Design and rationale for the Influenza vaccination After Myocardial Infarction (IAMI) trial

A registry-based randomized clinical trial

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Background Registry studies and case-control studies have demonstrated that the risk of acute myocardial infarction (AMI) is increased following influenza infection. Small randomized trials, underpowered for clinical end points, indicate that future cardiovascular events can be reduced following influenza vaccination in patients with established cardiovascular disease. Influenza vaccination is recommended by international guidelines for patients with cardiovascular disease, but uptake is varying and vaccination is rarely prioritized during hospitalization for AMI.

Methods/design The Influenza vaccination After Myocardial Infarction (IAMI) trial is a double-blind, multicenter, prospective, registry-based, randomized, placebo-controlled, clinical trial. A total of 4,400 patients with ST-segment elevation myocardial infarction (STEMI) or non-STEMI undergoing coronary angiography will randomly be assigned either to in-hospital influenza vaccination or to placebo. Baseline information is collected from national heart disease registries, and follow-up will be performed using both registries and a structured telephone interview. The primary end point is a composite of time to all-cause death, a new AMI, or stent thrombosis at 1 year.

Implications The IAMI trial is the largest randomized trial to date to evaluate the effect of in-hospital influenza vaccination on death and cardiovascular outcomes in patients with STEMI or non-STEMI. The trial is expected to provide highly relevant clinical data on the efficacy of influenza vaccine as secondary prevention after AMI. (Am Heart J 2017;189:94-102.)

Background Regardless of the progress in medical and invasive treatment strategies, cardiovascular disease remains the leading cause of death globally. Inflammation is regarded to play a central role in the atherosclerotic process from initiation of atherosclerosis to progression and rupture of atherosclerotic plaques.\(^1\) Initiation of the inflammatory process in atherosclerosis is multifactorial, including endogenous triggers such as oxidized low-density lipoprotein cholesterol. In addition, exogenous pathogens have been suggested to initiate the inflammatory response.\(^2\) A
relationship between influenza and cardiovascular events was described in an early study of influenza epidemics from 1915 to 1929 including the 1918-1920 pandemic. Accumulating observational studies have subsequently documented similar associations. In a self-controlled case series study (ie, cases acted as their own control in periods when not exposed) of more than 22,000 patients, the risk for acute myocardial infarction (AMI) during the first 3 days after medical contact for acute respiratory infection was significantly increased (incidence ratio 4.19, 95% CI 3.18-5.53). In a case-control study of more than 11,000 cases of AMI and outpatient controls, the adjusted odds ratio for AMI risk in the 7 days following respiratory infection was 2.10 (95% CI 1.38-3.21), and the risk of stroke was doubled. However, influenza vaccination protects against future cardiovascular events was investigated in a self-controlled case-series study of more than 8,000 patients diagnosed with AMI and vaccinated against influenza 1 or more times during a 6-year study period. The incidence of AMI was significantly reduced in the 60 days following vaccination, and this was more pronounced for early seasonal vaccinations before mid-November. In an Australian study of 275 cases of inpatients with AMI and an equal number of matched controls, the adjusted odds ratio for AMI risk in the 7 days following respiratory infection was 2.10 (95% CI 1.38-3.21), and the risk of stroke was doubled.

Whether influenza vaccination protects against future cardiovascular events was investigated in a self-controlled case-series study of more than 8,000 patients diagnosed with AMI and vaccinated against influenza 1 or more times during a 6-year study period. The incidence of AMI was significantly reduced in the 60 days following vaccination, and this was more pronounced for early seasonal vaccinations before mid-November. In an Australian study of 275 cases of inpatients with AMI and outpatient controls without AMI, influenza (positive influenza antibody titers) was an unrecognized comorbidity in more cases than controls but after adjustment for background factors influenza was not a predictor of AMI. However, influenza vaccination was found to be significantly protective against AMI (odds ratio 0.55, 95% CI 0.15-0.65).

