TEMERTY FACULTY OF MEDICINE
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Infections and Vaccinations: Connections and Impact on CV Disease

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Presenter Disclosure

Dr. Jacob A. Udell

Infection and vaccinations: Connections and impact on CV disease

Relationships with financial sponsors:

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- **Other:** N/A

Poll #1

I consider optimizing GDMT in my patients with CVD during routine outpatient clinic assessments:

1. Yes
2. No

Poll #2

I include checking/recommending evidence-based viral infection vaccinations for cardiopulmonary risk reduction in my patients with CVD when optimizing GDMT:

1. Yes
2. No
3. Sometimes
4. I should but don’t know how

Poll #3

The CV benefit of an annual flu shot is comparable to standard GDMT:

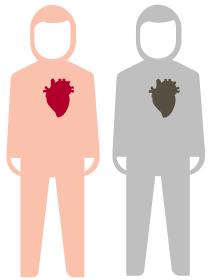
1. No
2. Yes
3. Maybe, show me the data

Learning Objectives

By the end of this session, participants will be able to:

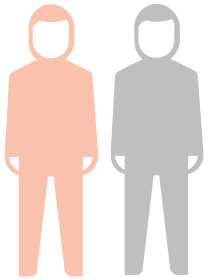
1. Explain interplay between immune response and pathophysiology between cardiovascular disease (CVD) and susceptibility to viral infections like influenza, herpes zoster (shingles), respiratory syncytial virus (RSV) and COVID-19
2. Highlight key data demonstrating the association between viral infections and downstream CV complications in patients with or at risk of CVD
3. Analyze the evidence for vaccination against viral infections as a strategy to reduce the risk of complications from infections and discuss practical considerations for cardiovascular specialists

Patients with or at Risk of CVD are at Higher Risk of Morbidity and Mortality from Viral and Other Respiratory Infections



Compared with patients without heart failure, **patients with heart failure** are at higher risk from infectious diseases

- **Twice** as likely to develop herpes zoster[1]
- **Increased in-hospital morbidity and mortality** following influenza infection[2]
- **4–33 times higher** incidence of hospitalization with RSV[3]
- **Poorer outcomes** when hospitalized for pneumonia[4]
- **Higher risk** of hospitalization or death due to influenza[5]



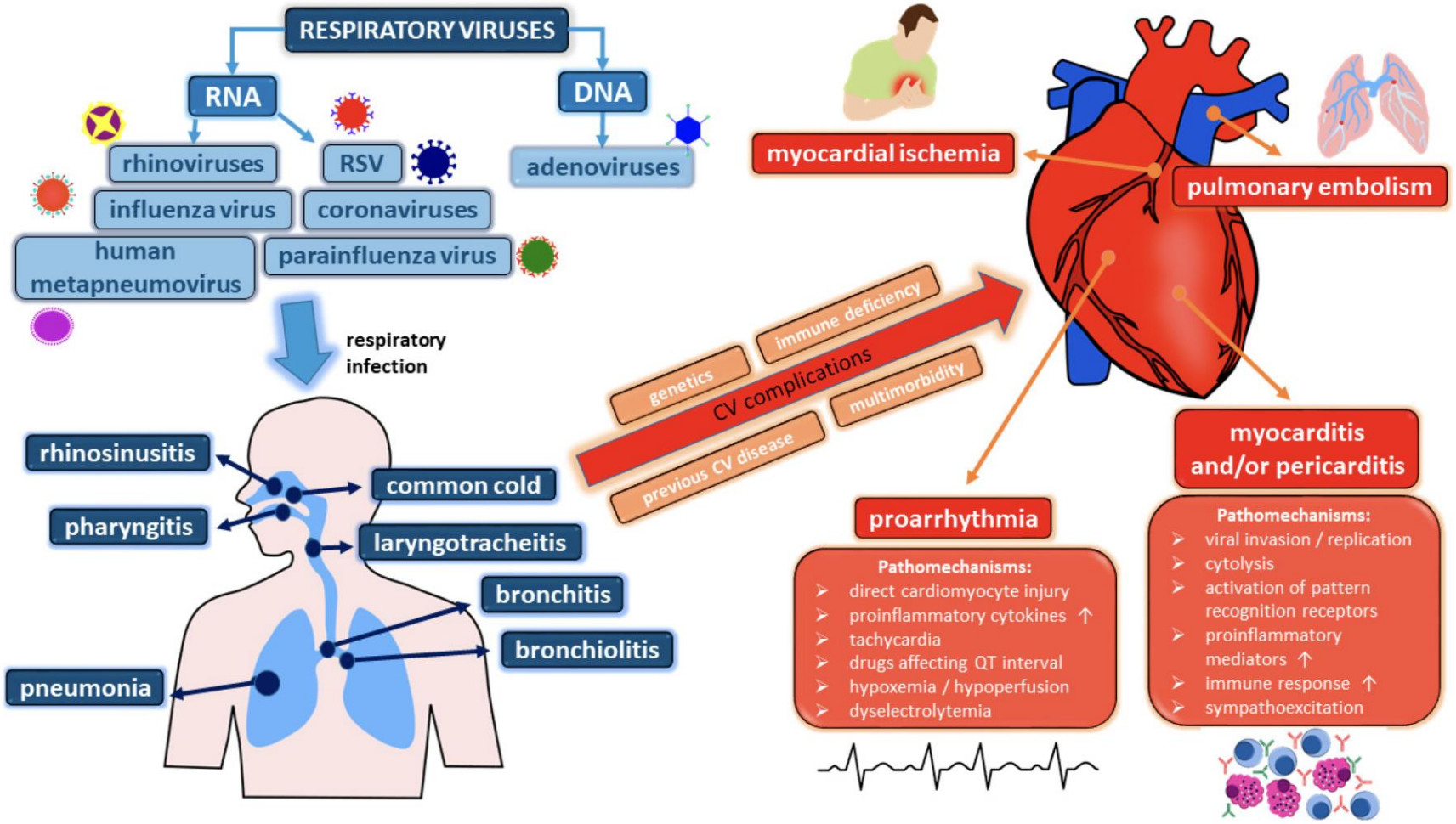
Compared with patients without diabetes, **patients with diabetes** are at higher risk from infectious diseases

- **5.5-18.0 times higher** incidence of hospitalization with influenza infection[6]
- **2.4–6.4 times higher** incidence of hospitalization with RSV in adults aged ≥50[3]
- **7%-33% higher** incidence of post-herpetic neuralgia (PHN) in those with HZ[7]
- **2.27–4.26 higher** risk of TB infection and **36%-112% higher** rate of treatment failure and death[8]

HZ, herpes zoster; TB, tuberculosis; RSV, respiratory syncytial virus

1. Wu PH *et al. BMC Infect Dis* 2015;15:17; 2. Panhwar MS *et al. J Am Coll Cardiol HF* 2019;7:112–117; 3. Branche AR *et al. Clin Infect Dis* 2022;74:1004–1011; 4. Thomsen RW *et al. J Gen Intern Med* 2008;23:1407–1413; 5. Hak E *et al. Epidemiol Infect* 2001;126:261–268. 6. Mertz D et al. BMJ 2013;347:f5061; 7. Forbes HJ et al. Neurology 2016;87:94–102. 8. Baker MA *et al. BMC Med* 2011;9:81.

Intersection of Respiratory Virus Infections and Adverse Cardiovascular Events

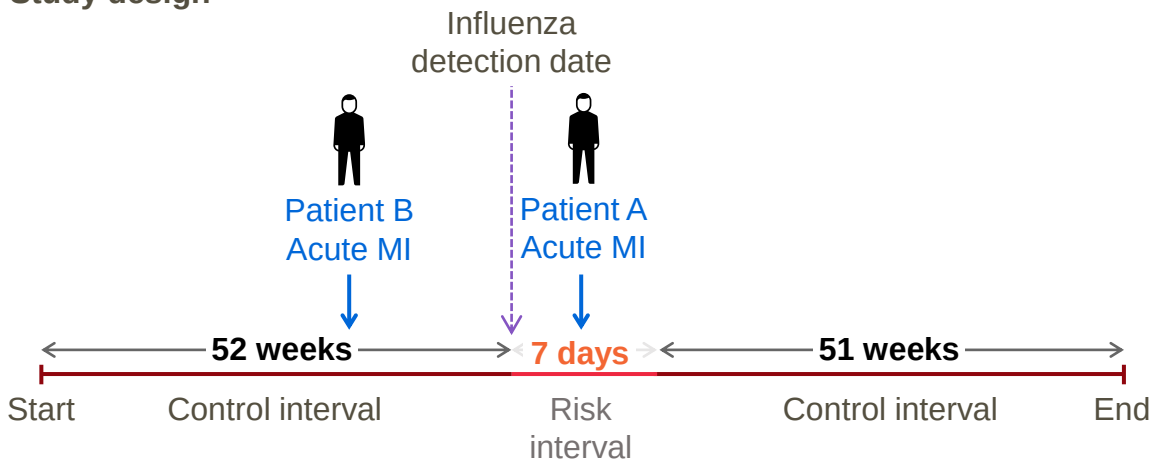


Franczuk *et al.* 2023. *Biomedicines*. **11:** 71

Lab-confirmed Influenza, RSV and Other Respiratory Infections Can Trigger an Acute MI[1]

