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FASTTRACK CLINICAL RESEARCH
Clinical trials

Influenza vaccination strategy in acute coronary syndromes: the VIP-ACS trial

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Abstract

Aims To evaluate whether a strategy of double-dose influenza vaccination during hospitalization for an acute coronary syndrome (ACS) compared with standard-dose outpatient vaccination (as recommended by current guidelines) would further reduce the risk of major cardiopulmonary events.

Methods and results Vaccination against Influenza to Prevent cardiovascular events after Acute Coronary Syndromes (VIP-ACS) was a pragmatic, randomized, multicentre, active-comparator, open-label trial with blinded outcome adjudication comparing two strategies of influenza vaccination following an ACS: double-dose quadrivalent inactivated vaccine before hospital discharge vs. standard-dose quadrivalent inactivated vaccine administered in the outpatient setting 30 days after randomization. The primary outcome was a hierarchical composite of all-cause death, myocardial infarction, stroke, unstable angina, hospitalization for heart failure, urgent coronary revascularization, and hospitalization for respiratory causes, analysed by the win ratio method. Patients were followed for 12 months. During two influenza seasons, 1801 participants were included at 25 centres in Brazil. The primary outcome was not different between groups, with 12.7% wins in-hospital double-dose vaccine group and 12.3% wins in the standard-dose

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vaccine group {win ratio: 1.02 [95% confidence interval (CI): 0.79–1.32], $P = 0.84$}. Results were consistent for the key secondary outcome, a hierarchical composite of cardiovascular death, myocardial infarction and stroke [win ratio: 0.94 (95% CI: 0.66–1.33), $P = 0.72$]. Time-to-first event analysis for the primary outcome showed results similar to those of the main analysis [hazard ratio 0.97 (95% CI: 0.75–1.24), $P = 0.79$]. Adverse events were infrequent and did not differ between groups.

Conclusion Among patients hospitalized with an ACS, double-dose influenza vaccination before discharge did not reduce cardiopulmonary outcomes compared with standard-dose vaccination in the outpatient setting.

Clinical Trial Registration ClinicalTrials.gov number: NCT04001504

Structured Graphical Abstract

Key Question

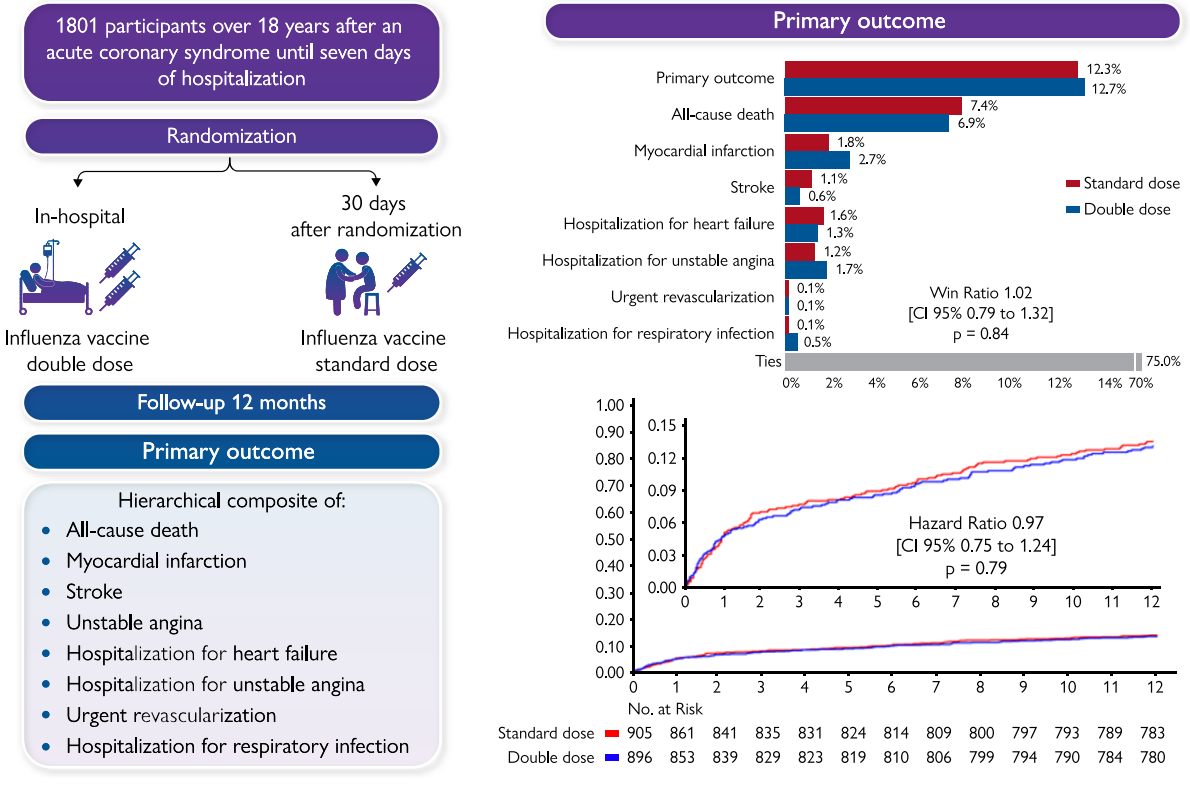
Influenza vaccination improves cardiovascular outcomes in high-risk patients following an acute coronary syndrome (ACS). Yet the ideal timing and dosage remain unclear.

Key Finding

In-hospital double dose influenza vaccination given at discharge in patients admitted with ACS did not reduce the rates of major cardiovascular and pulmonary events at 12 months as compared with the standard dose vaccination given 30 days after discharge.

Take Home Message

Among patients hospitalized with an ACS, double dose influenza vaccination before discharge does not reduce cardiovascular and pulmonary outcomes compared with standard dose vaccination.



Summary of the Vaccination against Influenza to Prevent cardiovascular events after Acute Coronary Syndromes (VIP-ACS) main findings. Among patients hospitalized for ACS, in-hospital double-dose influenza vaccination did not reduce the rates of major cardiovascular and pulmonary events at 12 months as compared with standard-dose vaccination 30 days after randomization. (*Left panel*) Summary of the design and primary outcome of the VIP-ACS trial. (*Right upper figure*) The primary outcome was a hierarchical composite analysed by unmatched win ratio method. (*Right lower figure*) The primary outcome was a time-to-event analysis with the use of unadjusted Cox proportional hazards models.