Some prospective randomized clinical trials of influenza vaccination to patients with coronary artery disease have been conducted. The FLUVACS study randomized 301 patients (200 with AMI and 101 for whom percutaneous coronary intervention [PCI] was scheduled) to either influenza vaccine or a control group. The risk of death due to cardiovascular causes significantly decreased during a 1-year follow-up period in the intervention compared with the control group (6% vs 17%, respectively). In the FLUCAD study, 658 patients with angiographic evidence of coronary artery disease were randomized to receive either influenza vaccination or placebo. A significant protective effect of influenza vaccination was seen against coronary ischemic events (hazard ratio [HR] 0.54, 95% CI 0.29-0.99) after a median follow-up of 298 days. In a prospective randomized open trial with blinded end points, 442 patients with acute coronary syndrome (ACS) were randomized to influenza vaccination or no treatment. The primary combined end point of 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, 95% CI 0.57-0.86). A meta-analysis of previous randomized trials in patients with ACS and of randomized trials in patients of risk for cardiovascular disease comprising a total of 6,735 patients found that influenza vaccine was associated with a lower risk of composite cardiovascular events (2.9% vs 4.7%, risk ratio 0.64, 95% CI, 0.480-0.86). The pathophysiological background for a putative benefit of influenza vaccination in ACS may comprise protective effects from inflammation, anticoagulant effects, and prevention of increased metabolic demand with infection. It is conceivable that influenza increases cytokine production, leading to plaque destabilization, plaque rupture, and triggering of the coagulation cascade. B cells may play a role in atherogenesis, and the humoral response following an influenza vaccination stimulus involves multiple B-cell subsets, generating a multifaceted humoral response that provides protective antibodies which might contribute to the possible protection against ACS.

The scientific community strongly advocates that a sufficiently powered prospective randomized clinical trial on influenza vaccination as secondary prevention in cardiovascular disease is carried out. The need for such a study was highlighted in a Cochrane review concluding that additional higher-quality evidence is necessary to confirm whether influenza vaccination is effective in preventing cardiovascular disease.

In the Swedish Coronary Angiography and Angioplasty Registry, detailed information on all patients undergoing coronary angiography in Sweden is registered, and similar registries exist in Denmark (Western Denmark Heart Registry) and Norway (NORIC). Although registry and database information by nature is retrospective, we will in the present study use national registries as prospective platforms for conducting a randomized clinical multicenter trial, the rationale being that with standardized and validated information coupled to health care registries by social security number, almost complete follow-up can be assured with limited extra work related to conducting a trial. Another important advantage of using registries as platforms for randomization is the opportunity to include a large number of patients over a relatively short time period, thus allowing investigation of hard end points such as death, myocardial infarction, stent thrombosis, revascularization, and stroke. The concept of a registry-based randomized clinical trial was recently introduced and carried out with success in Sweden, Iceland, and Denmark in the 7,244-patient TASTE trial on thrombus aspiration in ST-segment elevation myocardial infarction (STEMI). In this study, we use a registry-based randomized clinical trial design with adjudication of events to test whether in-hospital influenza vaccination after ACS protects against future cardiovascular disease.

Methodology

Hypothesis, and primary and secondary end points

The Influenza vaccination After Myocardial Infarction (IAMI trial) is a multicenter, prospective, randomized,
registry-based, controlled clinical trial in patients with STEMI or non-STEMI undergoing coronary angiography. We test the hypothesis that influenza vaccination (Vaxigrip, Sanofi Pasteur) is superior to placebo (saline) in reducing all-cause death, a new AMI, or stent thrombosis (first occurring) during the first year after STEMI or NSTEMI (primary end point). Secondary end points are each of the components of the end points in the composite primary end point evaluated separately and time to cardiovascular death, revascularization, stroke, rehospitalization for heart failure, and length of hospital stay at 1 year. All baseline information will be obtained from coronary angiography and angioplasty registry databases in which a number of variables are routinely registered directly in the catheterization laboratory via Web-based interfaces on all patients undergoing coronary angiography and PCI. Clinical end point parameters will be obtained from continuous national health registries, from a standard questionnaire (at 7 days), and by a telephone interview (1 year). Patients will be followed up until 5 years, but end points beyond 1 year will be regarded as exploratory only.

Study population and patient selection

The IAMI study is ongoing in 13 centers in Sweden and Denmark, and more centers and countries are expected to join. Recruitment started on October 1, 2016, and is expected to continue for 3 influenza seasons until March 1, 2019. The final results of the 1-year clinical composite end point are expected in August 2020.

