





Vaccination as a new form of cardiovascular prevention: a European Society of Cardiology clinical consensus statement

With the contribution of the European Association of Preventive Cardiology (EAPC), the Association for Acute Cardiovascular Care (ACVC), and the Heart Failure Association (HFA) of the ESC

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Abstract

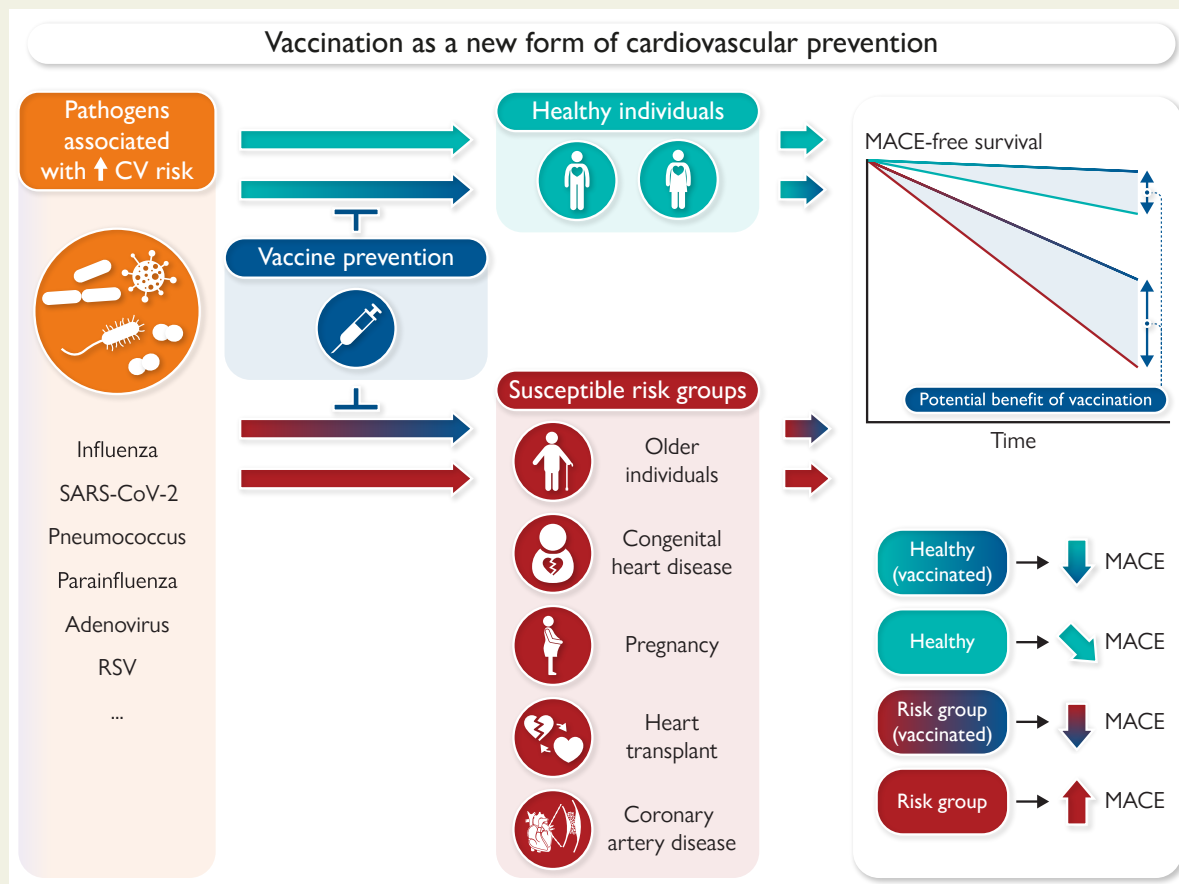
Vaccination is increasingly acknowledged as an effective preventive measure not only against specific infections, but also for the prevention of cardiovascular disease in high-risk patients. Specifically, a growing body of evidence suggests that vaccines against influenza, SARS-CoV-2, respiratory syncytial virus, herpes zoster, and other viruses significantly reduce infection and for influenza the incidence of major adverse cardiovascular events in vaccinated individuals.

