Aims We have previously reported a significant benefit of vaccination against flu on the incidence of a single and composite end-point of death, myocardial infarction or recurrent ischaemia in patients with myocardial necrosis and planned percutaneous coronary interventions. To determine whether the observed benefits of vaccination against flu were maintained beyond the winter season a 1-year follow-up was conducted.

Methods and results During the winter season, we enrolled prospectively 200 myocardial infarction patients admitted in the first 72 h, and 101 planned angioplasty/stent patients (PCI) without unstable coronary artery disease, prior by-pass surgery, angioplasty or tissue necrosis. Only four patients failed to meet the inclusion criteria. Participants were randomly allocated to receive flu vaccination or remain unvaccinated on top of standard medication (control group). The study was conducted in hospitalized patients with the aim to test the potential beneficial effect of flu vaccination in a secondary prevention scenario. Under intention to treat analysis the incidence of the primary end-point cardiovascular death at 1 year was significantly lower among patients receiving vaccination, 6% as compared with controls, 17% (relative risk with vaccine as compared with controls, 0.34; 95% confidence interval (CI), 0.17 to 0.71; \( P = 0.002 \)). The triple composite end-point occurred in 22% of the patients in the vaccine group vs 37% in controls, hazard ratio 0.59, 95% CI 0.4 to 0.86) \( P = 0.004 \). The beneficial effect was mainly detected in acute myocardial infarction patients (four events in the active arm vs 21 in the control group, \( P = 0.0002 \) [95% CI 0.19, 0.07–0.53]), and Cox regression analyses revealed that there was a greater benefit with flu vaccination in patients at high risk according with the TIMI score, and those with non-ST-segment deviation myocardial infarction (95% CI: 0.13 [0.03–0.52])

Conclusions Influenza vaccination may reduce the risk of death and ischaemic events in patients suffering from infarction and post-angioplasty during flu season. This effect was significantly evident at 1-year follow-up. Larger confirmatory studies are needed to evaluate the real impact on flu vaccination on outcome after acute coronary syndromes.

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Despite the early benefits shown from the original studies on the effect of anti-thrombotic therapy on acute coronary syndromes,1–4 the event rates in patients who present with myocardial necrosis remain high at both post in-hospital days and 1 year thereafter. Indeed, death or new infarction occurs in approximately six of 100 patients by 1 month. An additional six deaths or myocardial infarctions per 100 patients can be expected despite aspirin therapy, and the revascularization rate is close to 9% from 1 month to 1 year.5

A more aggressive medical approach (early cardiac revascularization when appropriate) was also used for moderate to high-risk patients with myocardial infarction to lower the incidence of ischaemic events over time.6 Nevertheless, the incidence of subsequent adverse events still remains high.7

The understanding of the conditions that determine the new ischaemic events remains an unresolved issue.

Previous research has implicated inflammation as a critical component in the growth and development of atherosclerotic plaques, and several possible aetiologies including a prothrombotic state, autoimmune reactions, and infection are potentially linked to the severity of atherosclerotic disease.8

We have recently published a significant benefit of a single intramuscular dose of a flu vaccination to reduce cardiovascular death, and combined traditional end-point rates at 6 months of follow-up.9 We report here the results of 1-year follow-up of the Flu Vaccination Acute Coronary Syndromes (FLUVACS) study.

**Methods**

**Study design and population**

This study was a randomized, prospective, multicentre, parallel group, and controlled pilot study. The Data Review Board Committee members for adjudicating final end-points at 1-year follow-up were totally blinded. The entry criteria for enrolment, study design and treatment protocol, as well as end-point definitions have been published before.9 Briefly, 301 patients (200 suffering from acute ST or non-ST-segment elevation myocardial infarction, and 101 patients for planned angioplasty) were included into the study from six care units in Argentina. The Institutional Review Board approved the study, and informed consent was obtained from all patients. The analysis comprised two different cohorts of patients: A clinical group including those patients with final diagnosis of myocardial infarction (ST or non-ST segment elevation myocardial infarction), occurring during the last 72 h, and an intervention group of patients suffering from acute ST or non-ST-segment elevation myocardial infarction, and 101 patients for planned angioplasty/stenting.

