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

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Medical Epidemiology

VIP-ACS – Vaccination against Influenza to Prevent cardiovascular events after Acute Coronary Syndromes

Win ratio method for composite outcomes

Introduction

- ACSs represent the leading cause of death and disability globally.

- Influenza infection is associated with increased risk of CV events.

  (influenza triggers the inflammatory immune responses → promote instability of coronary lesions→ rupture or erosion)

Introduction

- A meta-analysis of RCTs (influenza vaccination vs. placebo or control)

  45% reduction in major adverse CV events in a recent ACS.

  [RR: 0.55; 95% CI: 0.41–0.75]

- Recent studies → increased vaccine dose considerably improves immunogenicity against influenza, resulting in fewer respiratory tract infections and hospitalizations.

- Yet ideal timing and dosage remain unclear (for high-risk population)

Aim of the study

Population: patients hospitalized with an ACS

Double dose influenza vaccine
(in-hospital)

Vs.

Standard dose influenza vaccine
(30 days after randomization)

Reducing the risk of major cardiopulmonary events

Methods


5mL vial (10 doses)
Influenza Virus Vaccine
Flu
Vaccine
0.5mL equals one adult dose
For intramuscular injection
Rx Only

Methods

Population

- Patients aged 18 years or older hospitalized with ACS
- 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
- 1 March until 30 November during the 2020 season

Methods

Key exclusion criteria

- 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,
- Pregnant or breastfeeding women.

Methods

Setting – 25 health centres in Brazil

The study

- Led by an academic steering committee and
- Sponsored by a grant from the Brazilian Ministry of Health.

- The study was registered with ClinicalTrials.gov (NCT04001504).

Randomization

Randomly assigned (1:1) to receive double dose or standard dose vaccine.

Concealed randomization; with the use of a central, interactive automated web-based system, REDCap™ software, stratified by research centre, using blocks of 8, 10, and 12.

Open label design; but the blinded adjudication of outcomes and blinded for statisticians and data analysts

Intervention

- VIP-ACS used a quadrivalent inactivated influenza vaccine (Fluarix®, GlaxoSmithKline Biologicals NL daer SmithKline Beecham Pharma GmbH & Co, Wavre, Belgium)

Double dose → during the index hospitalization, as soon as possible after randomization

Standard dose → 30±5 days after randomization during outpatient follow-up

Intervention

Follow-up visits

- 30±5 days, 6 months±10 days, and 12 months±20 days after randomization to monitor adverse events and potential study outcomes.

- 7±2 days after study vaccine administration to monitor any local or systemic adverse reaction to the vaccine.

Outcomes

The primary outcome

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

A hierarchical composite of MACE

- CV death,
- myocardial infarction,
- stroke

Outcomes

Other secondary outcomes → 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,
- hospitalization for respiratory or pulmonary infections including COVID-19.

Outcomes

Safety outcomes

- Serious adverse events reported through 12 months.
- Adverse events of special interest related to vaccination during the first 7 days after vaccine administration.

Impact of the COVID-19 pandemic

1. National influenza vaccination campaign
2. Patients objected to return for in-person visits
3. Widespread use of face masks (→ potentially attenuated the effect of the study intervention)

Protocol amendment was done

(prior to study termination and database lock)

- Change from time-to-event analysis to win ratio method
- Recalculation of required sample size (→ power 82.6% to detect treatment effects)

Statistical analysis

1. **Unmatched win ratio method**, as described by Pocock *et al*. **(Primary analysis)**
2. Unadjusted Cox proportional hazards models
3. Subgroup analyses
4. Safety analysis