Keywords Acute coronary syndrome • Influenza vaccine • Mortality • Myocardial infarction • Stroke • Hospitalization • Immunization

Introduction

Acute coronary syndromes (ACSs) represent the leading cause of death and disability globally.[1] Large-scale randomized evidence has established the efficacy of interventions for ACS, such as percutaneous coronary intervention, antiplatelet therapy, thrombolysis, beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and high-intensity lipid-lowering therapies. Despite these well-established therapies, a substantial residual risk for recurring major cardiovascular (CV) events persists after an ACS.[2] Therefore, effective, safe, and easy-to-administer therapies for this patient population are needed.

Observational studies suggested that recent influenza infection is associated with increased risk of CV events.[3] Influenza infection triggers the inflammatory immune responses and promotes instability of coronary lesions vulnerable to rupture or erosion.[4] In this regard, influenza vaccination could represent a potential therapy to prevent CV events. A meta-analysis of randomized clinical trials comparing influenza vaccination vs. placebo or control showed a 45% relative risk [RR: 0.55; 95% confidence interval (CI): 0.41–0.75] reduction in major adverse CV events (MACEs) after 12 months in patients following a recent ACS.[5] However, the impact of early vaccination after an ACS has not been compared against standard of care vaccination after discharge or in the outpatient care setting.[6] Among patients who suffered an ACS, the recurrence of events in the first 3 months after the index hospitalization is higher compared with longer follow-up[7,8] and early in-hospital vaccination may be a more effective strategy for risk reduction.

Recent studies have also suggested that increased vaccine dose considerably improves immunogenicity against influenza epitopes, resulting in fewer respiratory tract infections and hospitalizations.[9] Since patients with CV disease (CVD) have been shown to build a lower humoral immune response to standard-dose influenza vaccine than those without CVD, the double-dose influenza vaccination could be an interesting strategy for this high-risk group.[10,11] Previous data have shown its safety and efficacy in enhancing humoral responses to influenza subtypes, which may be critical for reducing infection,[12] and subsequent CV events.

In order to assess the effect of increased dosage of influenza vaccine early after an ACS, we designed the Vaccination against Influenza to Prevent cardiovascular events after Acute Coronary Syndromes (VIP-ACSs) study, a pragmatic, active-controlled, randomized open-label clinical trial with blinded adjudication of outcomes, evaluating double-dose quadrivalent influenza vaccination administered during a hospitalization for ACS vs. standard-dose quadrivalent influenza vaccine administered at the outpatient setting.

Methods

Study design and population

VIP-ACS was an academic-led, pragmatic, randomized, superiority, multicentre, open-label, active-controlled trial with blinded outcome adjudication. The study was registered with ClinicalTrials.gov (NCT04001504). We included patients aged 18 years or older hospitalized with ACS (with or without ST-segment elevation) within 7 days of hospital admission not previously vaccinated for the current influenza season. Patients were enrolled between 1 July until 30 November during the 2019 season and 1 March until 30 November during the 2020 season. These recruitment periods were selected to match periods of high circulation of influenza virus in the Southern Hemisphere. Key exclusion criteria were previous vaccination with the season's influenza vaccine, history of hypersensitivity or anaphylaxis to any vaccine component, history of Guillain-Barré syndrome within 6 weeks of an influenza vaccination, and pregnant or breastfeeding women. Detailed eligibility criteria are presented in the Supplementary material online.

The study was designed and led by an academic steering committee and sponsored by a grant from the Brazilian Ministry of Health. The funding source had no role in study design, data collection, sites selection, data management, statistical analysis, or decision to publish the manuscript. Details about study oversight and organization are provided in the Supplementary material online.

Because of the limited funding and logistical issues in manufacturing placebo, we chose the trial to have an open-label design; however, we were careful in reducing ascertainment bias by the blinded adjudication of outcomes. Moreover, our statisticians and data analysts remained blinded to safety and efficacy outcomes between study groups until database lock.

Randomization

Patients were randomly assigned (1:1) to receive double-dose quadrivalent inactivated vaccine during the ACS hospitalization, as early as possible and prior to discharge, or standard-dose quadrivalent inactivated vaccine 30 ± 5 days after randomization. Concealed randomization was performed with the use of a central, interactive automated web-based system, REDCap™ software, stratified by research centre, using blocks of 8, 10, and 12.

Intervention and procedures

High-dose trivalent or quadrivalent vaccines are unavailable in Brazil. Therefore, we selected a double-dose strategy, based on previous studies that showed safety and efficacy to increase the immune response compared with the standard-dose in high CV risk patients.[10,11]

VIP-ACS used a quadrivalent inactivated influenza vaccine (Fluarix®, GlaxoSmithKline Biologicals NL daer SmithKline Beecham Pharma GmbH & Co, Wavre, Belgium) in double dose or standard dose of 0.5 ml, administered intramuscularly. Patients assigned to the double-dose quadrivalent inactivated vaccine group were vaccinated during the index hospitalization, as soon as possible after randomization, administered sequentially in two doses, one in each limb, whereas patients assigned to the standard-dose quadrivalent inactivated vaccine were vaccinated 30 ± 5 days after randomization during outpatient follow-up, one dose in preferable patient's limb. To avoid survival bias, study follow-up started at randomization, regardless of vaccination timing.

We used an active control rather than placebo because currently influenza vaccination is considered standard of care for influenza prevention in Brazil, being formally recommended by the Ministry of Health and local guidelines for high CV risk patients.[13] Therefore, we considered there was no equipoise to conduct a placebo-controlled trial testing influenza vaccination in Brazil. The study was funded by Brazilian Ministry of Health to test a new strategy for vaccination using a quadrivalent influenza vaccine for ACS patients compared with standard of care vaccination, based on current Brazilian guidelines.

All patients were asked to return for in-person clinical visits at 30 ± 5 days, 6 months ± 10 days, and 12 months ± 20 days after randomization, in order to monitor adverse events and potential study outcomes. Moreover, at 7 ± 2 days after study vaccine administration, patients were contacted specifically to collect data about any local or systemic adverse reaction to the vaccine. During the coronavirus disease 2019 (COVID-19) pandemic, a protocol amendment allowed for telephone calls rather than in-person visits for patient follow-up and collecting data on clinical events. Site staff were required to report any suspected clinical outcome at study case report forms and provide source documents (including copy of electronic health records where applicable) to be reviewed by the independent Clinical Events Committee, who performed a blinded adjudication of all study outcomes. Narratives of serious adverse events were also reviewed by study team in order to capture triggers for potential unreported study outcomes.