An increase in heart attacks from 3.3/week to 20/week

Study design



N=364 acute MI hospitalisations (332 patients) who had a lab-confirmed influenza diagnosis

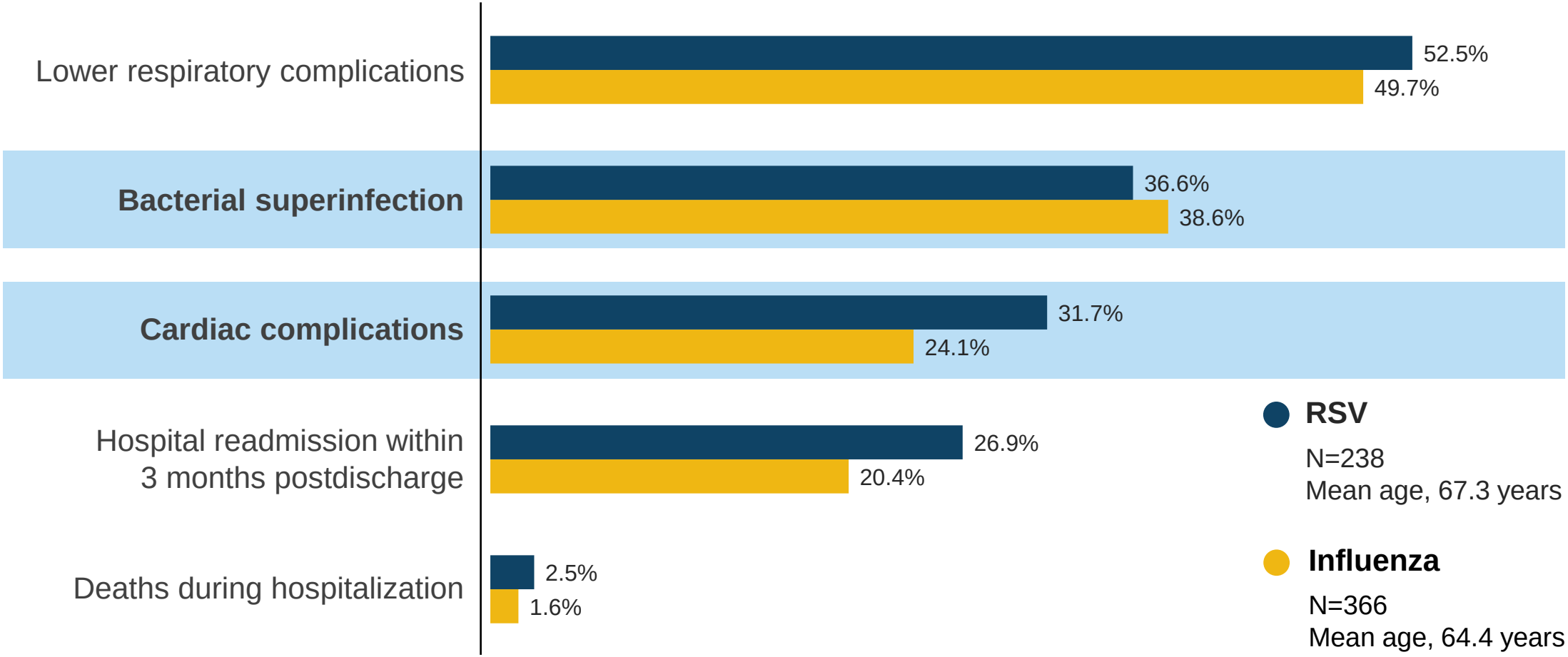
Exposure	Risk ratio (95% CI)
Influenza	
Days 1–7	**6.05 (3.86–9.50)**
Days 8–14	0.60 (0.15–2.41)
Days 15–28	0.75 (0.31–1.81)
Influenza A	**5.17 (3.02–8.84)**
Influenza B	**10.11 (4.37–23.38)**
RSV	**3.51 (1.11–11.12)**
Other resp. viruses	2.77 (1.23–6.24)
Other resp. infection	3.30 (1.90–5.73)

CI, confidence interval; MI, myocardial infarction; RSV, respiratory syncytial virus

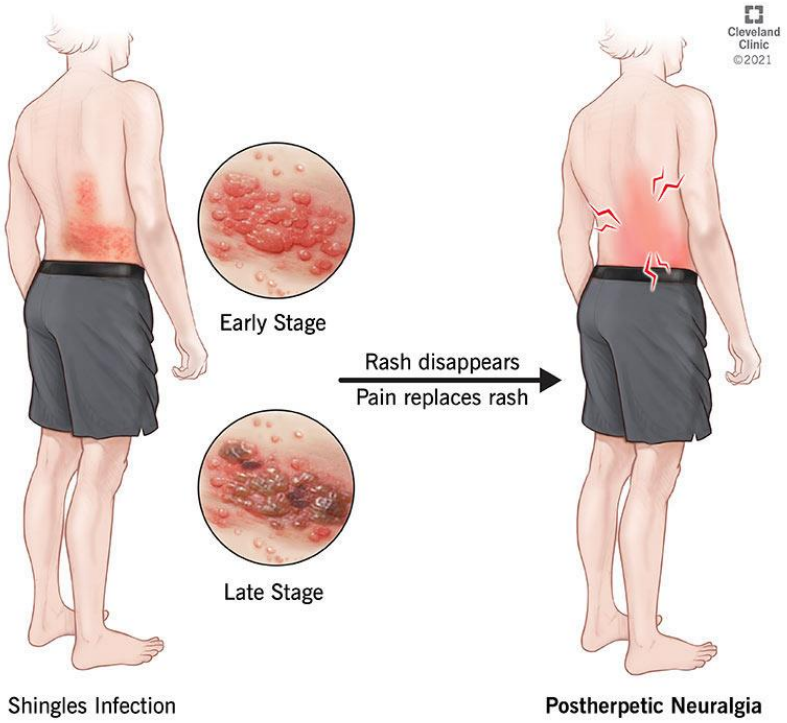
Self-controlled case series study design – patients acted as their own control in periods when they were not exposed vs when they were exposed to influenza and other respiratory viruses in Ontario, Canada.