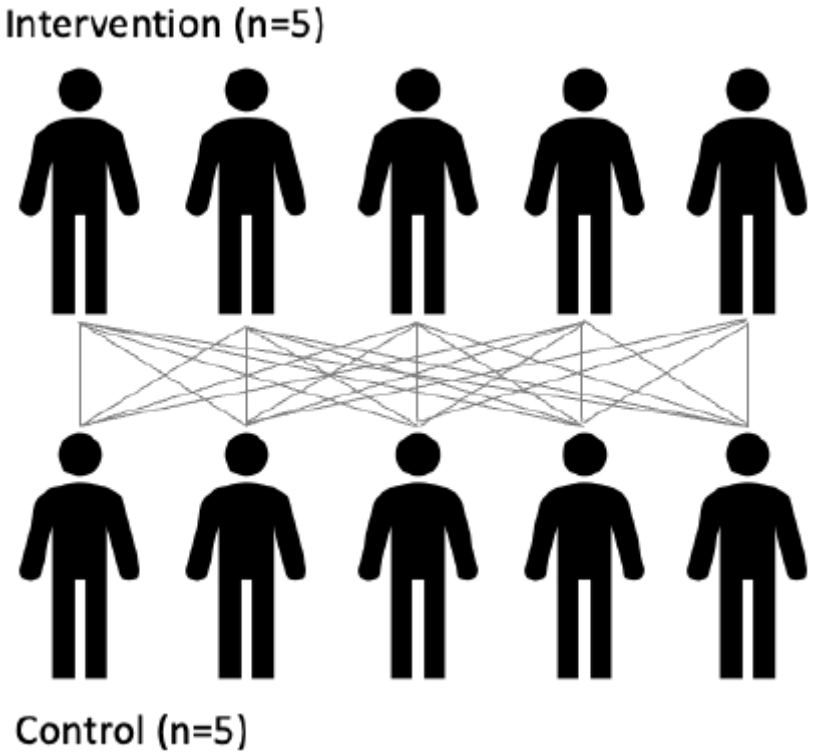
Intention-to-treat population comprising all patients who underwent randomization.

A *P*-value of <0.05 was defined as statistically significant.

The R software, version 4.2.0.

Steps of win ratio analysis (unmatched approach)

Step 1: Forming pairs



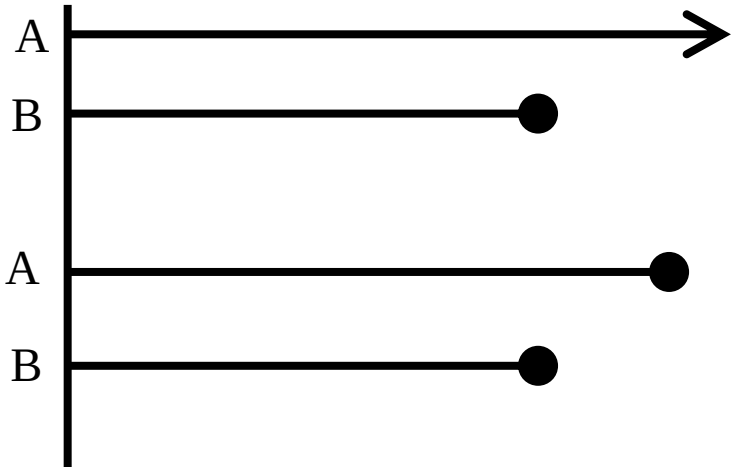
- Every patient in the intervention group pairs with every patients in the control group

Nt x Nc = 5 x 5 = 25 pairs

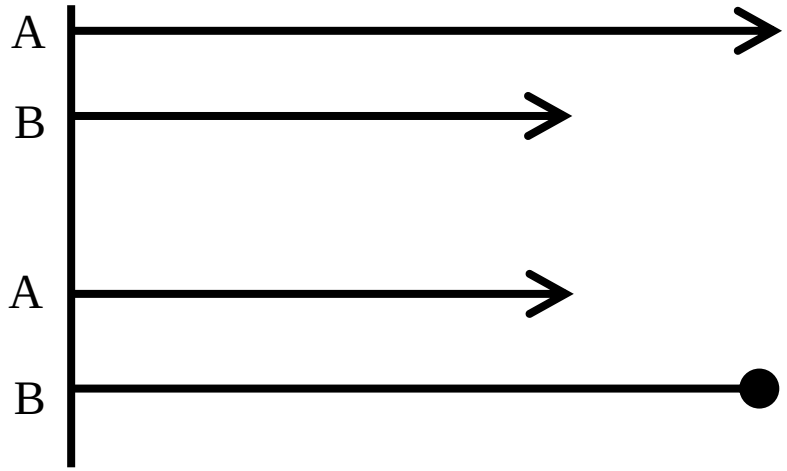
Steps of win ratio analysis (unmatched approach)