Impact of the COVID-19 pandemic

In 2020, due to the COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2, several issues impacted recruitment and trial operations. First, influenza immunization rates increased dramatically with anticipation of national vaccination campaign from the Brazilian public health authorities to prevent respiratory co-infections,[14] which directly affected patient eligibility. Second, enrolment was constrained as patients objected to return for in-person visits, despite the permission given by the steering committee to provide vaccination using other means, such as residential visits and new clinical offices exclusive for vaccinations. Finally, widespread use of face masks reduced spread of transmittable respiratory illnesses and could have potentially attenuated the effect of the study intervention. Due to these issues, the steering committee decided to modify the primary outcome analysis and recalculate the required sample size, while retaining adequate power to reliably assess the effect of double dose in-hospital influenza vaccination vs. standard-dose outpatient vaccination. This decision was made prior to study termination and database lock and blinded to the study results. In October 2021, it was determined that primary outcome would change from a time-to-event analysis to a clinical hierarchical composite outcome analysed by win ratio method, which resulted in reduction in sample size estimate. The trial protocol was amended in accordance with the CONSERVE-SPIRIT extension statement[15] and approved by the research ethics committees of all participating centres. The statistical analysis plan was adjusted accordingly.

Trial outcomes

The primary outcome was a hierarchical composite of all-cause death, myocardial infarction, stroke, hospitalization for unstable angina, hospitalization for heart failure, urgent coronary revascularization, and hospitalization for respiratory infections (excluding hospital admissions for COVID-19). The key secondary outcome was a hierarchical composite consisting of CV death, myocardial infarction and stroke (MACE). Secondary outcomes were the individual components of all-cause death, CV death, myocardial infarction, stroke, hospitalization for unstable angina, myocardial revascularization (urgent), myocardial revascularization (urgent and non-urgent), hospitalization for heart failure, stent thrombosis, hospitalization for respiratory or pulmonary infections, and hospitalization for respiratory or pulmonary infections including COVID-19. All outcomes were assessed during a 12-month follow-up period. In addition, all study outcomes and causes of death were adjudicated using standardized definitions by an independent clinical events committee, whose members were unaware of randomized treatment assignments. Detailed outcome definitions are provided in the Supplementary material online. Safety outcomes were serious adverse events reported through 12 months. Additionally, we collected adverse events of special interest related to vaccination during the first 7 days after vaccine administration.

Statistical analysis

Details of the sample size calculations and modifications during the trial as well as statistical methods are outlined in the Supplementary material online. Based on simulations, the 1801 patients enrolled until that time would provide 82.6% power to detect treatment effect, assuming a hazard ratio (HR) of 0.72 for all components of the combined primary outcome. This effect magnitude was based on a previous meta-analysis of randomized trials, where influenza vaccination resulted in RR reduction of 55% in CV events compared with placebo or no vaccination among patients with a recent ACS.[16]

The primary outcome was analysed by the unmatched win ratio method,[17] as described by Pocock *et al.*[18] Using this method, every patient from the early double-dose influenza vaccine group is compared against every patient from the late standard-dose influenza vaccine group. Initially, the pairs were compared for time until death, truncated at 12 months. If both patients died, the 'winner' of the comparison was the one who had a longer time between the time of randomization and the date of death. If the match was tied (both patients died within the same follow-up time or both remained alive until the final 12-month visit), they were classified according to that one who experienced any of the non-fatal events first in the following hierarchical order: myocardial infarction, stroke, hospitalization for unstable angina, hospitalization for heart failure, urgent coronary revascularization, and hospitalization for respiratory infections (excluding COVID-19). The win ratio represents the total number of wins divided by the total number of losses between the two study groups. Thus, a win ratio >1.0 reflects a better outcome in the in-hospital double-dose vaccination group. The key secondary outcome was also analysed by the win ratio method.

The primary and key secondary outcomes were also analysed by unadjusted Cox proportional hazards models. Similarly, secondary outcomes of all-cause mortality, mortality from CV causes, myocardial infarction, stroke, hospitalization for unstable angina, need for myocardial revascularization (urgent and non-urgent), hospitalization for heart failure, transient ischaemic attack, hospitalization for respiratory infections, hospitalization for COVID-19, and stent thrombosis were analysed by unadjusted Cox proportional hazards models. Pre-specified subgroup analyses were conducted according to sex, age, ACS presentation, diabetes, smokers, race, previous heart failure, myocardial infarction, stroke, percutaneous coronary intervention, coronary artery bypass graft, history of chronic lung diseases, previous COVID-19 infection, time to hospitalization, influenza season, enrollment year, and region of the country, and were presented with the win ratio statistic within each stratum.[19]

Efficacy analyses were performed on the intention-to-treat population comprising all patients who underwent randomization. Safety analyses were conducted in all patients who received at least one dose of influenza vaccine, considering the group to which the patient was allocated. A *P*-value of <0.05 was defined as statistically significant. Analyses were performed with the R software, version 4.2.0.

Compliance with ethical standards

This trial conformed to the recommendations of the Declaration of Helsinki and International Council on Harmonization guidelines on medical research in humans. The trial protocol was approved by all research ethics committees of participating centres before starting enrolment. All patients provided written informed consent before participation.

Results

Baseline characteristics and trial interventions

From 19 July 2019 to 30 November 2020, 5362 patients were screened at 25 centres in Brazil, and 1801 were randomized, 896 to the intervention group and 905 to the control group. A total of 276 (15%) patients were enrolled in the 2019 influenza season and 1525 (85%) in the 2020 season. By the end of the study, vital status was available for all but one patient (*Figure 1*).

The groups were well balanced with respect to baseline characteristics (*Table 1*). Median age was 56.7 years, 541 (30%) were women, 495 (27.5%) had history of diabetes, and 292 (16.2%) had prior myocardial infarction. Median time from hospital admission to randomization was 2 days [interquartile range (IQR): 1–5] in the double-dose group and 3 days (IQR: 1–5) in the standard-dose group. Among the index ACS events, 48.7% were ST-elevation myocardial infarction, 35.1% were non-ST-elevation myocardial infarction, and 16.2% were unstable angina. A total of 1462 patients (81.2%) were on beta-blockers, 1719 (95.4%) on statins, and 1768 (98.2%) on dual antiplatelet therapy at baseline and 1210 patients (67.2%) underwent percutaneous coronary intervention for the index event.

