as vaccinated or not for the purpose of regression analysis. Receipt of influenza vaccination was also associated with higher HR of death or recurrent MI (HR = 1.92; 95% CI: 1.18-3.11; $P = 0.009$). These results were not surprising given that patients who had received influenza vaccination had a significantly higher load of comorbidities than those who had not, very similar to patients who had received pneumococcal vaccination.

To correct for the multiple significant univariate variables identified above, they were all entered into a multivariate Cox regression model along with a receipt of influenza or pneumococcal vaccination. After correcting for all the other clinical variables, neither receipt of influenza (HR = 1.56; 95% CI = 0.79-3.06; $P = 0.200$) nor pneumococcal vaccination (HR = 0.83; 95% CI = 0.40-1.72; $P = 0.616$) was associated with adverse combined outcomes of death or recurrent MI (Table 3).

DISCUSSION

In our cohort of patients presenting with a STEMI and undergoing primary PCI, receipt of pneumococcal vaccination was not associated with improvements in adverse combined outcomes of all-cause mortality or

Table 3 Multivariate predictors of death or recurrent MI

Patient characteristic	HR	95% CI	*P* value
Age>65 years	2.54	1.31-4.93	0.006
Smoking within 1 year	0.59	0.31-1.13	0.115
History of CVA	1.01	0.30-3.42	0.986
History of CHF	1.37	0.31-5.94	0.677
Pulmonary edema on presentation	4.00	1.76-9.09	0.001
Cardiogenic shock on presentation	2.17	1.14-4.10	0.018
Serum creatinine >1.0	2.51	1.47-4.30	0.001
Body mass index >25	0.77	0.44-1.35	0.360
Influenza vaccination	1.56	0.79-3.06	0.200
Pneumococcal vaccination	0.83	0.40-1.72	0.616

MI: Myocardial infarction, CHF: Congestive heart failure, CVA: Cerebrovascular accident, HR: Hazard ratio, CI: Confidence interval

recurrent MI. In fact, in univariate regression modeling, there was increased risk of adverse outcomes in patients who had received the pneumococcal vaccination. However, patients who had received pneumococcal vaccination were older, with a higher burden of comorbidities. Once these clinical factors were corrected for statistically in a multivariate regression model, patients with pneumococcal vaccination were at no different risk of mortality or recurrent MI as compared to those without receipt of pneumococcal vaccination.

We also looked at influenza vaccination status for the season preceding the time of the index hospitalization for STEMI. Patients who had received pneumococcal vaccination were much more likely to have received influenza vaccination. This was not surprising as the indications for both vaccines are very similar and healthy behaviors would be expected to run together. Like pneumococcal vaccination, influenza vaccine was associated with higher risk of death or recurrent MI in a univariate model, an association that disappeared once pertinent clinical variables were corrected for.

Our findings are in sharp contrast to the study reported by Lamontagne *et al*. who reported an adjusted odds ratio of 0.53 for MI in patients who had received pneumococcal vaccination as compared to controls.[12] Unlike our study, where the statistically significant differences were driven largely by mortality and not recurrent MI, the study by Lamontagne *et al*. was not designed to look at mortality differences. It is possible that the controls chosen from the surgical floors are likely to be a healthier population than those admitted to medical floors with a suspected ACS or found to have had an MI. It is also likely that the immunization status of the control population is an indirect marker of healthy behavior[19] This point is also high-lighted by our own study cohort where patients who had been immunized to pneumococcal vaccination, had a high (82%) incidence of being vaccination against influenza as well.

Prior study of veteran population presenting with a suspected ACS/non-ST-elevation MI revealed a decrease in all-cause mortality at 6-month in patients who had received pneumococcal vaccination, with or without the receipt of influenza vaccine.[18] The beneficial effect reported was largely driven again by all-cause mortality and not by differences in rates of recurrent MI. Unlike our study, this was a cohort of patients with "suspected" ACS, many of whom did not have an ACS. Another concerning limitation was an inability to distinguish between in-hospital and discharge medications. Differences in rates of prescription of cardiac medication could confound the results significantly, and account for the beneficial effect seen as patients likely to seek pneumococcal vaccination are also likely to be a more medically compliant population.

One of the largest, prospective, population-based cohort study from Spain failed to show a beneficial effect of pneumococcal vaccination in altering the risk of acute MI or death from acute MI.[17] Their findings were similar to the study reported by Tseng *et al*. that failed to demonstrate a beneficial effect of pneumococcal vaccination in preventing MI or stroke in men over 45 years of age.[13] Our study findings are in agreement with these. We chose a relatively high-risk group of patients; those presenting with a STEMI and all eligible and undergoing primary PCI. Our study cohort from that standpoint was fairly homogenous as far as cardiac pathology is concerned in that everyone had underlying coronary artery disease and a major presentation of it. Yet we failed to demonstrate a beneficial effect of pneumococcal vaccination in this high-risk group. On the contrary, patient who had received prior pneumococcal vaccination had higher mortality, a reflection likely of these patients having significantly more comorbid conditions. Indeed, after correcting for these comorbidities, there was no effect noted of pneumococcal vaccination on all-cause mortality/recurrent MI.