This clinical consensus statement examines the existing literature and accumulated evidence and offers practical clinical advice on vaccination timing and target demographics, specifically addressing complex clinical scenarios with a focus on cardiovascular conditions. It includes guidelines for vaccinating vulnerable populations such as immunosuppressed individuals, patients with congenital heart disease, and pregnant women as well as safety and potential complications of the procedure.

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Graphical Abstract



Pathogens with increased cardiovascular (CV) risk: vaccine prevention against pathogens such as influenza and pneumococcus can reduce the risk for major adverse cardiovascular events (MACE). The benefit is particularly strong in susceptible risk groups such as older individuals, patients with congenital heart disease, heart transplant or coronary artery disease, as well as in pregnant women. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2, RSV, respiratory syncytial virus.

Keywords COVID-19 • Infection • Influenza • Pneumococcus • Respiratory syncytial virus

Introduction

Vaccination is a critical topic in policymaking and healthcare strategies, and generated great discussion in the public arena, in particular since the COVID-19 pandemic. A recent consensus document objectively examined the cardiovascular (CV) risks associated with infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its vaccines, addressing public concerns, while highlighting potential mitigation strategies.¹ The pandemic has underscored the CV complications that can arise from viral respiratory infections, which may ultimately increase the risk of myocardial infarction, arrhythmias, heart failure and death. Major adverse cardiovascular events (MACE) as well as heart failure continue to be an overwhelming global public health issue, with heart failure affecting approximately 64 million people worldwide.^{2–6} In an era of increasing recognition of prevention as crucial for reducing the CV disease (CVD) burden, vaccinations could become a foundational pillar of preventive strategies alongside other established measures.

Therefore, it is essential for healthcare professionals to acquire and maintain a robust understanding of the latest evidence on this topic, in

particular indications and application of vaccines and their potential complications. This article provides a comprehensive analysis of the public health implications of CV complications from bacterial and viral infections and summarizes the current evidence on how current vaccines can mitigate untoward CV effects associated with these conditions. Additionally, it evaluates the potential risks associated with vaccination and offers strategies for their management, particularly in vulnerable populations such as pregnant women, patients with congenital heart disease (CHD), and immunocompromised individuals.

Public health impact of cardiovascular disease and prevention strategies

Cardiovascular disease is the leading cause of death globally. Age-standardized CVD mortality varies by region and in 2022 ranged from 73.6 per 100 000 in high-income Asia Pacific to 432.3 per 100 000 in Eastern Europe.⁷ Coronary artery disease (CAD) affects

over 300 million individuals worldwide, accounting for the largest proportion of mortality, and resulting in the highest disease burden as measured by disability-adjusted life years, estimated at 2276 per 100 000.⁷ While incidence rates and mortality have decreased in high-income countries over the last few decades, its prevalence currently at 3610 per 100 000, will continue to climb due to the obesity epidemic and its metabolic risk factors as well as an ageing population.⁷ Thus, CVD will continue to substantially impact society and healthcare systems. Prevention strategies beyond those currently used are therefore paramount to reduce the overall burden of CVD.

A comprehensive prevention plan for CVD encompasses both behavioural and biological factors. Among classical CV risk factors, exposure to elevated levels of low-density lipoprotein cholesterol accounts for approximately 40% of deaths due to CAD frequently associated with vascular and systemic inflammation.^{8,9} Elevated levels of inflammatory biomarkers, such as high-sensitivity C-reactive protein or interleukin (IL)-6 have also been associated with the risk for atherosclerotic CVD on top of classical CV risk factors.¹⁰ Any infection is associated with a burst of inflammation. Therefore, preventing inflammation offers a novel avenue for CV risk reduction.