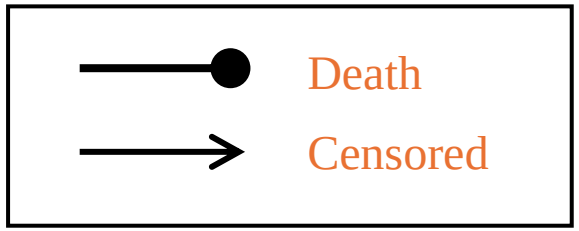
Step 2: Deciding win or lose

A win on death



Ties on death

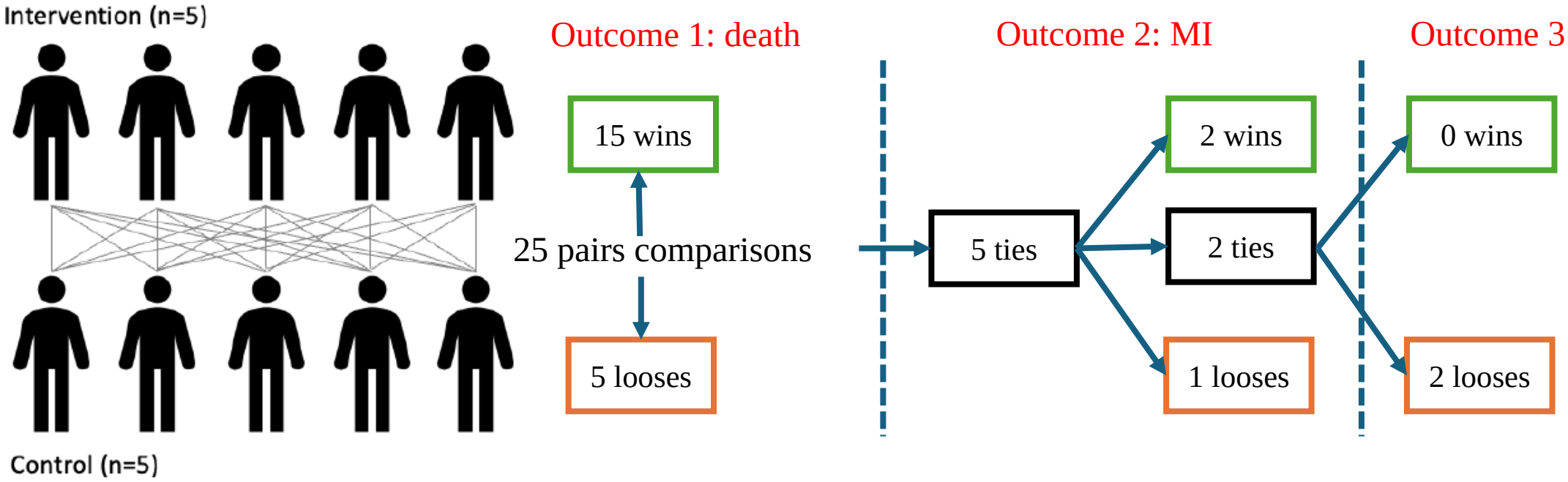




Steps of win ratio analysis (unmatched approach)

Step 3: Calculating win ratio

Outcome _ Hierarchy/order



$$\text{Win ratio} = \frac{\text{No. of wins}}{\text{No. of losses}} = \frac{17}{8} = 2.125$$ *(Odds* of intervention group faring better)

$$\text{Probability} = \frac{2.125}{1 + 2.125} = 0.68 \text{ or } 68\%$$ *(Probability* of intervention group faring better)