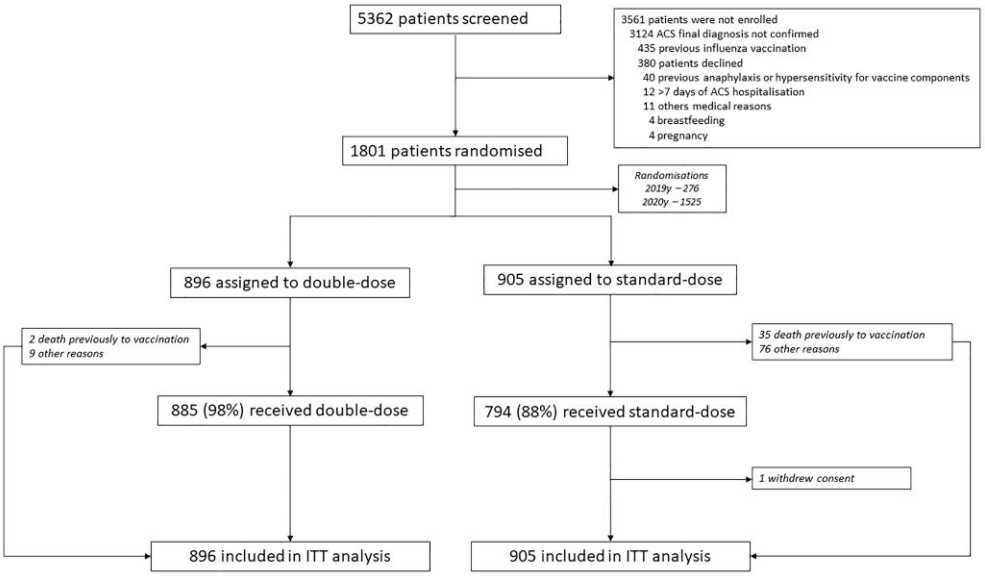


Figure 1 CONSORT—trial profile and analysis.

Vaccination was administered in 885 participants (98%) in the double-dose vaccine group at a median of 0 days (IQR: 0–0) after randomization, and 794 participants (88%) in the standard-dose vaccine group at a median of 34 days (IQR: 31–39) after randomization. In the standard-dose vaccine group, 292 (32.2%) participants were vaccinated after the programmed 30 ± 5 day visit and 40 (5%) received non-trial trivalent inactivated influenza vaccination. A total of 11 patients did not receive study intervention in the double-dose group: two died before vaccination and nine patients did not receive vaccine due to other reasons. In the standard-dose group, 111 patients did not receive the study vaccine: 35 died before vaccination and 76 refused to return to the clinic to receive outpatient vaccine mainly due to constraints related to the COVID-19 pandemic.

Primary outcome

The hierarchical analysis of all-cause death, myocardial infarction, stroke, hospitalization for unstable angina, hospitalization for heart failure, urgent coronary revascularization, and hospitalization for respiratory infections (excluding COVID-19 causes) was not significantly different between groups. The number of wins was 102 504 (12.7%) in the double-dose quadrivalent inactivated vaccine group and 99 968 (12.3%) in the standard-dose quadrivalent inactivated vaccine group [win ratio 1.02 (95% CI: 0.79–1.32), $P = 0.84$] (*Figure 2A*). Total number of ties was 608 408 (75.0%) (see Supplementary material online, *Figure S1A*). A total of 118 (13.2%) patients in the double-dose quadrivalent inactivated vaccine group and 123 (13.6%) patients in the standard-dose vaccine group presented at least one component of the primary outcome.

Time-to-first event analysis for the primary outcome showed results similar to those of the main analysis [HR: 0.97 (95% CI: 0.75–1.24) $P = 0.79$] (*Figure 3A*).

A sensitivity analysis including hospitalization for COVID-19 in the component of respiratory infection from the primary outcome reached similar results to those of the main analysis [win ratio 1.00 (95% CI: 0.78–1.28), $P = 0.99$] (see Supplementary material online, *Figures S2 and S3*). Similar results were obtained when this expanded outcome was analysed by a time-to-first event approach [HR 0.99 (95% CI: 0.77–1.27) $P = 0.95$] (see Supplementary material online, *Figure S4*).

Secondary outcomes

The key secondary outcome (hierarchical composite of CV death, myocardial infarction, and stroke) was not significantly different between vaccination groups [win ratio 0.94 (95% CI: 0.66–1.33), $P = 0.72$] (*Figure 2B*). Total number of ties was 703 992 (86.8%) (see Supplementary material online, *Figure S1B*). Time-to-first event analysis for the key secondary outcome yielded similar results [HR 1.06 (95% CI: 0.75–1.51), $P = 0.73$] (*Figure 3B*).

At 12 months, the incidence of all-cause death [HR 1.08 (95% CI: 0.77–1.51) $P = 0.67$] and of CV death [HR: 1.25 (95% CI: 0.77–2.03) $P = 0.36$] was not significantly different between groups, nor was the incidence of myocardial infarction [HR: 0.88 (95% CI: 0.49–1.59) $P = 0.68$] (see Supplementary material online, *Figure S5A–C*). Similar results were observed for stroke, hospitalization for unstable angina, myocardial revascularization (urgent and non-urgent), hospitalization for heart failure, stent thrombosis, hospitalization for respiratory infections, hospitalization for respiratory infections including COVID-19 admissions (*Table 2*).

Events occurred during the initial 2-week period after randomization were similar between groups (see Supplementary material online, *Table S2*).

The hospitalizations for respiratory infections including COVID-19 were zero in the double-dose group and four in the standard-dose group for patients recruited in 2019. For patients recruited in 2020, there were 19 events in the double-dose group and 14 events in the standard-dose group. A total of nine deaths were caused by COVID-19, six in the double-dose group and three in the standard-dose groups.

Subgroup analysis

Results for the primary outcome were consistent across all pre-specified subgroups (*Figure 4*). Of note, there was no significant