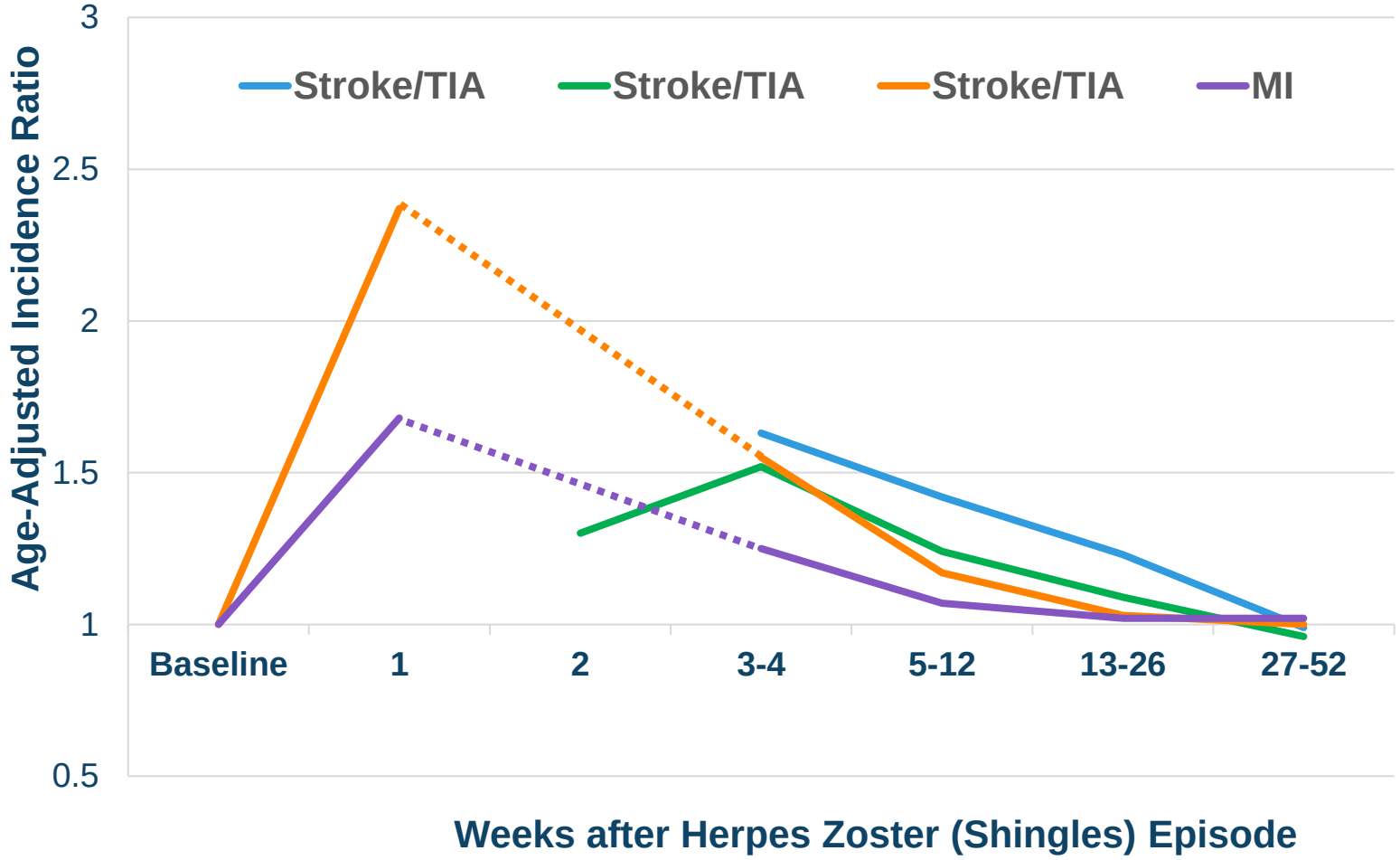
Kwong JC *et al. N Engl J Med* 2018;378:345–353

Rates of Complications w/ Respiratory Infection Hospitalizations Similar between RSV and Influenza



Herpes Zoster (Shingles) Associated with an Increased Risk of MI/Stroke



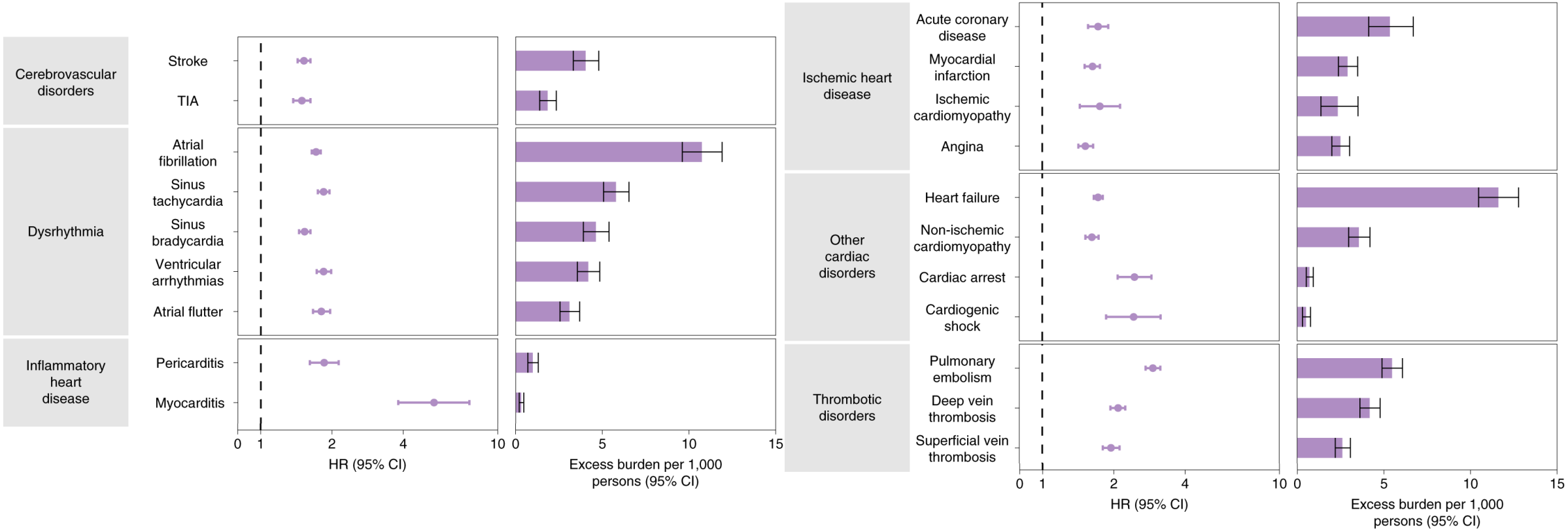


Self-controlled case series study design – patients acted as their own control in periods when they were not exposed vs when they were exposed to herpes zoster (shingles) diagnosis.

Wu PH et *al. J Clin Med* 2019;8(547):1-15. doi:10.3390/jcm8040547.
Langan SM, *et al. Clin Infect Dis* 2014;58:1497-1503. Schink T, *et al*. *PLoS ONE* 2016;11:e0166554. Minassian C, *et al. PLoS Med* 2015;12:e1001919.

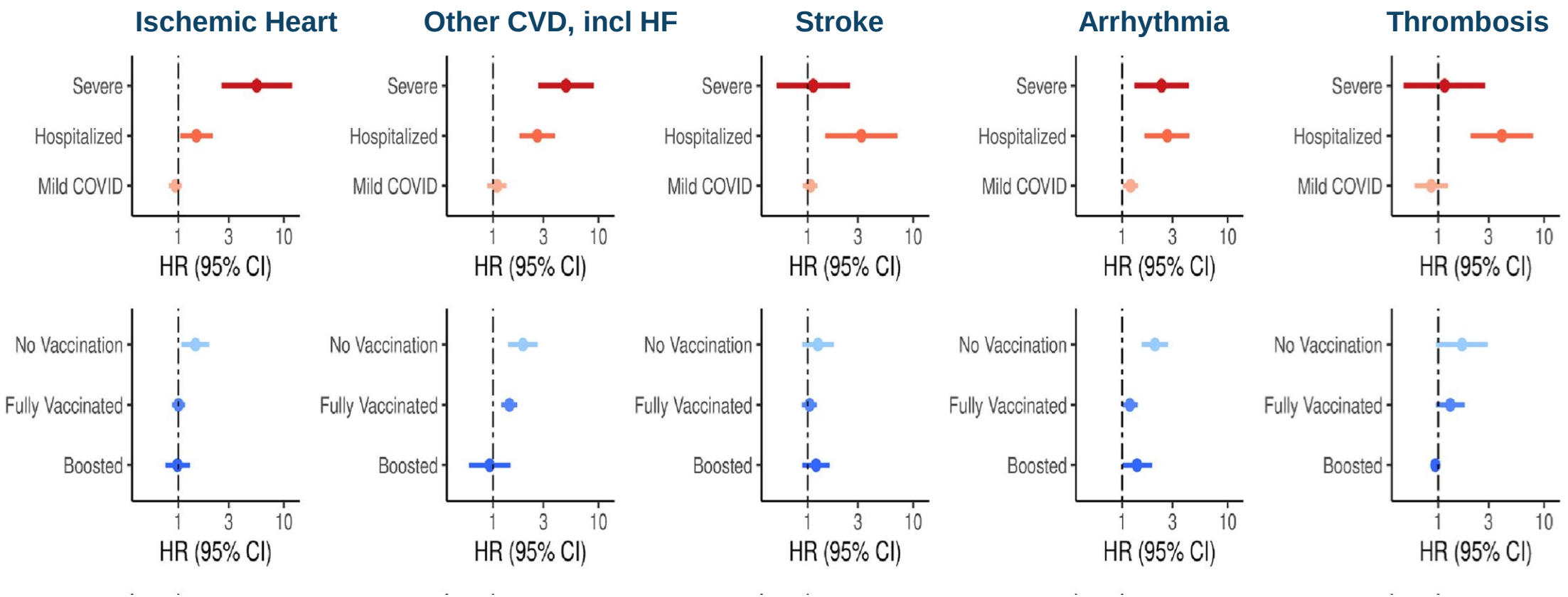
COVID-19 Increases Risk of CV Events[1,2]