**Kayla Chiew 2023 Composite outcomes and making sense of the 'win ratio'*

Results

Image: www.aafp.org

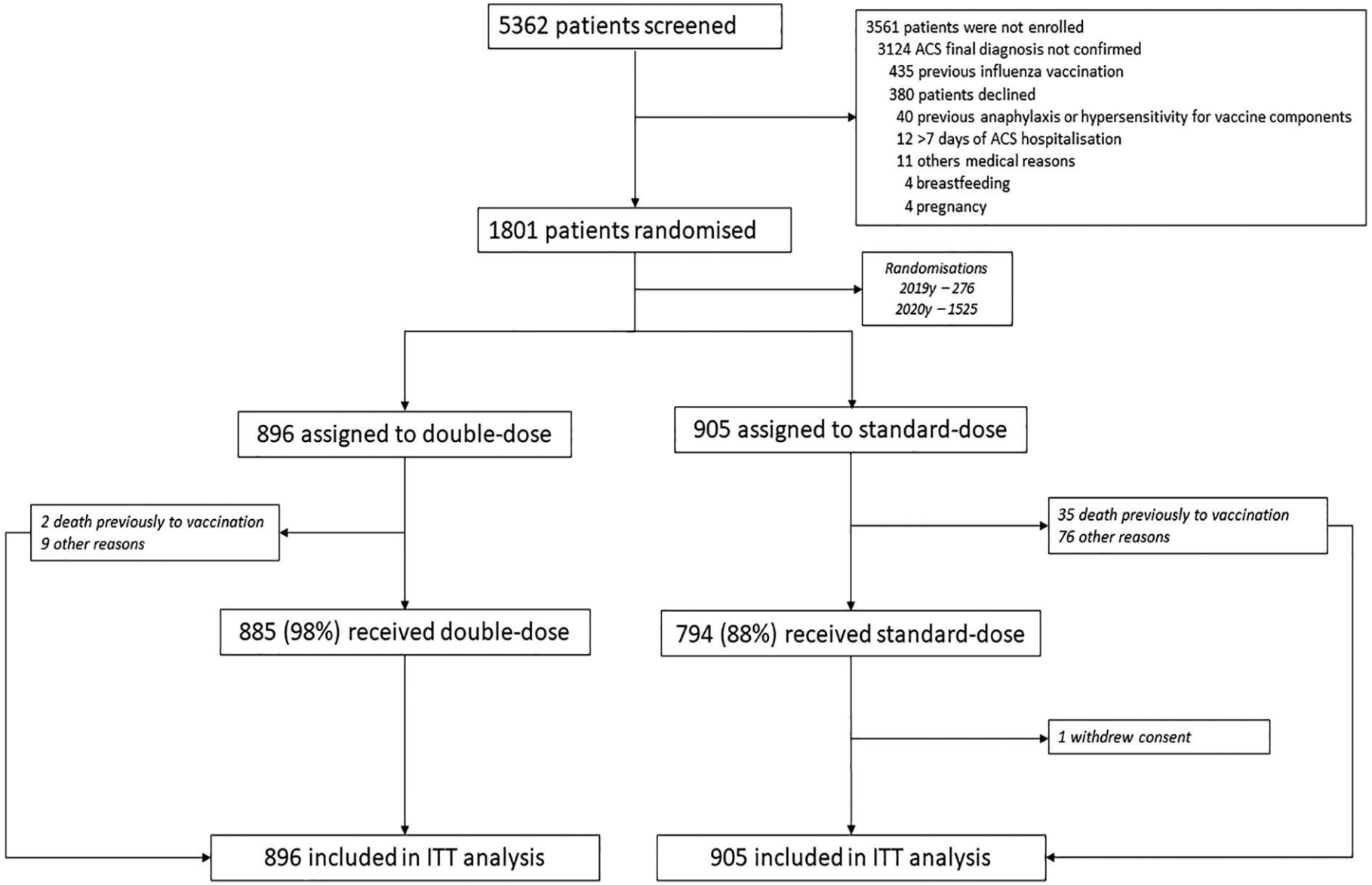


Figure: CONSORT—trial profile and analysis.

Baseline characteristics of patients

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)

Baseline characteristics of patients (Cont.)

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)