Individuals for inclusion are recruited among patients referred to the participating centers for coronary angiography/PCI because of STEMI or NSTEMI (Figure 1). Patients will be recruited during the influenza season only (from October 1 until March 1) and will not receive any honorarium for participation. STEMI is defined by chest pain suggestive for myocardial ischemia for ≥30 minutes and ≤24 hours, and an electrocardiogram with new ST-segment elevation in ≥2 contiguous leads of ≥0.2 mV in leads V2-V3 and/or ≥0.1 mV in other leads or a probable new-onset left bundle-branch block. NSTEMI is defined by a combination of onset of symptoms such as central chest pain or aggravated angina pectoris, with or without an electrocardiographic change with ST-segment lowering or an inverted T-wave, and rise and/or fall of troponin-T or troponin-I above the established margin of an AMI. In addition, referral to coronary angiography/PCI, age ≥18 years, and written informed consent are required for inclusion.

The exclusion criteria are influenza vaccination within 12 months prior to inclusion or the subject anticipating to be vaccinated during the current influenza season; indication for influenza vaccination (as per investigator’s discretion); previous allergic reaction to influenza vaccine; suspicion of febrile illness or acute; ongoing infection; hypersensitivity to the active substances or ingredients of Vaxigrip or against any residues, such as eggs (ovalbumin or chicken proteins); endogenic or iatrogenic immunosuppression that may result in reduced immunization response; inability to provide informed consent; age< 18 years; or previous randomization in the IAMI trial.
Ethics and safety

The World Health Organization recommends seasonal influenza vaccination to subjects with chronic medical conditions (http://www.who.int/mediacentre/factsheets/fs211/en/). Conducting a randomized clinical trial in which half of the patients will receive placebo might therefore be considered unethical. However, influenza vaccination of patients with ischemic heart disease is typically performed out of hospital and not during hospitalization, and annual influenza vaccination coverage for the Scandinavian countries approaches only roughly 50% of target populations. Because the present clinical trial only intends to include patients not vaccinated within 12 months prior to inclusion and not considering being vaccinated during the current influenza season, the trial will increase vaccination coverage in the target population.

Influenza vaccine can be safely administered to this patient population. Influenza vaccination shortly following PCI was tested in the FLUVACS study where the majority of patients had a recent STEMI or NSTEMI (N = 200). Vaccination was carried out within 72 hours from symptom onset without any vaccine-related adverse events being reported. A large case series of more than 20,000 persons with a first AMI and 19,000 persons with a first stroke who received influenza vaccine reported no increase in the risk of AMI or stroke in the first 3 months after influenza vaccination. Following study inclusion, some patients could be anticipated to decide to accept influenza vaccination at a later stage during the same influenza season. For patients who received active vaccination as part of the study, additional vaccination does not impose a health risk.

The trial is conducted in accordance with the ethical principles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly in Helsinki, Finland, in 1964 and subsequent versions and has been approved by the regional ethical review board of Uppsala, Sweden, and Region Midtjylland, Denmark, and by the Medical Products Agencies of both countries (EudraCT no. 2014-001354-42). The trial is registered under www.clinicaltrials.gov: NCT02831608.

Randomization and treatment protocol.

Following informed consent, patients will be randomized using an online randomization system. Randomization is performed in a 1:1 fashion in blocks by treating
Figure 3

Timing of vaccination (upper panel, dotted line) and follow-up (fu) at 12 months (lower panel). STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction.

center (Figure 2). Block randomization is by a computer-generated random number list, and patients, investigators, and all medical staff, except for the unblinded study nurses administering vaccination, are kept blinded to the allocation. Because the majority of baseline, procedural, and outcome information is available from registries in the participating countries, the accompanying dedicated electronic case report form is simple with only few additional questions.