Myocardial infarction patients: At admission, 200 patients met the criteria for ST-segment elevation myocardial infarction, or non-ST-segment myocardial infarction according with a new consensus.10 They were allocated in two groups: Group A: received a single unique intramuscular vaccination containing 0.5 ml of A/Moscow/10/99-like virus, A/New Caledonia/20/99 (H1N1)-like virus, and AB/Sichuan/379/99-like virus. Follow-up telephone visits were scheduled at 6, and 12 months post-treatment. Group B, served as a control group.

PCI-stenting group: The second group included 101 subjects derived for planned stenting angioplasty at two sites in Buenos Aires City. Prior to procedure, 51 of them received vaccination, and 50 were followed as a control group.

Although the timing of influenza activity vary by region, vaccine administered after May in the Southern Hemisphere was made as in the Northern Hemisphere after November usually is recommended, since is likely to be beneficial in the majority of influenza seasons.11 The timing of patient enrolment was as follows: during the month of May 2001, 80 patients were vaccinated, 35 during June, 21 on July representing 91% of the population assigned to vaccine group. Twelve patients were vaccinated in August 2001, and finally three patients at the very beginning of September 2001. This strategy was made since we presumed that a non-specific stimulation of the immune system could drive in lower subsequent ischaemic events beyond the impact of prophylaxis against influenza infection.

**End-points**

One-year follow-up was obtained in a prospective manner, with each site responsible for telephone contact of all randomized patients. In the 3% of cases where patients were lost to follow-up through telephonic contact, a study investigator to assess the patient status conducted a home visit. For the 1-year follow-up, the same end-point definitions were used, and the time to first cardiovascular death end-point was the primary outcome. Secondary aims were to assess the time to the first composite triple end-point of cardiovascular death, myocardial infarction, and re-hospitalization for severe recurrent ischaemia.

The confirmation of end-points during the 1-year follow-up was based on the following definitions.

Cardiovascular deaths were considered do to fatal myocardial infarction, sudden death, death in the hospital after possible myocardial infarction or death do to heart failure or another coronary cause. Confirmed cardiovascular death by their own physicians contacted through relatives or a death registry confirmed by the site in which the patient died. Death for other reasons was not considered as a primary end-point.

Recurrent ischaemia was defined as prolonged chest pain with new ST-T changes in at least two contiguous leads (ST elevation or depression ≥ 0.1 mV and/or T wave inversion) while the patient was receiving optimal medical therapy (two anti- ischaemia drugs plus aspirin), motivating re-hospitalization.

Acute myocardial infarction was defined as any value of creatine kinase-MB (CK-MB) above normal, and at least 5% of total CK; or total CK value to at least twice the upper limit of normal reference range. Q-wave MI was defined as chest pain lasting 20 min or more followed by the appearance of new significant Q waves (≥ 0.03 s) in at least two leads in the ECG.

If more than one end-point was observed in the same patient, the pre-specified protocol assigned the one considered the worse in sequence: severe recurrent ischaemia motivating re-hospitalization vascularization, myocardial infarction, cardiovascular death. The triple composite end-point was defined as death, acute myocardial infarction, and re-hospitalization for recurrent ischaemia, requiring coronary artery by pass surgery or angioplasty.

The data monitoring team, located at Favaloro Foundation, was blinded.

**Statistical analysis**

The analyses for the 1-year follow-up were carried out according to the intention-to-treat principle. Statistical comparisons between groups were made using the time to event with the Kaplan–Meier survival technique (two-sided, log-rank test, alpha=0.05).
A chi square statistic was calculated to test differences between proportions, obtained by simple percentages. The Cox proportional hazards model, with univariate and stepwise procedures, was used to evaluate the proportional risk associated with several covariates. Significant level used for the inclusion into and exclusion from the model in the stepwise procedure was 5%. Variables evaluated were age, sex, smoker or non smoker status, diabetes, ST or non-ST segment elevation myocardial infarction, TIMI risk score < or > than 6.12 Hazards ratios and 95% confidence intervals were also calculated by means of the Cox proportional hazards model.