Hierarchical order

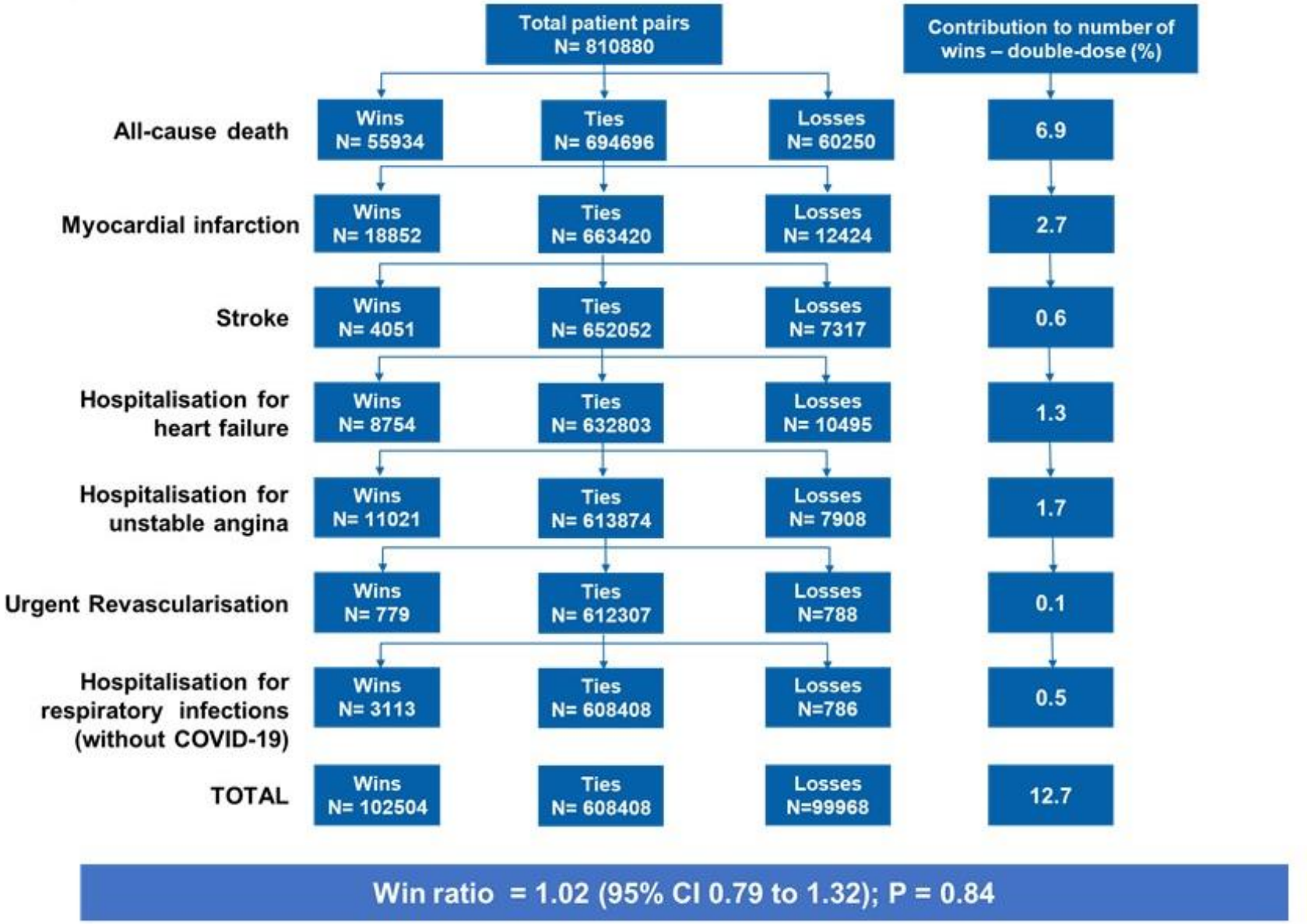


Figure: Win ratio analysis for primary outcome

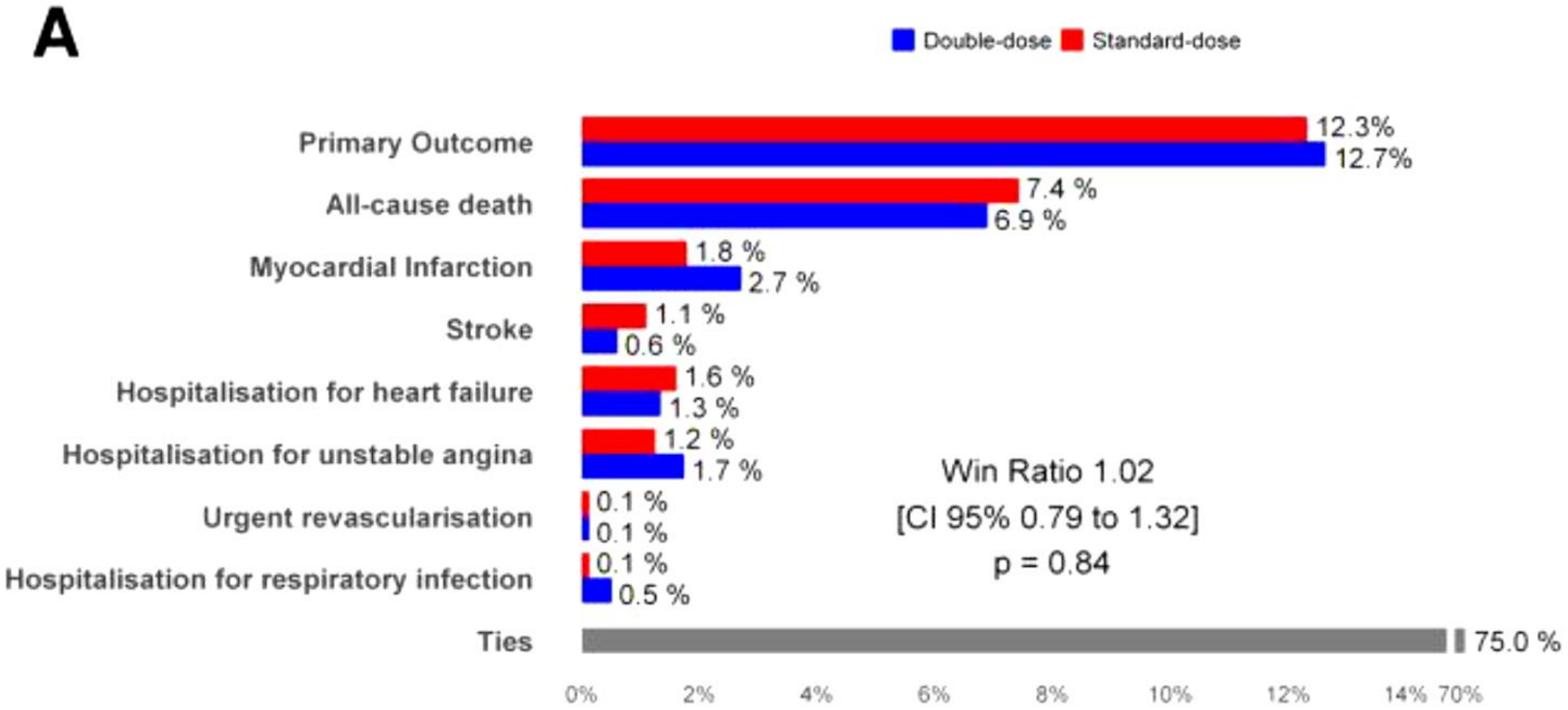


Figure: Win ratio analysis for primary outcomes and components

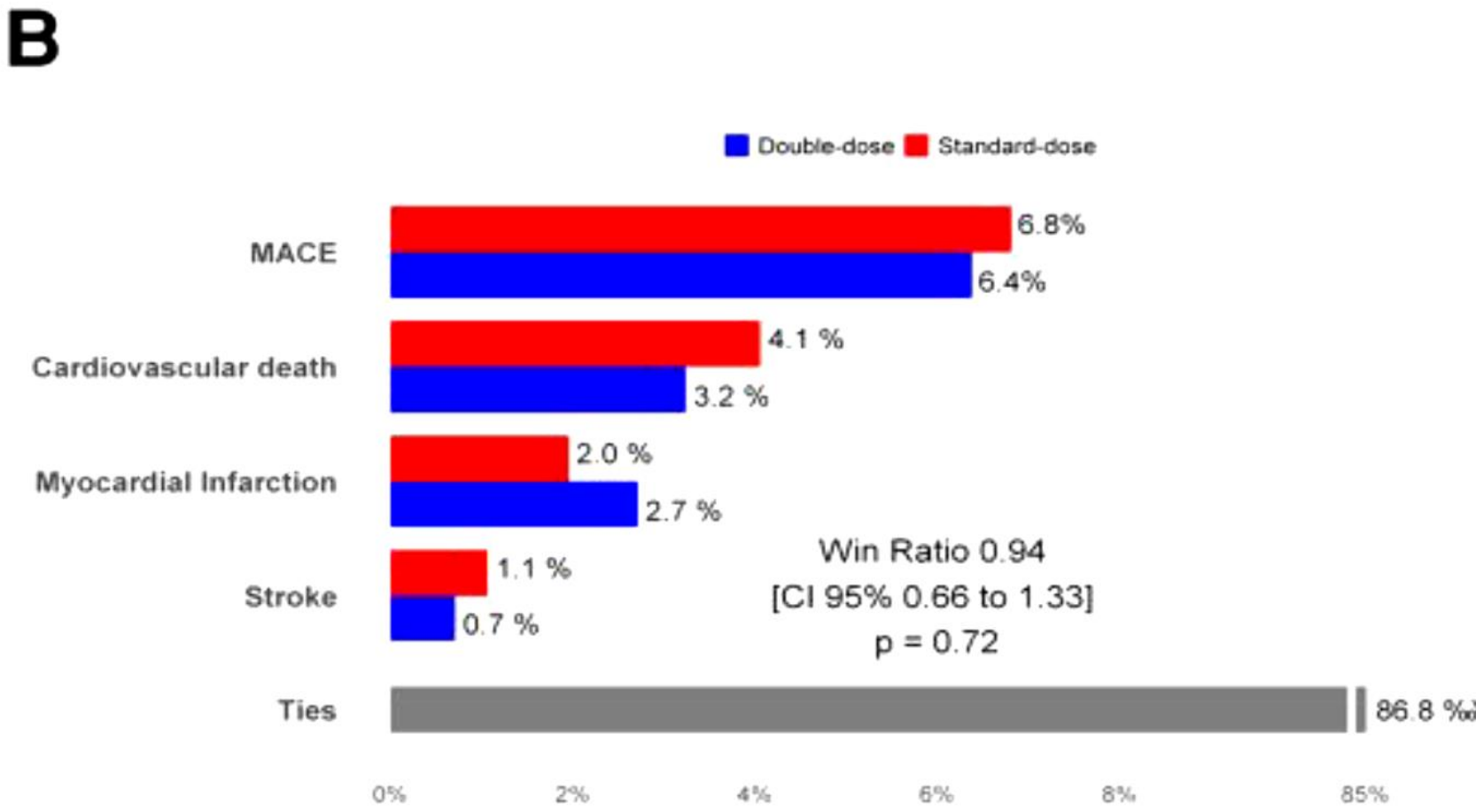