One or more unblinded study nurses at each center, not otherwise involved or participating in the study, will prepare the study medication (Vaxigrip/placebo). Placebo will be obtained from each center’s ordinary medical supply. According to randomization, Vaxigrip is administered in a prefilled syringe or the same volume of placebo (0.5 ml sterile sodium chloride) is drawn up in a syringe just before the vaccination. A list of information regarding what has been given to each patient (Vaxigrip/placebo) and when (date and time) is prepared, signed and kept by the unblinded study nurses. To ascertain blinding, the nurses will place a piece of foil around the syringe to ensure that the patient cannot see what is administered during the vaccination. The influenza vaccination, or placebo, is administered up to 72 hours following coronary angiography/PCI (Figure 3). In the early phase of the study NSTEMI patients were allowed to receive vaccine/placebo 24 hours prior to invasive procedure. But since this strategy could complicate interpretation of events associated with index invasive procedure of being study-related or not we amended a 72 hour post-procedure vaccination window for all patients to the protocol. Patients will be observed for 20 minutes after vaccination/placebo to monitor, and potentially treat, side effects. The influenza vaccine (Vaxigrip, Sanofi Pasteur · suspension for injection in pre-filled syringe) may be administered as a deep subcutaneous injection which is chosen to minimize the risk of bleeding. Lifelong low-dose aspirin is encouraged but will be according to national and local clinical routine. Also, duration of P2Y12 inhibitor treatment and other pharmacological therapies are left to the discretion of the treating physician.

Demographic data and procedure-related data are entered into the national coronary angiography registries which are coupled to national health quality registries via personal identification numbers. Data entered at study inclusion will be used for analysis. Patients in the study will not attend any follow-up visits (except for patients in the immunogenicity sub-study). At 7 days after the vaccination patients will be requested to return a postage paid standard questionnaire to assess if any adverse event has occurred following vaccination (Online Table). The end points will be monitored using national health quality registries. Moreover, a 12 month telephone interview with the patients or first degree relatives will be carried out to collect information on influenza-like illness, influenza vaccination and hospitalizations missed in registry searches.

Primary and secondary end points and end point definitions

The primary end point is time to all-cause death, hospitalization for a new myocardial infarction or stent thrombosis (first occurring) within 1 year. These data will be obtained from national health registries and the 12 month telephone interview. All primary end points up to 1 year will be adjudicated by a central adjudication committee.

Secondary end points are:

1. Time to all-cause death at 1 year.
2. Time to cardiovascular death at 1 year.
3. Time to definite stent thrombosis at 1 year.
4. Time to unplanned revascularization at 1 year.
5. Time to hospitalization for AMI at 1 year.
6. Time to cardiovascular death, a new AMI or stent thrombosis (first occurring) at 1 year.
7. Time to stroke at 1 year.
8. Time to hospitalization for heart failure at 1 year.
9. Length of index hospital stay (safety end point).

From a hypothesis generating perspective we aim to follow up patients through registries beyond 1 year and up to 5 years. Because influenza may precipitate plaque rupture, it is possible that a single influenza vaccination in the early phase after an AMI may stabilize non-culprit coronary plaques. End points beyond 1 year will be regarded as exploratory. New PCI, aortocoronary bypass operations and stent thromboses are followed in national health quality registries.

For the primary end point of death, all reasons for death, i.e. cardiac, non-cardiac or unknown are used. Myocardial infarction is registered as International Classification of Diseases-10 codes I21, I21.4 and I22. Heart failure as I50.3 and stroke as I63.9. A central adjudication will be performed for all reported primary and secondary end points for the 1-year follow up according to the 2014 ACC/AHA key data elements and definitions for cardiovascular end point events in clinical trials. Every site will prepare source documents for the event for central adjudication by an independent clinical end point committee blinded to the patients’ assigned treatment.

Substudy of vaccine immunogenicity

The primary aim of one substudy in selected centers is to evaluate the immune response to influenza vaccination in ACS patients. The geometric mean titer of antibodies (with 95% CIs) and pre-/post-vaccination ratios are calculated. Seroconversion rate is defined as at least a 4-fold increase in titer. The secondary aim is to relate the vaccine response to changes in inflammatory markers (cytokines, atheroprotective antibodies). The response to influenza vaccine has been shown to be suboptimal in elderly (>65 years) compared with younger (<44 years) individuals. Moreover, statins may influence the vaccine response. In a recent observational study the antibody response to influenza vaccine was found to be significantly lower in elderly (>65 years) statin users compared with non-statin users. Blood samples are taken on two occasions; before vaccination and 4 weeks (+/− 2–3 days) after vaccination.