Table 1 Characteristics of the patients at baseline

	Double-dose ($n = 896$)	Standard-dose ($n = 905$)	Total ($n = 1801$)
Age (years), median (IQR)	56.6 (49.3–63.6)	55.7 (49.5–62.6)	56.7 (49.4–63.1)
Female sex, *n* (%)	273 (30.5)	268 (29.6)	541 (30.0)
Time from hospital admission to randomization (days), median (IQR)	2 (1–5)	3 (1–5)	3 (1–5)
Race or ethnic group, n (%)			
White	529 (59.0)	521 (57.6)	1050 (58.3)
Asian	1 (0.1)	2 (0.2)	3 (0.2)
Black	117 (13.1)	151 (16.7)	268 (14.9)
Pardo[a]	249 (27.8)	229 (25.3)	478 (26.5)
Indigenous	0 (0.0)	2 (0.2)	2 (0.1)
Smoking status, n (%)			
Never smoking	320 (35.7)	348 (38.5)	668 (37.1)
Former smoking	252 (28.1)	237 (26.2)	668 (37.1)
Current smoking	324 (36.2)	320 (35.4)	644 (35.8)
Diabetes, *n* (%)	258 (28.8)	237 (26.2)	495 (27.5)
Hypertension, *n* (%)	628 (70.1)	607 (67.1)	1235 (68.6)
Dyslipidaemia, *n* (%)	239 (26.7)	241 (26.6)	480 (26.7)
Heart failure, *n* (%)	43 (4.8)	44 (4.9)	87 (4.8)
Atrial fibrillation, *n* (%)	17 (1.9)	17 (1.9)	34 (1.9)
Chronic renal failure,[b] *n* (%)	15 (1.7)	11 (1.2)	26 (1.4)
Chronic obstructive pulmonary disease, *n* (%)	14 (1.6)	13 (1.4)	27 (1.5)
Previous myocardial infarction, *n* (%)	146 (16.3)	146 (16.1)	292 (16.2)
Previous stroke, *n* (%)	31 (3.5)	28 (3.1)	59 (3.3)
Previous percutaneous coronary intervention, *n* (%)	87 (9.7)	95 (10.5)	182 (10.1)
Previous coronary artery bypass graft, *n* (%)	35 (3.9)	37 (4.1)	72 (4.0)
Concomitant medications, n (%)			
Acetylsalicylic acid	880 (98.2)	888 (98.1)	1768 (98.2)
ADP receptor blockers	841 (93.9)	841 (92.9)	1684 (93.4)
Beta-blocker	733 (81.8)	729 (80.6)	1462 (81.2)
ACEi or ARB	735 (82.0)	740 (81.8)	1475 (81.9)
Statins	853 (95.2)	866 (95.7)	1719 (95.4)
Fibrinolytic therapy, *n* (%)	100 (11.2)	91 (10.1)	191 (10.6)
Percutaneous coronary intervention at index ACS, *n* (%)	610 (68.1)	600 (66.3)	1210 (67.2)
Acute coronary syndrome, n (%)			
Unstable angina	147 (16.4)	144 (15.9)	291 (16.2)
Non-ST-elevation myocardial infarction	326 (36.5)	305 (33.7)	631 (35.1)
ST-elevation myocardial infarction	421 (47.1)	456 (50.4)	877 (48.7)

ACS, acute coronary syndrome; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ADP, adenosine diphosphate; IQR, interquartile range.
[a]Pardo, mixed race and ethnic group subjects.
[b]Chronic renal failure, creatinine >2.5 mg/dl.

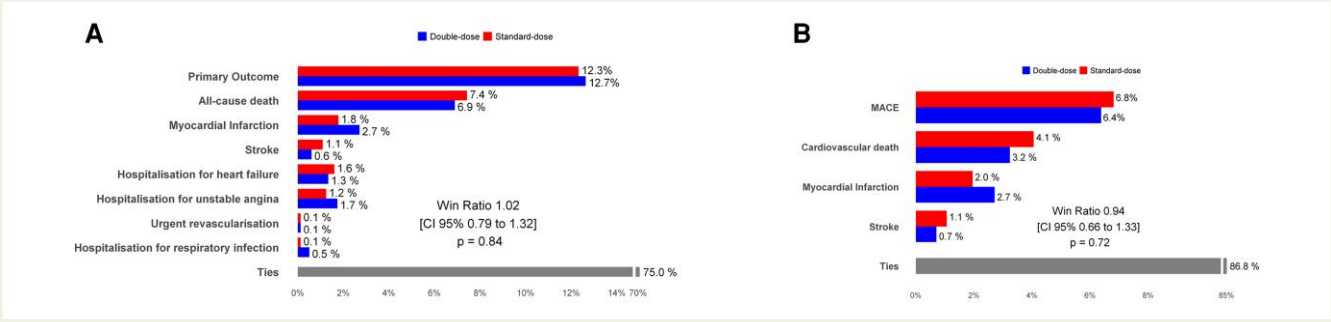


Figure 2 Primary efficacy outcomes and components. The win ratio was calculated using a non-parametric pairwise comparison for each outcome. (*A*) Primary outcome, a hierarchical composite of time to all-cause death, myocardial infarction, stroke, hospitalization for unstable angina, hospitalization for heart failure, urgent coronary revascularization and hospitalization for respiratory infection*; evaluated at 12 months. (*B*) Key secondary outcome of major adverse cardiovascular events (cardiovascular death, myocardial infarction, and stroke) at 12 months. Data are presented as point estimates and 95% CI with two-sided *P*-value. Day zero (T0) was the day of randomization for both study groups. *Excluded COVID-19 confirmed cases.

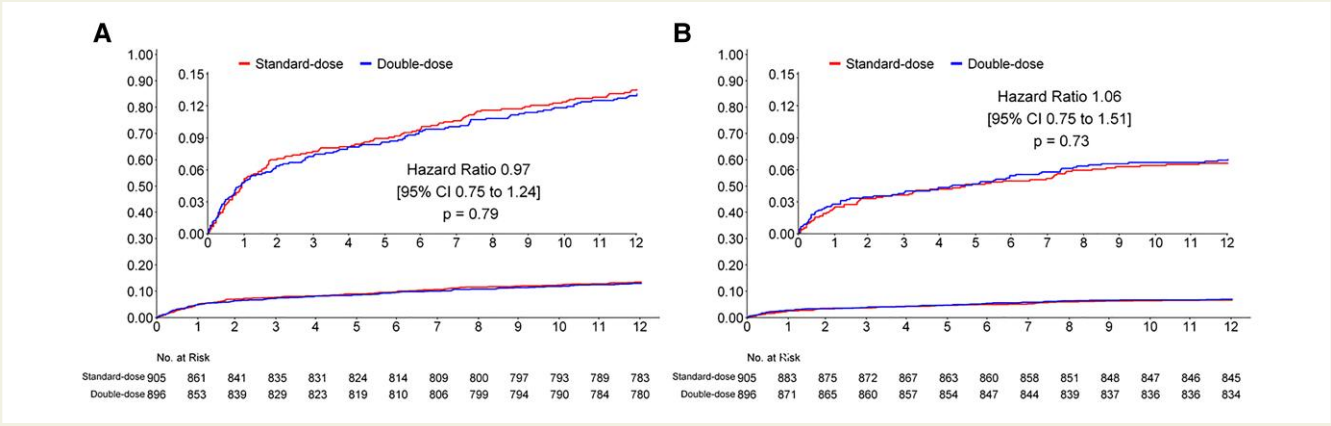


Figure 3 Kaplan–Meier event curves using Cox regression for primary outcome as time-to-first event analysis. (*A*) Primary outcome, a composite of all-cause death, myocardial infarction, stroke, hospitalization for unstable angina, hospitalization for heart failure, urgent coronary revascularization or hospitalizations for respiratory infection (excluding COVID-19)*. (*B*) Key secondary outcome of major adverse cardiovascular events (cardiovascular death, myocardial infarction, and stroke) at 12 months. Day zero (T0) was the day of randomization for both study groups. *Excluded COVID-19 confirmed cases.

heterogeneity for the primary outcome when patients were stratified according to influenza seasons.