A US retrospective COVID-19 case-control* database analysis estimated risks and 12-month burdens of incident post-acute COVID-19 cardiovascular outcomes[1]



* Using national healthcare databases from the US Department of Veterans Affairs with presented analysis conducted using a cohort of 153,760 individuals with COVID-19, as well as 5,637,647 individuals as contemporary controls. HR = hazard ratio; CI, confidence interval; TIA, transient ischemic attack; US, United States. 1. Xie Y et al. *Nat Med* 2022; 28(1),583–590; 2. Patone M *et al. Nat Med* 2022; 28(1),410-422

Risk of Cardiovascular, Stroke, and Thrombotic Events by Severity of COVID-19 Infection + Vaccination Status

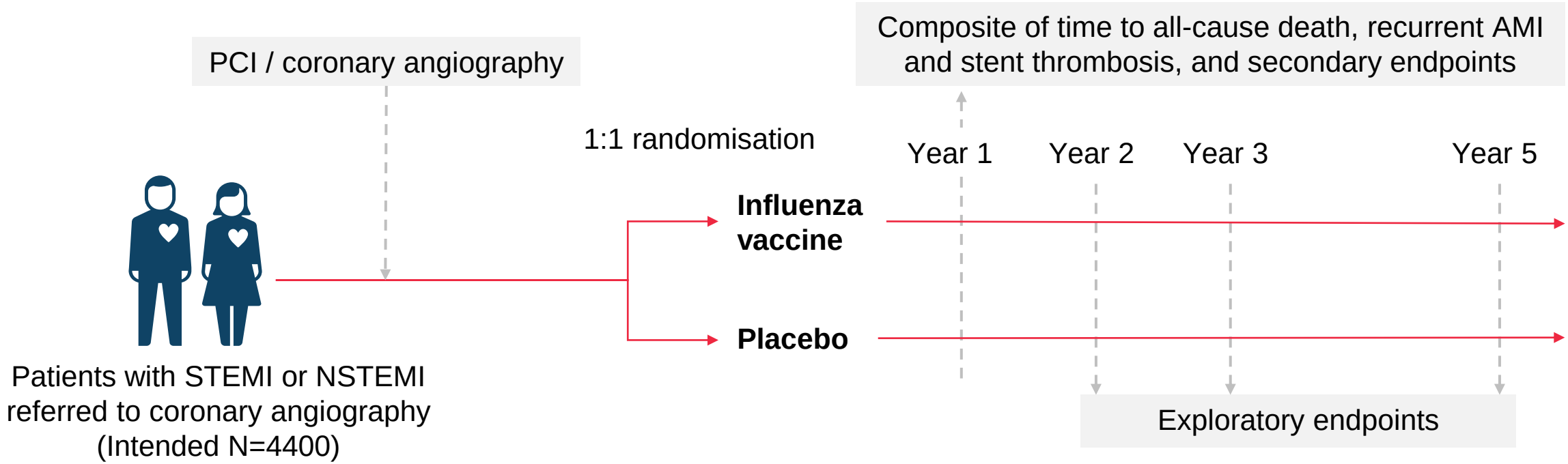


* Using national healthcare databases from Singapore

1. Lim JT *et al. Clin Infect Dis* 2024;78:70-79.

IAMI Trial: Influenza Vaccine for CV Risk Reduction in Patients with Acute MI (and Stable CAD)

Influenza vaccination After Myocardial Infarction (IAMI) trial



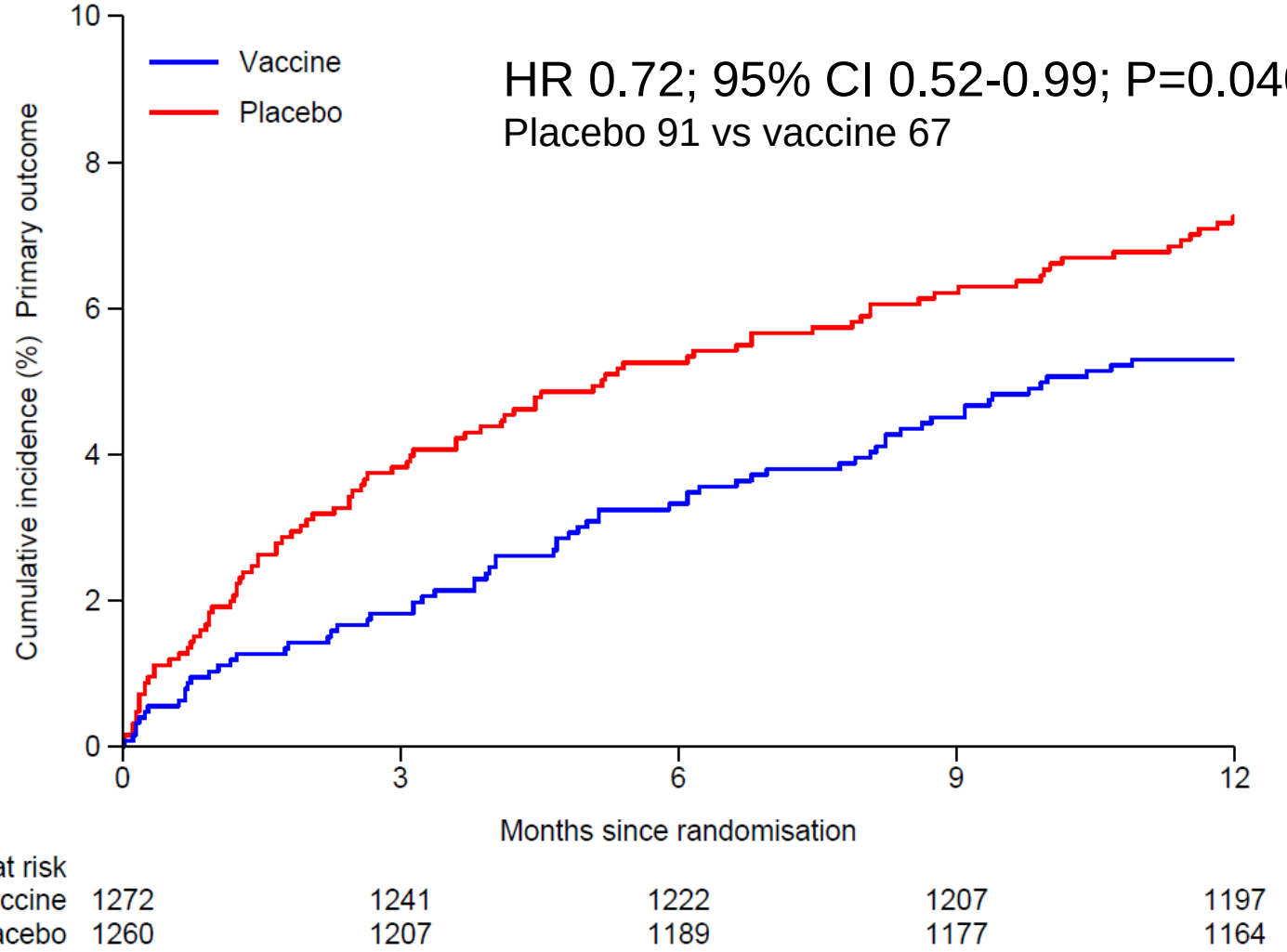
NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; RCT, randomised controlled trial; STEMI, ST-elevation myocardial infarction

Fröbert O *et al. Am Heart J* 2017;189:94–102.