Figure: Win ratio analysis for key secondary outcome and components

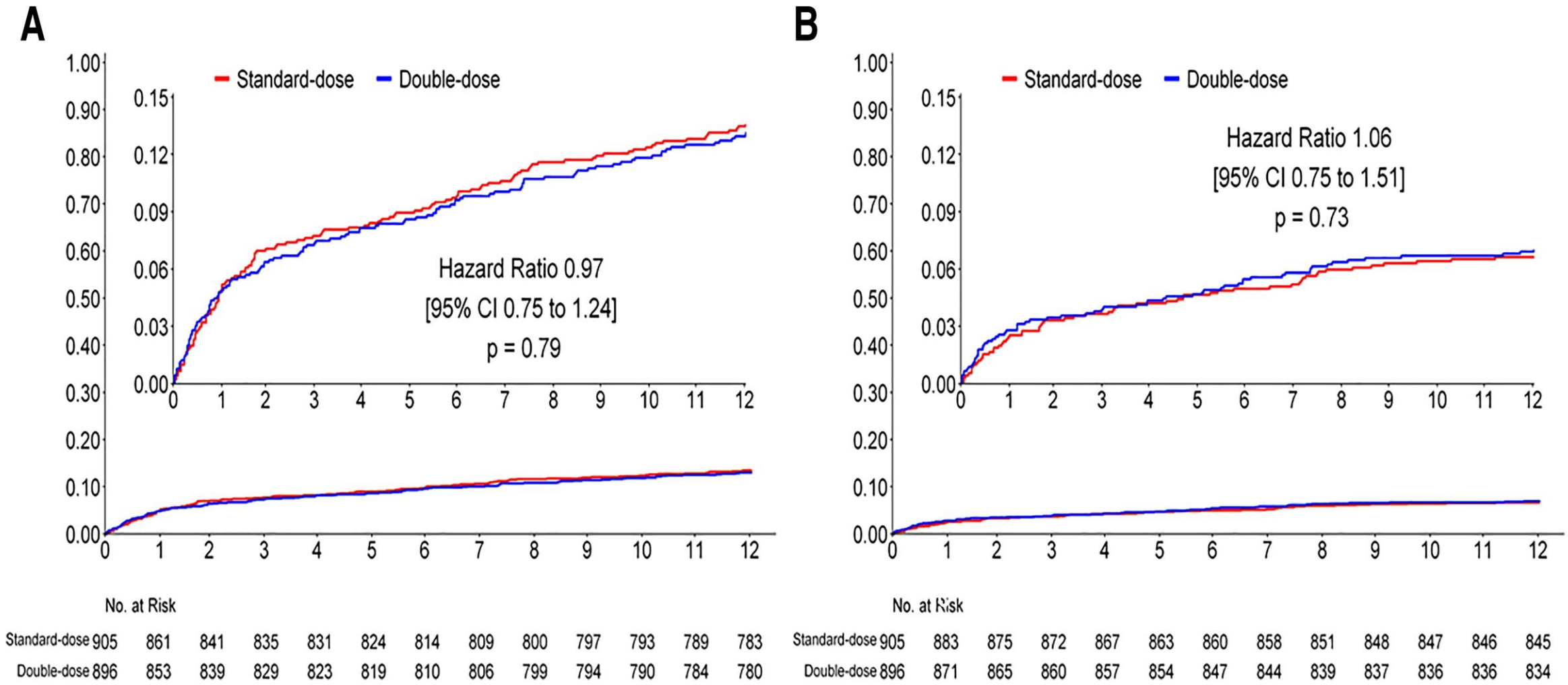


Figure: Kaplan–Meier event curves using Cox regression for primary outcome as time-to-first event analysis. (A) Primary outcome, (B) Key secondary outcome

Table: Kaplan–Meier event curves using Cox regression for secondary outcome as time-to-first event analysis

Outcome	Double-dose ($n = 896$)	Standard-dose ($n = 905$)	Total ($n = 1801$)	Measure	*P*-value
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

Figure: Primary outcome in all pre-specified subgroups.