Adverse events

Data on safety are provided in *Table 3*. Overall, influenza vaccination was well tolerated in both randomized groups. Solicited local and systemic adverse events were similar in the double-dose quadrivalent inactivated vaccine group compared with the standard-dose quadrivalent inactivated vaccine group. The most frequent vaccine-related adverse event was injection site pain (9.5%); fatigue, nausea, and general pain were lower than 2% in both groups.

A total of 47 (5.2%) patients in the standard-dose group and 49 (5.4%) in the double-dose group reported serious adverse events. A total of 111 serious adverse events were reported, 56 in the double-dose group, and 55 in the standard-dose group. For specific organs, a total of 15 (1.7%) patients in the double-dose group and 7 patients (0.8%) in the standard-dose group reported respiratory adverse events (see Supplementary material online, *Table S1*).

Discussion

In VIP-ACS, a pragmatic, randomized, active-comparator trial of patients hospitalized with ACS, a double-dose quadrivalent influenza vaccine during hospitalization did not improve cardiopulmonary outcomes at 12 months when compared with standard-dose outpatient vaccination after discharge (*Structured Graphical Abstract*). Results were consistent for different analytical methods (win ratio and Cox proportional hazards models), for secondary outcomes and for prespecified subgroups of interest, including individuals older than 60 years, with no heterogeneity across different influenza seasons. Participants who received the double-dose vaccine reported similar injection site reactions as those who received standard dose, and there were no differences in self-reported systemic reactions or investigator-reported adverse events.

Several factors may have contributed to our findings. It is possible that a strategy of doubling the dose of influenza vaccine among patients with ACS was insufficient to enhance protection against cardiopulmonary events. In this sense, even though previous evidence suggested that high-dose influenza vaccine is superior to standard-dose vaccine in

Table 2 Primary and secondary outcomes

Outcome	Double-dose ($n = 896$)	Standard-dose ($n = 905$)	Total ($n = 1801$)	Measure	*P*-value
Primary outcome				*Win ratio (95% CI)*	
All-cause death, wins (%)	55 934 (6.9)	60 250 (7.4)			
Myocardial infarction, wins (%)	18 852 (2.7)	12 424 (1.8)			
Stroke, wins (%)	4051 (0.6)	7317 (1.1)			
Hospitalization for heart failure, wins (%)	8754 (1.3)	10495 (1.6)			
Hospitalization for unstable angina, wins (%)	11 021 (1.7)	7908 (1.2)			
Urgent revascularization, wins (%)	779 (0.1)	788 (0.1)			
Hospitalization for respiratory infections, wins (%)[a]	3113 (0.5)	786 (0.1)			
Composite	102 504 (12.7)	99 968 (12.3)		1.02 (0.79–1.32)	0.84
Primary outcome (sensitivity analysis)				*Win ratio (95% CI)*	
Primary outcome composite, wins (%)[b]	104 824 (12.9)	104 656 (12.9)		1.00 (0.78–1.28)	0.99
Key secondary outcome				*Win ratio (95% CI)*	
MACE,[c] wins (%)	51 750 (6.4)	55 238 (6.8)		0.94 (0.66–1.33)	0.72
Primary outcome (time-to-first event)				*Hazard ratio (95% CI)*	
Primary outcome composite, events (%)	169 (13.2%)	156 (13.6%)		1.08 (0.77–1.51)	0.67
Key secondary outcome (time-to-first event)				*Hazard ratio (95% CI)*	
MACE, events (%)	74 (7.0%)	60 (6.6%)		1.06 (0.75–1.51)	0.73
Secondary outcomes				*Hazard ratio (95% CI)*	
All-cause death, events (%)	69 (7.7)	65 (7.2)	134 (7.4)	1.08 (0.77–1.51)	0.67
Total cardiovascular death, events (%)	37 (4.1)	30 (3.3)	67 (3.7)	1.25 (0.77–2.03)	0.36
Myocardial infarction, events (%)	21 (2.3)	24 (2.7)	45 (2.5)	0.88 (0.49–1.59)	0.68
Stroke, events (%)	11 (1.2)	6 (0.7)	17 (0.9)	1.86 (0.69–5.03)	0.22
Hospitalization for unstable angina, events (%)	14 (1.6)	16 (1.8)	30 (1.7)	0.88 (0.43–1.81)	0.73
Myocardial revascularization (urgent), events (%)	9 (1.0)	10 (1.1)	19 (1.1)	0.91 (0.37–2.24)	0.84
Myocardial revascularization (urgent and non-urgent), events (%)	21 (2.3)	21 (2.3)	42 (2.3)	1.04 (0.55–1.85)	0.96
Hospitalization for heart failure, events (%)	23 (2.6)	21 (2.3)	44 (2.4)	1.11 (0.62–2.01)	0.72
Stent thrombosis, events (%)	4 (0.4)	4 (0.4)	8 (0.4)	1.01 (0.25–4.05)	0.98
Hospitalization for respiratory infections, events (%)	4 (0.4)	9 (1.0)	13 (0.7)	0.45 (0.14–1.46)	0.18
Hospitalization for respiratory infections,[b] events (%)	19 (2.1)	17 (1.9)	36 (2.0)	1.13 (0.59–2.18)	0.71

CI, confidence interval; MACE, major cardiovascular adverse events.
[a]Exclusion confirmed COVID-19 infections.
[b]Included confirmed COVID-19 infections.
[c]MACE: time-to-first cardiovascular death, myocardial infarction, or stroke event.

improving the humoral response to influenza virus subtypes and in increasing protection against severe respiratory disease,[20] it remains unclear whether this higher seroconversion translates into less pronounced inflammatory responses to viral infection and ultimately lower risk of MACE. On the other hand, our results are consistent with previous large-scale evidence that compared high vs. standard-dose influenza vaccination among high CV risk patients. In this regard, the Influenza Vaccine to Effectively Stop Cardio Thoracic Events and Decompensated Heart Failure (INVESTED) trial did not find a benefit of an increased dose vaccine vs. standard-dose vaccine in decreasing mortality or cardiopulmonary hospitalization [HR: 1.06 (95% CI: 0.97–1.17)] among outpatients with history of recent acute myocardial infarction (in the past 12 months) or heart failure hospitalization (in the past 24 months) and at least one additional risk factor.[21] In part, results from the INVESTED trial could be attributed to the absence of the additional influenza B strain in the vaccine used, and to the overall low effectiveness of the influenza vaccine during the study period. In our trial, to reduce risk of higher influenza B mismatch related to the trivalent vaccine in Brazil,[22] we chose to administer the quadrivalent vaccine to all patients. Conversely, it may well be the case that the standard-