Primary Endpoint: All-cause Mortality, MI, Stent Thrombosis

N = 2532

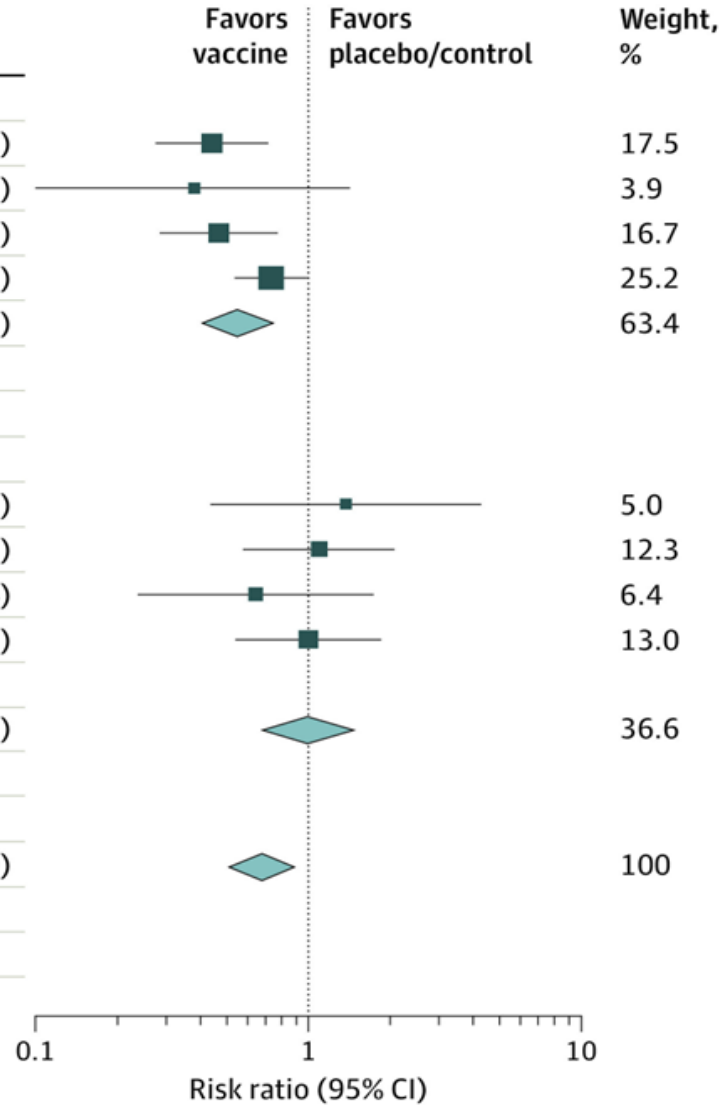
STEMI ~54%
NSTEMI ~45%
Stable CAD <1%



Fröbert O, *et al*. *Circulation* 2021;144:1476-1484.

Meta-Analysis of Influenza Vaccine RCTs for CV Risk Reduction

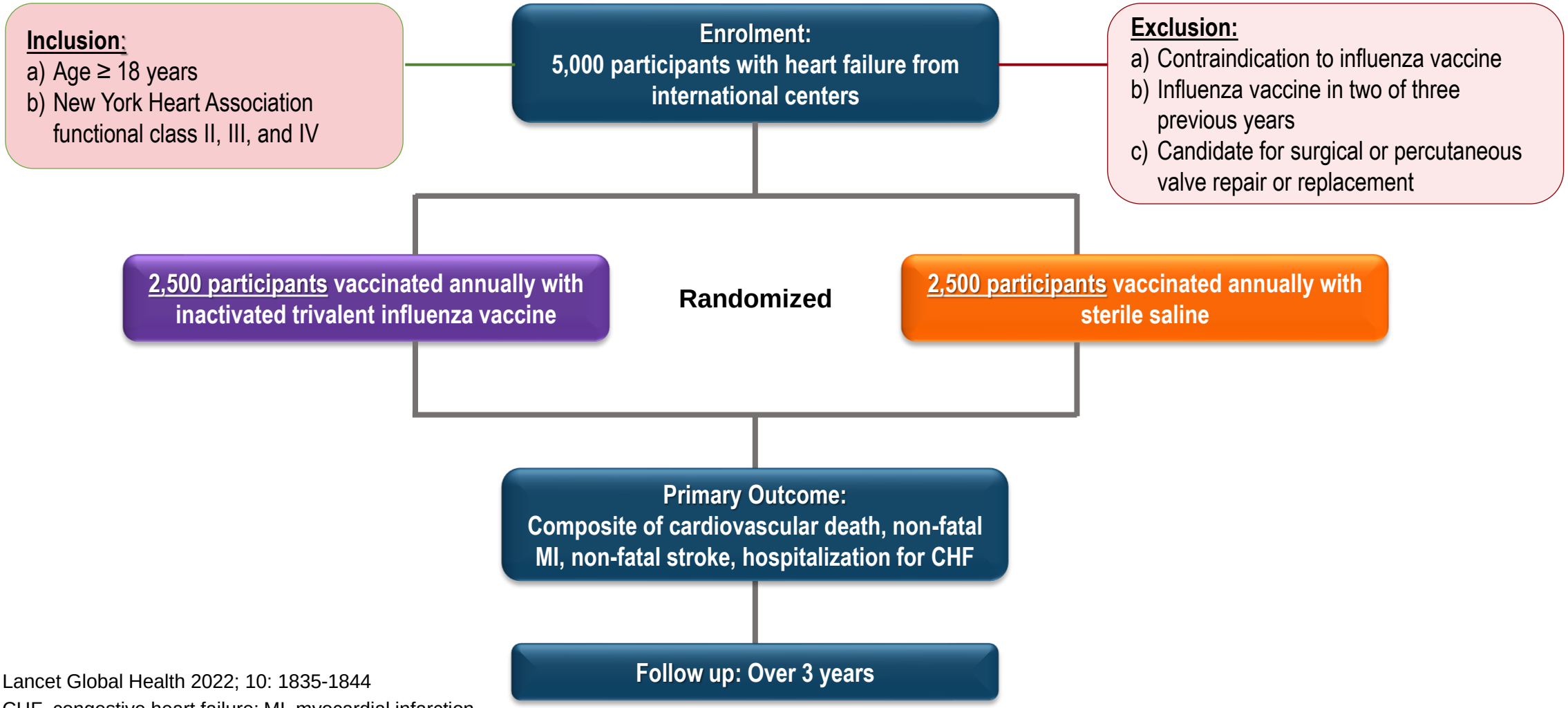
Study or subgroup	Vaccine Events	Vaccine Total	Placebo/control Events	Placebo/control Total	Risk ratio, (95% CI)	Weight, %
Recent ACS						
Gurfinkel et al,[19] 2004	18	96	41	97	0.44 (0.28-0.71)	17.5
Ciszewski et al,[20] 2008	3	83	7	74	0.38 (0.10-1.42)	3.9
Phrommintikul et al,[21] 2011	20	221	42	218	0.47 (0.29-0.77)	16.7
Frøbert et al,[7] 2021	67	1266	91	1258	0.73 (0.54-0.99)	25.2
Total events	108	1666	181	1647	0.55 (0.41-0.75)	63.4
Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 4.50$, df = 3 ($P = .21$); $I^2 = 33\%$						
Test for overall effect: z = 3.78 ($P < .001$)						
Stable outpatients						
Govaert et al,[22] 1994	7	927	5	911	1.38 (0.44-4.32)	5.0
Gurfinkel et al,[19] 2004	14	49	13	50	1.10 (0.58-2.09)	12.3
Ciszewski et al,[20] 2008	6	242	10	259	0.64 (0.24-1.74)	6.4
De Villiers et al,[23] 2009	20	1620	20	1622	1.00 (0.54-1.85)	13.0
Frøbert et al,[7] 2021	0	6	0	2	Not estimable	
Total events	47	2844	48	2844	1.00 (0.68-1.47)	36.6
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.14$, df = 3 ($P = .77$); $I^2 = 0\%$						
Test for overall effect: z = 0.02 ($P = .98$)						
Total events	155	4510	229	4491	0.68 (0.52-0.90)	100
Heterogeneity: $\tau^2 = 0.05$; $\chi^2 = 11.27$, df = 7 ($P = .13$); $I^2 = 38\%$						
Test for overall effect: z = 2.73 ($P = .006$)						
Test for subgroup differences: $\chi^2 = 5.65$; df = 1 ($P = .02$); $I^2 = 82.3\%$						



ACS, acute coronary syndrome; CI, confidence interval; RCT, randomized controlled trial

Behrouzi B, Bhatt DL, Cannon CP *et al*… Udell JA. *JAMA Netw Open.* 2022;5:228873.

Influenza Vaccine to Prevent Adverse Vascular Events (IVVE) in Heart Failure



Lancet Global Health 2022; 10: 1835-1844

CHF, congestive heart failure; MI, myocardial infarction

Flu Vaccine in HF: Overall Results

	Influenza vaccine (N=2560)	Placebo (N=2569)	Influenza vaccine vs. Placebo	
	No. of events (%)	No. of events (%)	HR (95% CI)	P value
First primary	380 (14.8)	410 (16.0)	0.93 (0.81-1.07)	0.30
CV death	334 (13.0)	374 (14.6)	0.89 (0.77-1.04)	0.13
All Hosp	388 (15.2)	455 (17.1)	0.84 (0.74-0.97)	0.01
HF Hosp	245 (9.6)	277 (10.8)	0.88 (0.74-1.04)	0.15
Pneumonia	61 (2.4)	104 (4.0)	0.58 (0.42-0.80)	0.0006

Lancet Global Health 2022; 10: 1835-1844.