Study monitoring and data safety monitoring

Sponsor of the trial is Örebro University Hospital in Sweden. The sponsor and the primary investigator ensure the conduct of the trial in accordance with the trial protocol, national laws, and internationally recognized GCP guidelines. Monitoring is provided by Avdelningen för kliniska prövningar, AKP in Örebro, Sweden, a full-service clinical research organization. Study sites are monitored to ensure the quality of the data and that the data are collected in accordance with the study protocol, principles of GCP, and local legislation. Data acquisition (electronic case report form, eCRF), merging of data with national registries and adverse event management is provided by an accredited clinical research organization, Lytics (Malmö, Sweden).

A maximum of 3 months following inclusion of the first 1000 patients a data safety monitoring board (DSMB) that include one infectious disease specialist, one clinical lecturer in public health and one epidemiologist, will monitor study end points from a blinded interim analysis. Variables to be assessed are all-cause death, a new myocardial infarction and stent thrombosis. Premature termination of the study will be mandated in the event that one of the treatment strategies shows statistical difference at the significance level $\alpha = 0.001$ for the composite of time to all-cause death, a new myocardial infarction or stent thrombosis.

Sample size calculation and statistical analysis

Sample size is calculated on the basis of three smaller randomized studies, demographic data from annual Swedish Coronary Angiography and Angioplasty Registry reports (accessible at http://www.ucr.uu.se/swedeheart/) and from the TASTE trial in which the number of high risk patients included was lower than expected. The combined 1-year primary end point of all-cause death, a new AMI or stent thrombosis is estimated at 10.0% (expected survival probability of 0.9) for individuals randomized to placebo. With a 5% two-sided significance level we calculated that 386 events would be needed to have 80% statistical power to detect a 25% reduction of the primary end point in the influenza vaccination group, corresponding to a hazard ratio of 0.75. With this estimation 2186 patients are needed per treatment arm, power calculation utilized with STATA release 14 (College Station, TX, USA). In order to control for dropouts and crossing from one group to the other (both were negligible in TASTE), 4400 patients will be included.

The data will be passed on from the participating centers to Örebro University Hospital where data management work and statistical analyses will be performed in collaboration with Lytics which is in charge of external web-randomization. The results will be analyzed according to the intention-to-treat principle, i.e. patients randomized to a certain group will be followed and assessed irrespectively of the actual treatment. Differences between groups in time-to-event end points will be assessed with the log-rank test. For the primary end point, patients will be censored at 1 year; analyses at other time points will be handled in a similar way. Survival probabilities will be displayed and calculated using Kaplan–Meier methodology. HRs with corresponding 95% CIs between study
groups will be calculated using Cox proportional hazard model. If violation to proportional hazard assumption is found time-dependent HR will be calculated and adjustment will be made for stratification variables, center and STEMI/NSTEMI.

Differences between study groups will be assessed with unpaired t-tests on original scale or log scale as appropriate. Ordinal variables will be assessed with chi-2 test for trend or Mann-Whitney U test and Pearson’s chi-square test or Fisher’s exact test will be used to test differences between proportions. Two-sided statistical significance levels of 5% will be used and estimates will be presented with 95% CIs.

Subgroup analyses will first and foremost be carried out for the primary end point and its components. All subgroup analyses of event data will be performed using a proportional hazards model with factors: treatment, subgroup, and treatment-subgroup interaction, and will be presented within-group HRs with 95% confidence intervals and the interaction p-value. The primary subgroup analyses will focus on the STEMI and NSTEMI populations and the effect of intervention in each of the three influenza seasons, with the purpose of evaluating effect in each subgroup.

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Discussion

In the IAMI study we investigate whether in-hospital influenza vaccination after AMI protects against future cardiovascular events. The potential gains of vaccinating patients with a high risk of future cardiovascular events, a risk which is pronounced in patients that just suffered an AMI, are considerable. A recent meta-analysis of high risk patients in 7 case-control studies of more than 17,000 patients found that influenza vaccination reduced the risk of AMI by 29%.

Since the possible impact of a simple, safe, inexpensive, once-per year vaccination seems evident it is notable that a clinical trial powered for hard clinical cardiovascular end points has not been carried out previously. One explanation could be that available data suffice. Results from registry findings, case-control studies and few small randomized trials suggest that influenza vaccination protects against cardiovascular disease. Influenza vaccination is guideline recommended by the American Heart Association and the American College of Cardiology (Class I, level of evidence B recommendation) and “may be considered” according to The European Society of Cardiology (Class IIb, level of evidence C). When all available information on the subject was condensed in a Cochrane review the conclusion was that additional high-quality evidence is necessary to confirm whether influenza vaccination is effective in preventing cardiovascular disease.