SUBGROUP	PRIMARY OUTCOME DOUBLE-DOSE (n = 896)	PRIMARY OUTCOME STANDARD-DOSE (n = 905)	Win ratio (95% CI)	P-value for interaction*
	no. of events/total no. (%)			
Sex				0.23
Male	79 / 623 (12.7%)	77 / 637 (12.1%)	0.94 [0.68 – 1.29]	
Female	39 / 273 (14.3%)	46 / 268 (17.2%)	1.20 [0.78 – 1.48]	
Age				0.47
≤ 60	66 / 589 (11.2%)	64 / 613 (10.4%)	0.91 [0.64 – 1.27]	
> 60	52 / 307 (16.9%)	59 / 292 (20.2%)	1.22 [0.84 – 1.77]	
ACS presentation				0.15
Unstable Angina	21 / 147 (14.3%)	16 / 144 (11.1%)	0.78 [0.41 – 1.51]	
STEMI	56 / 421 (13.3%)	56 / 456 (12.3%)	0.88 [0.61 – 1.28]	
NSTEMI	41 / 326 (12.6%)	51 / 305 (16.7%)	1.36 [0.90 – 2.06]	
Diabetes				0.83
No	64 / 638 (10.0%)	70 / 668 (10.5%)	1.03 [0.73 – 1.44]	
Yes	54 / 258 (20.9%)	53 / 237 (22.4%)	1.08 [0.74 – 1.59]	
Smokers				0.43
No	44 / 320 (13.8%)	42 / 348 (12.1%)	0.89 [0.58 – 1.36]	
Yes	74 / 576 (12.8%)	81 / 557 (14.5%)	1.10 [0.80 – 1.52]	
Race				0.43
White	68 / 529 (12.9%)	69 / 521 (13.2%)	1.02 [0.73 – 1.43]	
Non-White	50 / 367 (13.6%)	54 / 384 (14.1%)	1.01 [0.69 – 1.49]	
Previous heart failure				0.56
No	104 / 852 (12.2%)	108 / 858 (12.6)	1.01 [0.77 – 1.33]	
Yes	14 / 44 (31.8%)	15 / 47 (31.9%)	1.18 [0.56 – 2.47]	
Previous myocardial infarction				0.75
No	90 / 750 (12.0%)	95 / 759 (12.5%)	1.02 [0.77 – 1.37]	
Yes	28 / 146 (19.2%)	28 / 146 (19.2%)	1.04 [0.17 – 1.76]	
Previous stroke				0.18
No	110 / 862 (12.8%)	107 / 872 (12.3%)	0.94 [0.72 – 1.23]	
Yes	8 / 34 (23.5%)	16 / 33 (48.5%)	2.61 [1.09 – 6.25]	
Previous PCI				0.89
No	105 / 809 (13.0%)	108 / 810 (13.3%)	1.01 [0.77 – 1.32]	
Yes	13 / 87 (14.9%)	15 / 95 (15.8%)	1.11 [0.53 – 2.34]	
Previous CABG				<0.001
No	107 / 861 (12.4%)	122 / 868 (14.1%)	1.13 [0.87 – 1.46]	
Yes	11 / 35 (31.4%)	1 / 37 (2.7%)	0.07 [0.01 – 0.60]	
History of COPD				0.42
No	113 / 882 (12.8%)	118 / 892 (13.2%)	1.02 [0.79 – 1.33]	
Yes	5 / 14 (35.7%)	5 / 13 (38.5%)	1.00 [0.28 – 3.50]	
Prior COVID-19				0.97
No	103 / 771 (13.4%)	107 / 773 (13.8%)	1.02 [0.78 – 1.34]	
Yes	1 / 7 (14.3%)	2 / 13 (15.4%)	1.27 [0.12 – 13.46]	
Time from hospitalisation (in tertiles)				0.70
1st	42 / 282 (14.9%)	51 / 319 (16.0%)	1.08 [0.71 – 1.62]	
2nd	40 / 306 (13.1%)	36 / 294 (12.2%)	0.92 [0.58 – 1.45]	
3rd	36 / 308 (11.7%)	36 / 292 (12.3%)	1.03 [0.65 – 1.64]	
Influenza season				0.25
May to August	54 / 415 (13.0%)	63 / 420 (15.0%)	1.16 [0.80 – 1.67]	
Others	64 / 481 (13.3%)	60 / 485 (12.4%)	0.91 [0.64 – 1.30]	
Enrollment year				0.44
2019	21 / 140 (15.0%)	15 / 138 (10.9%)	0.69 [0.36 – 1.35]	
2020	97 / 756 (12.8%)	108 / 767 (14.1%)	1.09 [0.83 – 1.44]	
Regions of the country				0.95
North and Northeastern	43 / 272 (15.8%)	35 / 275 (12.7%)	0.78 [0.50 – 1.22]	
Others	75 / 624 (12.0%)	88 / 630 (14.0%)	1.16 [0.85 – 1.58]	

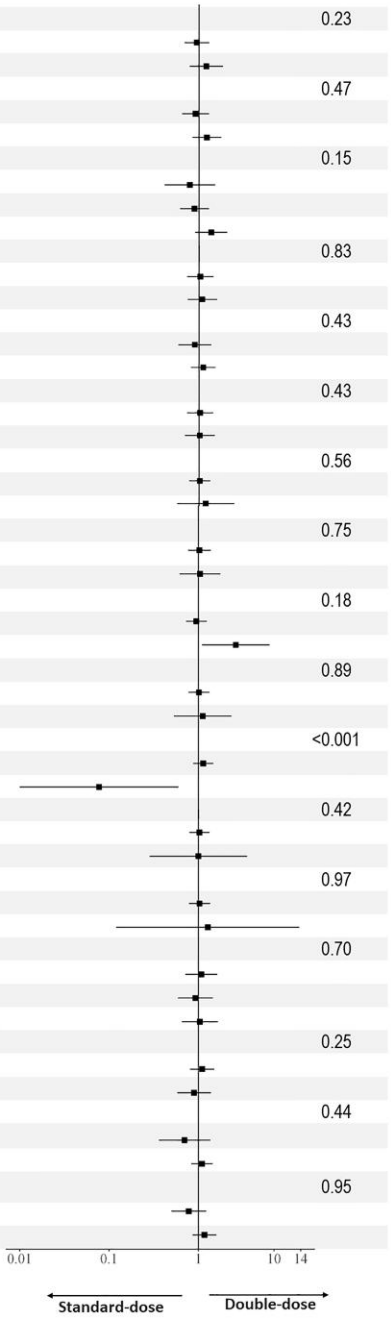


Figure 4 Primary outcome in all pre-specified subgroups. The win ratio was calculated using a non-parametric pairwise comparison for each outcome. Data are presented as point estimates and 95% CI with two-sided *P*-value. No adjustments for multiple testing were made. Day zero (T0) was the day of randomization for both study groups.STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; COPDs, chronic obstructive pulmonary diseases.

dose influenza vaccination is sufficient to prevent major cardiopulmonary outcomes in high CV risk patients, and, as such, increasing the influenza dose is not needed to achieve this goal.