CI, confidence interval; CV, cardiovascular; MI, myocardial infarction

Flu Vaccine in HF: Results During vs Outside Influenza Season

	Peak Influenza			Outside of Peak Season		
	Influenza vaccine	Placebo	Influenza vacc. vs Placebo	Influenza vaccine	Placebo	Influenza vacc. vs Placebo
	No. of events (%)	No. of events (%)	HR (95% CI)	No. of events (%)	No. of events (%)	HR (95% CI)
Primary EP	193.7 (7.7)	227 (9.4)	0.82 (0.68-0.99)	187 (7.5)	173 (6.9)	1.08 (0.88-1.33)
All Hosp	195 (7.8)	230 (9.2)	0.84 (0.69-1.01)	193 (7.9)	225 (9.1)	0.84 (0.70-1.03)
HF Hosp	128 (5.1)	124 (4.9)	1.03 (0.80-1.32)	117 (4.7)	153 (6.1)	0.76 (0.60-0.97)
Pneumonia	28 (1.1)	54 (2.1)	0.51 (0.32-0.81)	33 (1.3)	50 (2.0)	0.65 (0.42-1.01)

Lancet Global Health 2022; 10: 1835-1844.
HR, hazard ratio

INVESTED

NIH National Heart, Lung, and Blood Institute

Post-MI (12 months) or HF Hospitalization (24 months)

+ One additional risk factor:

Age ≥ 65, LVEF < 40%, DM, BMI > 30, eGFR < 60, prior MI, prior HF hosp., prior ischemic stroke, PAD, smoking

3 influenza seasons
2016/2017
2017/2018
2018/2019

RANDOMIZED 1:1 DOUBLE BLIND ANNUAL VACCINE STRATEGY

High Dose Trivalent Inactivated Influenza Vaccine

Standard Dose Quadrivalent Inactivated Influenza Vaccine

All other CV Rx per treating HCP

Followed up to 4 times a year

***Annual Vaccination* to assigned strategy**

Primary Endpoint

Death or Cardiopulmonary Hospitalization within each influenza season

Secondary Endpoints

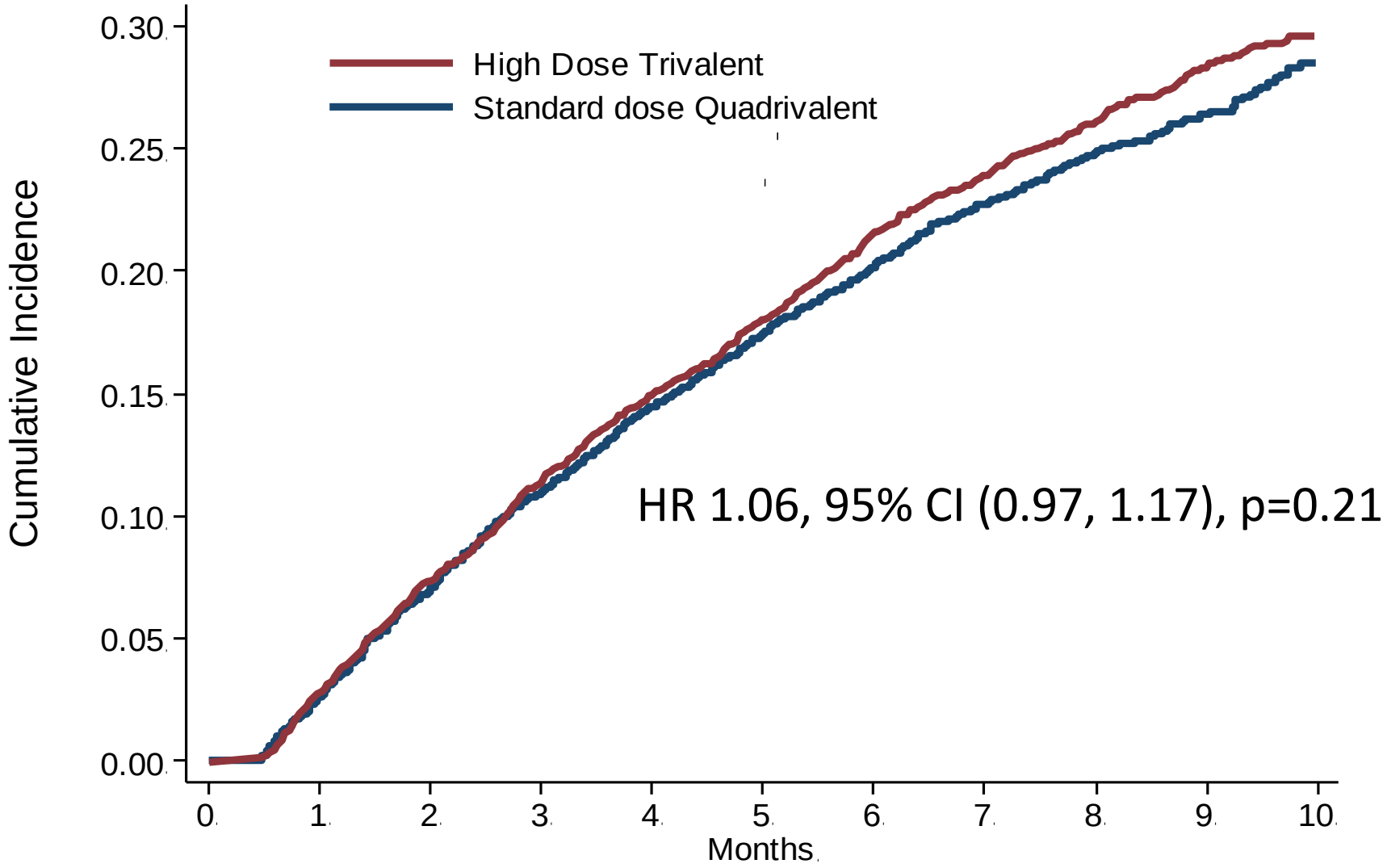
- **Total CV/pulmonary hospitalizations or all-cause death**
- **CV death or CV hospitalization**
- **All-cause death or CV/pulmonary hospitalizations**
- **Individual components of the primary efficacy endpoint**

Vardeny O, Kim K, Udell JA, et al. *JAMA* 2021;325:39-49.

INVESTED Primary Endpoint: All-cause Mortality or Cardiopulmonary Hospitalization

N = 5260

HF: 63%
MI: 37%
LVEF <40%: 43%



Vardeny O, Kim K, Udell JA, et al. *JAMA* 2021;325:39-49.

Canadian Recommendations: Influenza Vaccination

Recipient by age group	Vaccine types authorized for use	Recommendations
18-59 yrs	• IIV4-SD • IIV4-cc • RIV4 • LAIV4	• Any available vaccines should be used if no contraindications/precautions • LAIV not recommended if pregnant or with chronic health condition identified in List 1, incl. immune compromising conditions, and health care worker - Use IIV or RIV instead
60-64 yrs	• IIV4-SD • IIV4-cc • RIV4	• Any available vaccines should be used if no contraindications
65 yrs +	• IIV3-Adj • IIV4-SD • IIV4-HD • IIV4-cc • RIV4	• Any available vaccines should be used if no contraindications

Abbreviations:

ART: antiretroviral therapy
HAART: highly active antiretroviral therapy
IIV: inactivated influenza vaccine
IIV3-Adj: adjuvanted trivalent inactivated influenza vaccine
IIV4-cc: quadrivalent mammalian cell culture-based inactivated influenza vaccine
IIV4-HD: high-dose quadrivalent inactivated influenza vaccine
IIV4-SD: standard-dose quadrivalent inactivated influenza vaccine
RIV4: quadrivalent recombinant influenza vaccine
LAIV4: quadrivalent live attenuated influenza vaccine.

https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-10-influenza-vaccine.html

Canadian Recommendations: RSV Vaccination

- Authorized for use in Canada in adults 60+
- Awaiting NACI recommendations
- CDC Advisory Committee on Immunization Practices (ACIP):
  - Adults aged ≥60 years may receive a single dose of RSV vaccine, using shared clinical decision-making:
    - Consider patient's risk for severe RSV-associated disease
    - Epidemiologic evidence: persons ≥60 years who are at highest risk for severe RSV disease and might be most likely to benefit from vaccination include those with:
      - chronic medical conditions (lung diseases, incl. COPD and asthma)
      - **cardiovascular diseases (CHF, CAD)**
      - moderate or severe immune compromise (attributable to a medical condition or receipt of immunosuppressive medications/treatment)
      - diabetes mellitus

Melger et *al.*, 2023. *MMWR* 72: 793

RSV Vaccine Efficacy Against RSV-Lower Respiratory Tract Disease* with ≥1 Comorbidity, though Low Event Rates[1]