In measuring the time to an event for cases in which a patient had multiple end-points, the first event was taken into account. All patients without events and lost to follow-up were censored at the time of study termination or last contact. In some cases where it was only possible to establish whether a patient was alive or dead, the confirmation date determined the length of follow-up for mortality. However, if an earlier date was known at which full information was available, that date determined the length of follow-up in the analysis of all events.

Results

A total of 301 eligible patients were assigned to vaccine therapy (n=151) or control (n=150) through the randomization process. Nine patients (3%) had no follow-up information beyond 6 months. Complete 1-year follow-up event information was available in 292 patients (Fig. 1).

Demographic information was published elsewhere.9 There were no significant differences between groups.

At 6 months the first primary outcome – cardiovascular death–occurred in 2% of the patients in the vaccine group vs 8% in controls (relative risk with vaccine as compared with controls, 0.25; 95% CI 0.07 to 0.86; P=0.01). The triple composite end-point rates (a composite of cardiovascular death, nonfatal myocardial infarction, or severe ischaemia – occurred in 11% of the patients in the vaccine group vs 23% (relative risk 0.51; 95% CI 0.30 to 0.86; P=0.009).

One-year outcome

Of the 301 patients enrolled, 15 (5%) died within the initial 6-months of follow-up. There were no differences in terms of medical therapy between groups. All of the survival patients were on aspirin, 64% under beta-blockers, 57% under ACE inhibitors, and 34% of patients were treated with statins.

The first 15 patients who died during the 6 months of follow-up were originally reported. Total information was obtained from 292 patients (97% [96% in the active vaccination group and 98% in the control arm]).

Two patients assigned as controls were given flu vaccination during the follow-up period indicated by their own physicians. Two patients died from other reasons not attributable to cardiovascular origin.

The incidence of cardiovascular death at 1 year was statistically significant lower in the vaccination group as compared with controls (6% vs 17%, P=0.002, hazard ratio 0.34, 95% CI 0.17 to 0.71). Adding the two non-cardiovascular death (one in each group of patients) (10 patients vs 27 patients, P=0.003, hazard ratio 0.38, 95% CI 0.19–0.75). Fig. 2 shows the Kaplan–Meier estimates of the time to the cardiovascular death. No non-cardiovascular death was recorded.

Consistent with 6 months findings the incidence of the composite triple end-point at 1 year was also statistically significant lower in the vaccination arm as compared with controls (22% vs 37%, P=0.004, hazard ratio 0.59, 95% CI 0.4 to 0.86) (Table 1).

We also analysed as a secondary composite end-point of death or myocardial infarction. It was reached at 1 year in 14 patients of the vaccine group as compare with 24 patients of the control (risk reduction, 0.55 P=0.09).

At 12 months after randomization, the need for coronary revascularization was significantly less frequent among patients assigned to vaccine (5%) than among those assigned to control (9%).

Clinical myocardial infarction cohort

Seven of the patients were lost during the follow-up at 12 months. In the control group the incidence of the triple end-point of 19% vs 42% (P=0.0003; relative risk: 0.44 [0.27–0.71]). In terms of death, there were four events in the active arm vs 21 in the control group (P=0.0002 [95% CI 0.19, 0.07–0.53]) (Table 2).

PCI-stenting group

In the active group the incidence of the combined end-point rates were of 28% vs 26% (P=0.26).
Subgroup analyses

In Fig. 3, most of the subgroups of patients treated with flu vaccine showed a significant benefit compared to controls.

However, Cox regression analyses revealed that there was a greater benefit with flu vaccination in patients with non-ST-segment deviation ($P=0.00395$ CI: 0.13 [0.03-0.52]), older than 65 years old (95% CI 0.36: [0.14–0.92]), non-smokers, and those exposed at a high risk for future ischaemic episodes: TIMI risk score more than 6 (95% CI: 0.22 [0.06–0.82]).