Another potential explanation for our findings may be related to the ideal timing of influenza vaccination after an ACS. A meta-analysis of randomized trials comparing vaccination vs. no vaccination or placebo suggested that the benefits of the influenza vaccine for CV events reduction could be amplified among patients with recent ACS.[5,16] This hypothesis was subsequently tested by the Influenza vaccination After Myocardial Infarction (IAMI) trial.[23] This trial evaluated the intra-hospital use of a standard-dose quadrivalent inactivated influenza vaccine against placebo in post-myocardial infarction patients treated

Table 3 Solicited local and systemic adverse reactions ≤7 days after any dose

	Double-dose	Standard-dose	*P*-value
Local pain, *n* (%)	83 (9.5)	80 (10.2)	0.63
Injection site induration, *n* (%)	12 (1.4)	8 (1.0)	0.51
Erythema, *n* (%)	2 (0.2)	4 (0.5)	0.34
Fever			0.78
37.5°C–38.9°C, *n* (%)	22 (2.5)	17 (2.2)	–
≥39°C, *n* (%)	3 (0.3)	4 (0.5)	–
Fatigue, *n* (%)	16 (1.8)	9 (1.1)	0.25
Nausea, *n* (%)	11 (1.3)	11 (1.4)	0.80
General pain, *n* (%)	13 (1.5)	11 (1.4)	0.88
SAE (Guillain-Barrè syndrome, anaphylaxis reaction, skin and subcutaneous tissue disorders, and other medically attended related to SAE)	0	0	—

SAE, serious adverse events.
An adverse event was defined as any event not present before exposure to study vaccination or any event already present that worsened in intensity or frequency after exposure. Percentages were based on the number of participants in the safety set.

with percutaneous coronary intervention and found a 28% RR reduction for the primary outcome of time to all-cause death, acute myocardial infarction or stent thrombosis at 12 months of follow-up.[23] Moreover, event curves appeared to diverge early after randomization, suggesting that influenza vaccination might be considered as being part of in-hospital management after myocardial infarction. In our trial, we were unable to demonstrate that an early in-hospital vaccination strategy resulted in lower risk of clinically relevant events vs. a delayed outpatient standard vaccine dosing among patients with recent ACS. Different from the IAMI study, in our trial, use of a placebo or no vaccination control group was not feasible since according to the Brazilian national immunization program influenza vaccination is mandatory for all patients with coexisting conditions such as CVD, as well as for all patients >60 years. Of note, this position concurs with the current ACS guidelines, who recommend annual influenza vaccination as Class I for all patients with ACS.[24] However, there is no mentioning in the guidelines of how early the vaccine should be administered after a hospitalization for ACS. In this sense, the VIP-ACS study builds on prior evidence and suggests that influenza vaccination itself, regardless of the timing or dosing, should probably be offered to all patients after an ACS.

Regarding safety, the lack of a difference in self-reported systemic reactions adverse events may be explained by the double-dose being divided between limbs, potentially reducing likelihood of adverse reactions.

The neutral results from our trial may also be related to multiple constrains imposed by the COVID-19 pandemic. In the first wave of COVID-19 (2020), Brazilian health authorities anticipated the national influenza vaccination campaign, especially to elderly subjects, which impacted recruitment of patients in the VIP-ACS trial[14] and also decreased the effect of the planned intervention by diminishing viral spread. In addition, public health recommendations for face masks and physical distancing also reduced influenza virus circulation, and this may have attenuated any cardiopulmonary impact from in-hospital double-dose vaccination.[25,26] Additionally, in Brazil, during the COVID-19 pandemic, the influenza virus circulation was reduced, and there was also vaccine mismatch between circulating influenza B viruses and the influenza vaccine available at the time.[27–29] Finally, our results could also be explained by the play of chance.

Despite the neutral results from our trial, it should be reminded that influenza vaccination is crucial to prevent influenza-derived illness, as well as CV events and mortality. Vaccination at discharge could be implemented in hospital routines to improve coverage in high-risk patients, since this strategy may improve adherence and, as observed in our study and other similar reports,[23] was safe.

Study strengths and limitations

Our study has strengths such as the concealed allocation by a central web-based randomization system, intention-to-treat analysis, and blinded adjudication of outcomes by an independent clinical events committee. Moreover, despite the COVID-19 pandemic, follow-up was complete and only one out of 1801 patients could not have the vital status determined by the end of follow-up.

The VIP-ACS trial had limitations. First, trial enrolment and operations were affected by the COVID-19 pandemic, leading to a decision to amend the trial protocol, which resulted in revised sample size and early termination. However, this revision was made with change of the analytical method from a survival analysis (with Cox regression) to a hierarchical outcome analysed by the win ratio method. The win ratio method is a well validated and enabled the trial to preserve the planned study power.[17,18] It should also be noted that these decisions were made prior to unblinding and database lock, were approved by local regulatory bodies, and strictly followed the CONSERVE-SPIRIT reporting guidelines.[15] Second, the trial used an open-label design, however, all efficacy outcomes were adjudicated by an independent, blinded clinical events committee. Third, our trial was an investigator-initiated trial with limited funding, which did not allow for inclusion of double-dose outpatient and standard-dose in-hospital as additional randomized arms in the study design, limiting deeper additional conclusions about the ideal timing for vaccination. Fourth, our results could be explained by the lack of statistical power. Our power calculations were based on prior data from the literature[16] where patients presenting with a recent ACS derived a RR reduction of 55% for MACE with vaccine vs. control (placebo or no vaccination). Because we did not have a similar trial like ours testing two different strategies of vaccination (early double dose vs. delayed standard dose), we assumed that the magnitude of effect for our intervention could rely on a RR reduction of 28%. Even with this rationale, the trial could have been underpowered to detect a smaller effect. The fact that point estimates are close to the null and that secondary outcomes and sensitivity analyses are consistent with the primary outcome suggest, on the other hand, that lack of statistical power may not have been an issue. Fifth, there were 2% of patients in the double-dose in-hospital vaccine group and 12% in the standard-dose outpatient group who did not receive study intervention mainly due to constraints related to isolation measures during the COVID-19 pandemic. However, because the lack of adherence to study treatment was much higher in the control group, we understand that this finding might have biased the results against the null, since some patients in the control arm eventually did not receive vaccination.

Conclusions

In the VIP-ACS trial, a double-dose quadrivalent influenza vaccine before hospital discharge did not improve cardiopulmonary outcomes compared with outpatient standard-dose vaccination among patients hospitalized for ACS.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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