Season 1

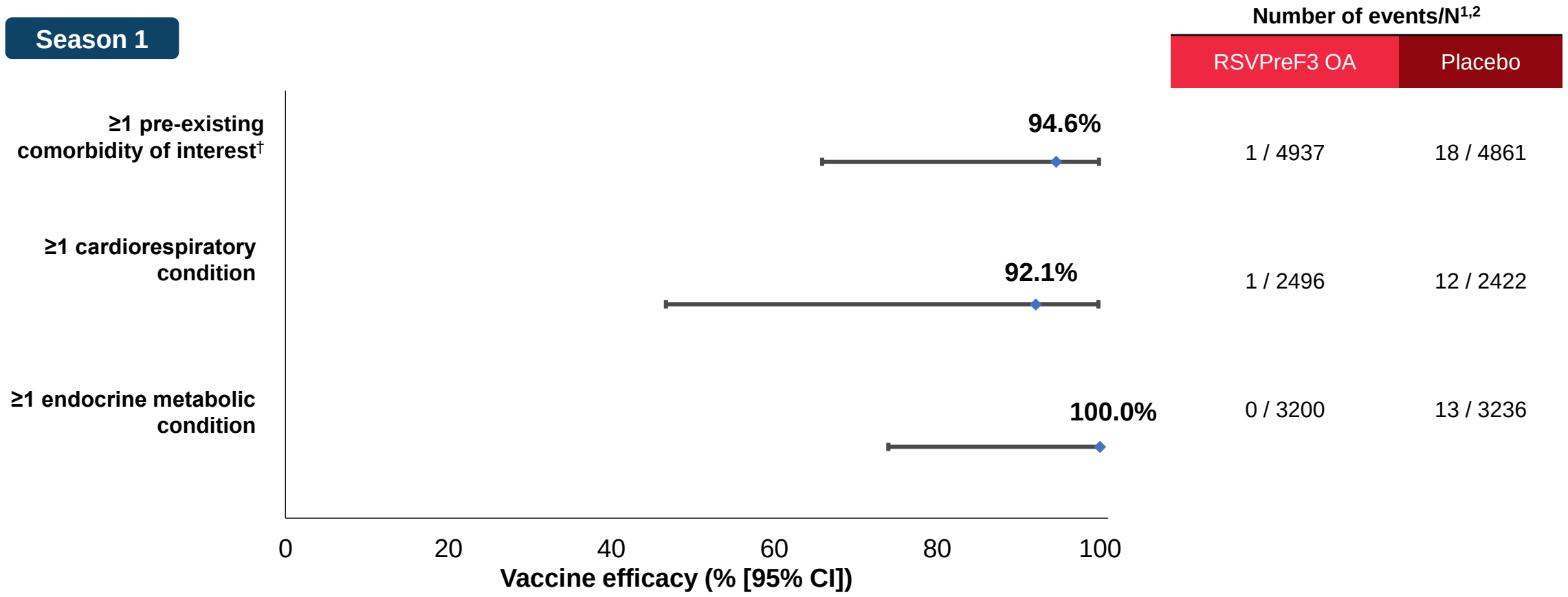


Figure adapted from GSK RSVPreF3 Vaccine for Respiratory Syncytial Virus (RSV) in Older Adults Presented at Vaccines and Related Biological Products Advisory Committee March 1, 2023. https://www.fda.gov/media/165649/download (accessed June 2023). *LRTD defined as ≥2 lower respiratory symptoms/signs for ≥24 hours including ≥1 lower respiratory sign, or ≥3 lower respiratory symptoms for ≥24 hours. All RSV cases confirmed by RT-PCR; †COPD, asthma, any chronic respiratory/pulmonary disease, diabetes type 1 or type 2, chronic heart failure, advanced liver or renal disease. COPD, chronic obstructive pulmonary disease; CI, confidence interval; LRTD, lower respiratory tract disease; RT-PCR, reverse-transcriptase polymerase chain reaction 1. GSK RSVPreF3 Vaccine for Respiratory Syncytial Virus (RSV) in Older Adults Presented at Vaccines and Related Biological Products Advisory Committee March 1, 2023. https://www.fda.gov/media/165649/download (accessed June 2023); 2. Papi A *et al. N Engl J Med* 2023;388(7):595–608

Canadian Recommendation: Herpes Zoster Vaccination

☑ The recombinant zoster vaccine (RZV) is only vaccine authorized for use in Canada

☒ Live-attenuated zoster vaccine (LZV) first authorized in 2008 was discontinued in 2023

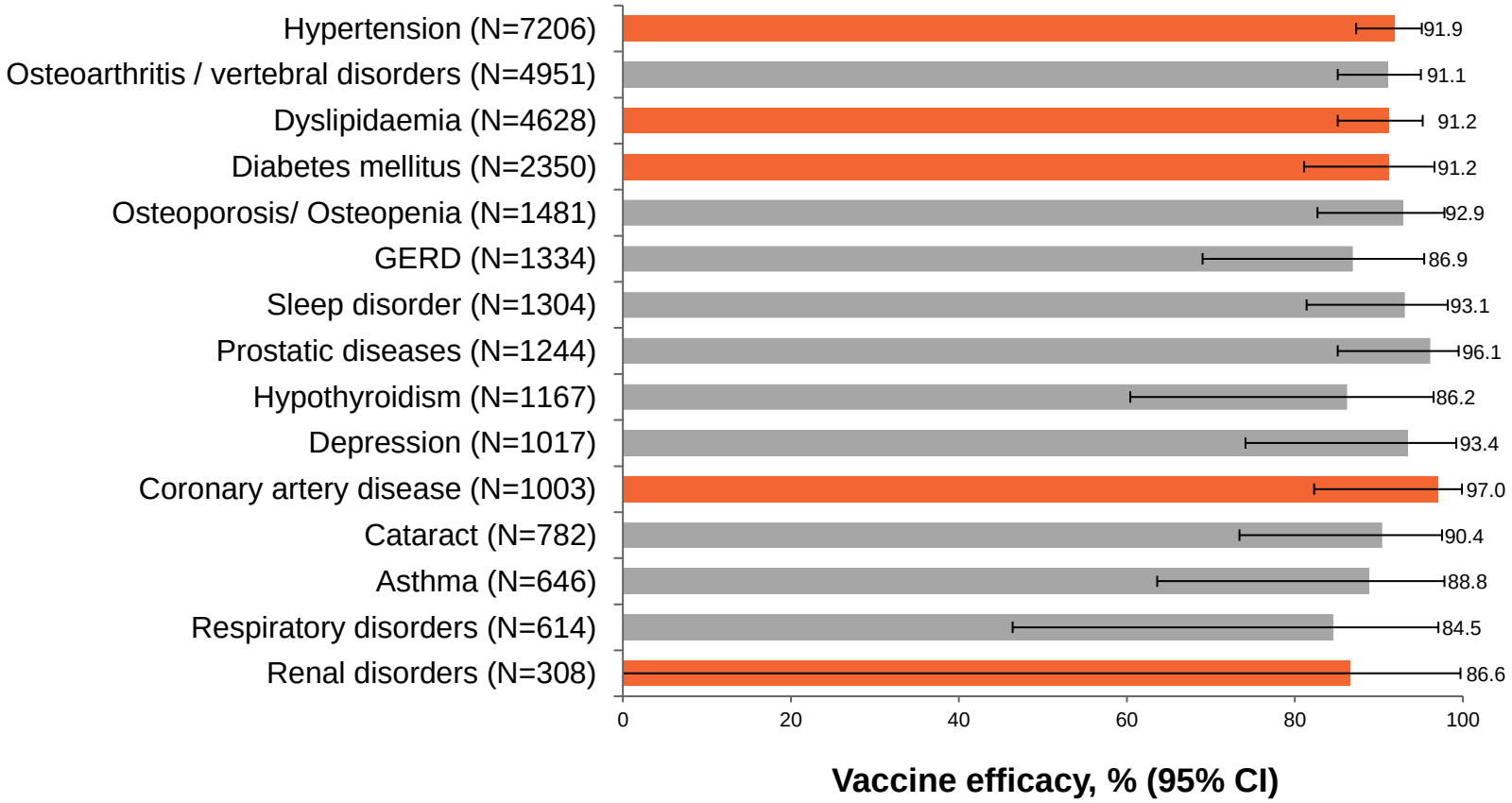
- RZV is recommended for individuals ≥50 years of age
  - without contraindications
  - who received LZV, or who have had a previous episode of HZ, should be vaccinated with RZV after at least one year
- RZV indicated for adults 18+ years who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy

https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-8-herpes-zoster-(shingles)-vaccine.html