A total of 84 patients suffered were admitted as an acute ST elevation myocardial infarction. In this
A subgroup of patients no statistically significant benefit of flu vaccination was detected over the control group.

Discussion

The trial was originally intended to vaccinate against flu a cohort of acute coronary patients and those planned for a percutaneous intervention. The Data Review Board Committee of the Investigation performed a second analysis after 12 months follow-up. In this analysis an unexpected significant reduction of cardiovascular death events was observed in the active group, specially the one with acute myocardial infarction.13

Intriguing associations were noted in the epidemiology of coronary artery disease to suggest a potential infectious influence. For example, rates of myocardial infarction and cardiac death increase in the winter and after influenza epidemics.14–16 Influenza vaccination in case-control studies has been reported to protect against myocardial infarction, primary cardiac death, and stroke.17–19 Those studies were conducted in the Northern Hemisphere.20

Because humoral response after vaccination stimulus may reflect migration of committed B-lymphocytes, elegant atherosclerotic animal models were developed for this purpose.

Dimayuga et al.21 investigated the effect of B-cell reconstitution in immune-deficiency Rag-1 knockout mice subjected to arterial injury. They found that the B cells modulated the response to arterial injury.

Caligiuri et al.22 found that splenectomy dramatically aggravated atherosclerosis in hypercholesterolaemic apoE knockout mice. They transferred of spleen cells from atherosclerotic apoE degrees mice and found a significant reduction disease development in young apoE degrees mice suggesting that B cell-associated protective immunity develops during atherosclerosis and reduce disease progression.

In addition to this, it is known that infected endothelial cells increase thrombin expression23 and decrease thrombomodulin expression. The secretion of von Willebrand factor24 and a reduction in prostacyclin production facilitates platelet adhesion. Most important to triggering coagulation may be the viral induced secretion of the powerful coagulant, tissue factor.25 We may speculate that anti flu vaccination could interfere during the thrombotic process.

It is worth to say that in the present study, in spite that the standard medication was equally balanced between groups during the follow-up period, there was an excessive rate of death at 1 year of follow-up. We realize that there are some inter-regional differences detected in clinical trials and it is plausible that general management could differ between sites and physicians participating in the study.26 This controversial issue is still under debate.27 Anyway, it is worth to say that 60% of patients who suffered an acute myocardial infarction did not receive any reperfusion strategy on admission mainly because a significant delay occurred in this country from the onset of symptoms to admission.9 This group of patients not reperfused properly is obviously exposed to an adverse course during the follow-up period.

![Fig. 3 Effect of vaccination against influenza on the relative risk and 95% confidence intervals (CI) for the combined triple end-point (cardiovascular death, myocardial infarction or severe recurrent ischaemia), in different subgroups of patients, obtained from the Cox proportional hazards model.13](https://academic.oup.com/eurheartj/article-abstract/25/1/25/619412)
Limitation of the present study

In those PCI patients we found no statistically significant differences between groups. The study in such sense was underpowered for the elective PCI group who are expected to have a low morbidity since the dominant problem is related to restenosis. By the other hand, it could be possible to think that vaccine against flu worsen the clinical outcome of patients allocated in this group. Unfortunately, this study had a limited sample size in order to respond this unresolved question.

It has been pointed out, the study showed a consistent benefit in most of the groups treated, essentially non-ST-segment elevation myocardial infarction, and subjects older than 65-years-old, as in those presenting a high risk score.

However, the reason why no clear benefit was detected among ST myocardial infarction patients is uncertain. In addition, we found that the vaccination prevented death mainly. We can only speculate that the flu vaccination could prevent those myocardial infarction exposed at the higher risk for a subsequent cardiovascular death. Other potential speculation could be the low rate of revascularizations among ST myocardial infarction patients during the study.

In other study using a non-traditional therapy (antibiotics) for acute myocardial infarction, a similar negative trend in Q-wave myocardial infarction subjects was considered as a limitation of the present study.

References