In order to navigate between ethics and guidelines on the one side and a strong wish from the scientific community to provide more evidence, on the other, the IAMI trial will only include patients not vaccinated during the last 12 months and not intending to be vaccinated in the current influenza season. It is interesting that despite recommendations and guidelines influenza vaccine uptake statistics and local practices do not indicate that influenza vaccine is systematically administered in-hospital after an ACS. Despite registry findings implying that a single yearly influenza vaccination may be as effective as statins after ACS most often vaccination is usually not performed in the coronary care unit, but in a primary care setting. Such a practice is likely associated with reduced compliance and the duration between discharge and influenza vaccination will likely vary. In IAMI we try to address both issues by recruiting patients shortly after admission with an ACS - a strategy which ensures higher patient compliance and a well-defined time interval between ACS and investigational vaccine administration.

When considering findings from the majority of previous registry studies on influenza vaccination and cardiovascular disease the question arises whether results are too good to be true. Subjects seeking influenza vaccination are typically healthier, have a higher level of education and are more concerned about their own well-being than subjects not being vaccinated. Such bias in observational studies is referred to as the healthy user effect (the propensity for patients who receive one preventive therapy to also seek other preventive services or partake in other healthy behaviors) or healthy adherer effect (patients who adhere to preventive therapy are more likely to engage in other healthy behaviors than their non-adherent counterparts) and is difficult to adjust for statistically. For example, observational studies have found a decrease in mortality of more than 50% following influenza vaccination - a benefit ten times greater than the estimated influenza mortality burden. Also lower rates of conditions not reasonably related to influenza infection, such as hospitalization for trauma and injury, have been observed with influenza
vaccination and the beneficial effects were even present before influenza season.38

Limitations

In the IAMI study we investigate the effect of a single, standard, trivalent influenza vaccine containing A- and B-type viral lineages. During the course of the study it is likely that quadrivalent influenza vaccine will become the standard and this will introduce heterogeneity when interpreting the final results.

In a large randomized controlled trial high-dose influenza vaccine reduced laboratory-confirmed influenza compared with standard dose influenza vaccine24 and high-dose influenza vaccine has now been approved in the USA and Canada for individuals over the age of 65 years. In the ‘iNFluenza Vaccine to Effectively Stop CardioThoracic Events and Decompensated heart failure (INVESTED)’ study (ClinicalTrials.gov number, NCT02787044), intending to include 9500 patients, the investigators will evaluate whether a high-dose vaccine strategy compared with a standard-dose vaccine strategy will be more effective in reducing cardiopulmonary hospitalization and mortality in heart failure and post-infarction patients. Since influenza vaccine/placebo in IAMI is administered in close proximity to a cardiovascular event, a condition with increased inflammatory activity, and because we wish to investigate an approved conventional therapy we chose to adhere to a standard dose strategy.

IAMI uses a hybrid registry-based randomized clinical trial methodology42 and a number of variables will be collected from existing registries and this ensures simplicity and lowers costs. The theoretic downside to this design is less rigorous validation of variables compared to a conventional clinical trial. However, the accuracy of the key parameters of the primary composite end point carries high accuracy15 and adjudication of registry events and events unobserved in registries will be carried out after the 12 months telephone follow-up and collection of source data. The registry-based design was introduced in a 7000+ patient study on thrombus aspiration with STEMI21 and later indirectly verified in an even larger conventional clinical trial with very similar outcomes.44

Health care professionals engaged in the IAMI trial are encouraged to receive influenza vaccination themselves during the study period but are not obliged to do so. Transmission of influenza from study health care professionals to patients thus cannot be excluded.

In conclusion, the IAMI trial is the largest randomized trial to date to evaluate the effect of in-hospital influenza vaccination on death and cardiovascular end points in patients with ACS. The trial is expected to provide highly relevant clinical data on the efficacy of in-hospital influenza vaccine as secondary prevention after AMI.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ahj.2017.04.003.

References