RZV Vaccination Against HZV by Comorbidity Subgroup

Pooled post-hoc analysis of ZOE-50 and ZOE-70 data showed RZV is efficacious in older adults with DM, consistent with its efficacy in the overall population

Vaccine efficacy against HZV for participants with medical conditions at enrolment,* over ~4 years' follow-up



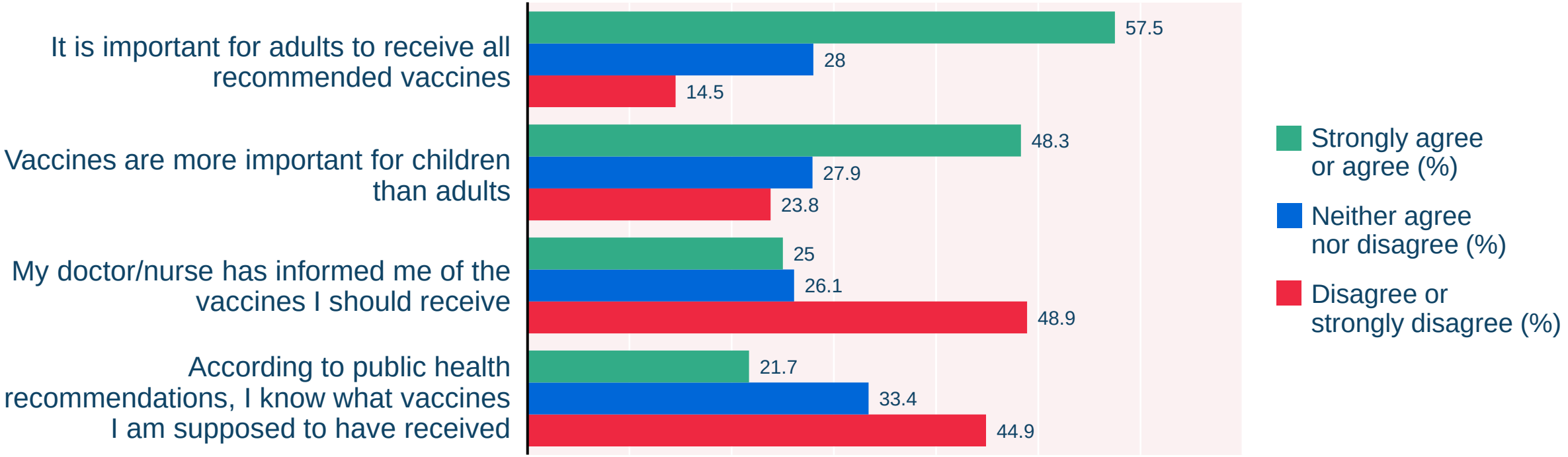
The numbers of SAEs, deaths and pIMDs were similar in the vaccine and placebo groups for each of the medical conditions

No safety concerns were identified based on baseline medical condition

Post-hoc subgroup analyses of safety and efficacy by participants' pre-existing conditions were exploratory. *No standard definitions were used in the diagnosis; therefore, each selected medical condition could vary with respect to severity, stage, treatment, progression or type (eg DM type). CI, confidence interval; DM, diabetes mellitus; GERD, gastro-oesophageal reflux disease; HZ, herpes zoster; pIMD, potential immune-mediated disease; RZV, recombinant zoster vaccine; SAE, serious adverse event. Oostvogels L *et al. Hum Vaccin Immunother* 2019;15:2865–2872. Lal H *et al. NEJM* 2015;372:2087–2096; 2. Cunningham AL *et al*. *NEJM* 2016;75:1019–1032.

However, Only 1 in 5 Canadian Adults are Aware of Which Vaccinations They Should Receive

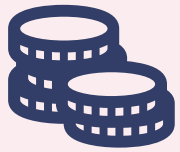
And approximately half have not been informed of which vaccines they need by physician/nurse



Study of 4,023 adults who completed a survey, 62 participated in focus groups; 1,167 healthcare providers (doctors, nurses, pharmacists) completed survey, 45 participated in focus groups. MacDougall DM, et al. BMJ Open 2015; 5:e009062.

Perceived Barriers to Immunization Differ Between Patients and Physicians

#1 Barrier to Vaccine Uptake Among Canadian Physicians[1]



Perceived Barriers of Cost

- **Cost** was seen as the number one barrier by **92% to 95%** of physicians
- Perceived barriers may **limit recommendations for vaccination**, particularly among older women or men

#1 Barrier to getting Vaccinated Among Canadian Adults[2]

Receiving an HCP Recommendation

- The number one reported barrier to vaccination for the general public was **not having a recommendation from an HCP**
- **Cost** was seen as a barrier by **only 18% (male)** and **19% (female) of participants**

- It is important to counsel patients on all available vaccines, without making any presumptions as to what they can or cannot afford

1. Steben et al. J Obstet Gynaecol Can. 2019;41:599-607; 2. Steben et al. J Obstet Gynaecol Can. 2019;41:1125-33.

Practice Points for Optimizing Immunization Rates in CV Patients

1 DISCUSS
Make it routine

Build a habit of talking about vaccination

Prioritize prevention
Ensure immunization discussions aren't lost amid other concerns

Take responsibility for the discussion
Don't assume another HCP will take the lead

2 RECOMMEND
Make it clear

Make the recommendation
Recommendations to vaccinate are a major factor in ensuring patient and primary care provider reassurance

Help your patient understand why
Ensure your patients understand their risk factors for potential complications of viral diseases and the importance of prevention

Take a presumptive approach
Telling rather than asking about vaccinations is seen as a stronger recommendation

3 ADMINISTER
Make it easy

Engage your allied health team to discuss, recommend, and administer vaccinations

Ensure patients know where they can go to receive their vaccines

Patient materials
Take advantage of or develop vaccination information to aid in counselling your patients

Add vaccination prompts to EMR and include vaccination recommendations in discharge plans

EMR, electronic medical record; HCP, health care provider.

Cumulative Impact of Evidence Based Acute MI Therapies on Cardiovascular Mortality

	Relative Risk	1y CV Mortality
None	- - -	13.2%
Aspirin/Lytic	↓ 42%	8.0%
Primary PCI	↓ 27%	5.8%
ACE inhibitor	↓ 16%	4.9%
Beta blocker	↓ 26%	3.6%
High Intensity Statin	↓ 24%	2.7%
P2Y12 Inhibitor (ticagrelor vs clopidogrel)	↓ 21%	2.2%
Influenza vaccine	↓ 41%	1.3%

Cumulative risk reduction in CV mortality if all evidence-based medical therapies are used:
Relative risk reduction: 90.3%. Absolute risk reduction: 11.9%, NNT = 9

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Infections and Vaccinations: Connections and Impact on CV Disease

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COVID-19 Vaccine Booster Recommendations

- For those previously vaccinated against COVID-19, NACI recommends a dose of the XBB.1.5-containing formulation of COVID-19 vaccine…if at least 6 months from previous COVID-19 vaccine dose or known SARS-CoV-2 infection (whichever is later).
- Immunization is particularly important for those at increased risk of COVID-19 infection or severe disease, e.g.:
  - Adults 65 years +
  - Residents of long-term care homes/other congregate living settings
  - Underlying medical conditions that place people at higher risk of severe COVID-19
  - Pregnant women
  - First Nations, Métis and Inuit communities
  - Members of racialized and other equity-deserving communities
  - People who provide essential community services
  - (Strong NACI Recommendation)

https://www.canada.ca/en/public-health/services/publications/vaccines-immunization/national-advisory-committee-immunization-addendum-guidance-use-covid-19-vaccines-fall-2023.html

COVID-19 Vaccine Recommendations (primary series): Myocarditis/pericarditis (mRNA Vaccines)

*"…primary series surveillance data in Canada, US and European Nordic countries suggest a **higher rate of myocarditis/pericarditis cases reported after vaccination with Moderna Spikevax original (100 mcg) compared to Pfizer-BioNTech Comirnaty original (30 mcg) vaccine,** especially among 12- to 29-year-old males following a 2nd dose of vaccine."*

- Evidence from bivalent and original mRNA COVID-19 vaccines across different age groups shows:
  - the **risk of myocarditis is lower following boosters compared to dose 2 of the primary series**
  - **no product-specific identifiable difference in the risk of myocarditis** following a booster dose
  - these observations were also seen in adolescents 12-17 years of age, however the use of Moderna Spikevax COVID-19 vaccines have been limited in those 5-17 years

As a result of this safety signal, Pfizer-BioNTech Comirnaty was preferentially recommended as a primary series for those between 12-29 years of age

https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-26-covid-19-vaccine.html#a5.2