In contrast to our own study, Eurich *et al*. have reported a 58% reduction in acute coronary events associated with pneumococcal vaccination in patients presenting with community acquired pneumonia within 90 days of their presentation.[16] These results remained unchanged after extensive adjustments for clinical variables as well as propensity score matching. However, the authors did conclude that they still could not completely exclude a "healthy vaccine" effect.

CONCLUSION

In our study, receipt of pneumococcal vaccination in a high-risk population presenting with a STEMI undergoing

a percutaneous intervention was not associated with differences in all-cause mortality or recurrent MI. The data in the literature remains conflicting with studies showing as much as a 50% reduction in cardiac events/all-cause mortality to studies like ours showing no benefit. Given that patients receiving pneumococcal vaccination maybe older, sicker and yet a more health-conscious population, thus confounding the data in either direction, as well as more likely to receive influenza vaccination ("health vaccine"), a prospective, randomized, controlled study will be required to clarify its cardio-protective role, if any, perhaps similar in design to the randomized trial showing benefit of the influenza vaccination.[8]

There are several limitations to our study. Our study population is small, almost exclusively Caucasian, and from one tertiary care community referral hospital. We did not have data on cause-specific mortality and utilized all-cause mortality as an outcome measure. We also did not have data on the incidence of pneumococcal infections preceding the index STEMI, to explore any causality. Despite these limitations, our study does not support any cardio-protective role for pneumococcal vaccination, and the indications for administration of pneumococcal vaccination should remain unchanged.

REFERENCES

1. Donna L. Hoyert PD, Jiaquan Xu. Deaths: Preliminary data for 2011. Natl Vital Stat Rep 2012;61:1-52.
2. Spencer FA, Goldberg RJ, Becker RC, Gore JM. Seasonal distribution of acute myocardial infarction in the second National registry of myocardial infarction. J Am Coll Cardiol 1998;31:1226-33.
3. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. N Engl J Med 2004;351:2611-8.
4. Musher DM, Rueda AM, Kaka AS, Mapara SM. The association between pneumococcal pneumonia and acute cardiac events. Clin Infect Dis 2007;45:158-65.
5. Gutstein DE, Fuster V. Pathophysiology and clinical significance of atherosclerotic plaque rupture. Cardiovasc Res 1999;41:323-33.
6. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation 2002;105:1135-43.
7. 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.
8. Gurfinkel EP, de la Fuente RL, Mendiz O, Mautner B. Influenza vaccine pilot study in acute coronary syndromes and planned percutaneous coronary interventions: The FLU vaccination acute coronary syndromes (FLUVACS) Study. Circulation 2002;105:2143-7.
9. Cannon CP, Braunwald E, McCabe CH, Grayston JT, Muhlestein B, Giugliano RP, *et al*. Antibiotic treatment of *Chlamydia pneumoniae* after acute coronary syndrome. N Engl J Med 2005;352:1646-54.
10. Muhlestein JB, Anderson JL, Carlquist JF, Salunkhe K, Horne BD, Pearson RR, et al. Randomized secondary prevention trial of azithromycin in patients with coronary artery disease: Primary clinical results of the ACADEMIC study. Circulation 2000;102:1755-60.
11. Binder CJ, Hörkkö S, Dewan A, Chang MK, Kieu EP, Goodyear CS, *et al*. Pneumococcal vaccination decreases atherosclerotic lesion formation: Molecular mimicry between *Streptococcus pneumoniae* and oxidized LDL. Nat Med 2003;9:736-43.
12. Lamontagne F, Garant MP, Carvalho JC, Lanthier L, Smieja M, Pilon D. Pneumococcal vaccination and risk of myocardial infarction. CMAJ 2008;179:773-7.
13. Tseng HF, Slezak JM, Quinn VP, Sy LS, Van den Eeden SK, Jacobsen SJ. Pneumococcal vaccination and risk of acute myocardial infarction and stroke in men. JAMA 2010;303:1699-706.
14. Siriwardena AN, Gwini SM, Coupland CA. Influenza vaccination, pneumococcal vaccination and risk of acute myocardial infarction: Matched case-control study. CMAJ 2010;182:1617-23.
15. Hung IF, Leung AY, Chu DW, Leung D, Cheung T, Chan CK, *et al*. Prevention of acute myocardial infarction and stroke among elderly persons by dual pneumococcal and influenza vaccination: A prospective cohort study. Clin Infect Dis 2010;51:1007-16.
16. Eurich DT, Johnstone JJ, Minhas-Sandhu JK, Marrie TJ, Majumdar SR. Pneumococcal vaccination and risk of acute coronary syndromes in patients with pneumonia: Population-based cohort study. Heart 2012;98:1072-7.
17. Ochoa-Gondar O, Vila-Corcoles A, Rodriguez-Blanco T, de Diego-Cabanes C, Hospital-Guardiola I, Jariod-Pamies M, *et al*. Evaluating the clinical effectiveness of pneumococcal vaccination in preventing myocardial infarction: The CAPAMIS study, three-year follow-up. Vaccine 2014;32:252-7.
18. Maliha Zahid IS, Good CB, Stone RA, Kim S, Fine MJ, Sonel AF. Associations between pneumococcal vaccination and adverse outcomes in patients with suspected acute coronary syndrome. Adv Infect Dis 2012;2:122-34.
19. Skowronski DM, Janjua NZ, Hottes TS, Patrick DM, De Serres G. Pneumococcal vaccination and myocardial infarction. CMAJ 2009;180:319.