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]	

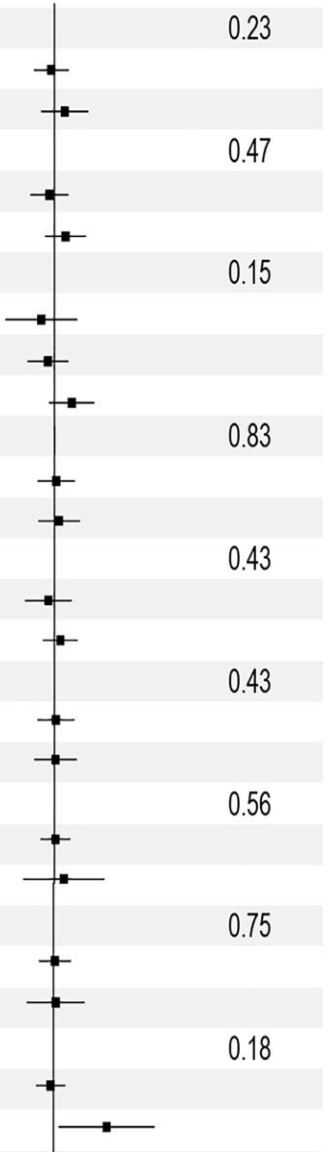


Figure: Primary outcome in all pre-specified subgroups. (cont.)

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]	

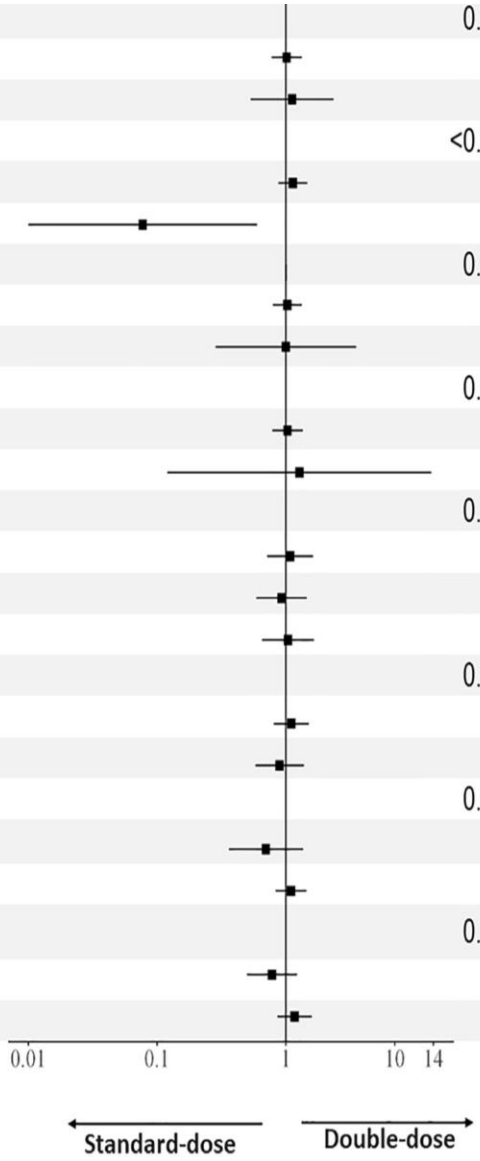


Table 3 Solicited local and systemic adverse reactions ≤7 days after any dose

	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	—

Discussion & Conclusion

Image: www.aafp.org

Discussion & conclusion

- A double-dose vaccine during hospitalization did not improve cardiopulmonary outcomes at 12 months among patients with ACS

- Results were consistent for different analytical methods, for secondary outcomes and for pre-specified subgroups.

- Self-reported systemic reactions or investigator-reported adverse events

→ not different between groups.

Discussion & conclusion

- The standard-dose influenza vaccination is sufficient to prevent major cardiopulmonary outcomes in high CV risk patients.

- The VIP-ACS study suggests that influenza vaccination itself, regardless of the timing or dosing, should probably be offered to all patients after an ACS.

Discussion & conclusion

Strengths

- Concealed allocation by a central web-based randomization system.
- Intention-to-treat analysis.
- Blinded adjudication of outcomes by an independent clinical events committee.
- Follow-up was complete despite the COVID-19 pandemic.

Discussion & conclusion

Limitations

COVID-19 pandemic affected

- Trial enrolment and operations, leading to a decision to amend the trial protocol, which resulted in revised sample size and early termination.

- 2% of patients in the double-dose vaccine group and 12% in the standard-dose group did not receive the intervention.

Thank you for your attention…

Photo: https://www.fiercepharma.com/