Viral and bacterial infections increase risk for major adverse cardiovascular events

Awareness has grown of the impact of viral and bacterial infection on the CV system and the extent to which infectious diseases can trigger CV morbidity and mortality. Indeed, pulmonary and systemic infections may influence CV health in a variety of ways, e.g. by increasing myocardial oxygen consumption and predisposing to ischaemic events in patients at risk, by stimulating inflammatory pathways that may trigger

coronary plaque rupture or erosion, and by depressing myocardial contractile function leading to or exacerbated heart failure. A recent study suggested that approximately 3% of deaths and 5% of hospitalizations with influenza or pneumonia may be attributed to influenza in patients with heart failure.¹¹

Influenza has long been associated with increased CV risk; the population attributable risk of influenza for CAD has been estimated at 3.9% (95% confidence interval [CI] 2.5%–5.3%).¹² Data from the Atherosclerosis Risk in Communities (ARIC) study suggested that each 5% increase in monthly influenza activity was associated with a 24% increase in hospitalization rates.¹³ SARS-CoV-2 contributed to a substantial increase in CV risk, especially early in the COVID-19 pandemic when population immunity was exceedingly low (Figure 1).^{14–18} Other respiratory infections, including respiratory syncytial virus (RSV), parainfluenza, adenovirus and pneumococcal pneumonia, have also been associated with increased CV morbidity and mortality.^{20,21}

Influenza and other respiratory infections increase the risk of MACE and heart failure through a variety of mechanisms, including induction of local and systemic proinflammatory and prothrombotic pathways destabilizing coronary plaques, and worsening of myocardial contractile function,²² leading to heart failure exacerbation, increasing myocardial oxygen consumption and in turn inducing ischaemia, triggering arrhythmias, and/or resulting in myocarditis. Influenza may directly infect coronary endothelial and smooth muscle cells.²³ In mice, endothelial infection results in decreased endothelial nitric oxide synthase expression.²³ Influenza A H3N2 can persist in atherosclerotic plaques and in the myocardium²⁴ up to several weeks following infection.²⁵ Infection also induces an enhanced production and release of proinflammatory cytokines and chemokines, which may destabilize the cap of atherosclerotic plaques.²³ Furthermore, infection may activate local and systemic proinflammatory and prothrombotic mediators including tissue factor among others, thereby increasing the risk of intravascular clot formation and MACE.

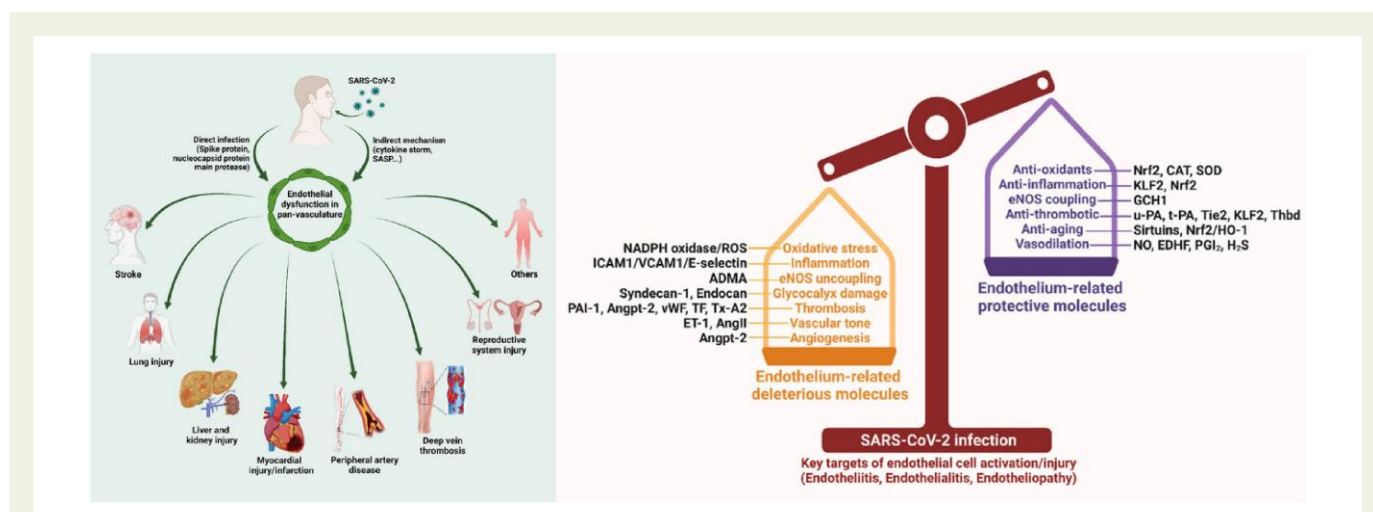


Figure 1 Pathogens such as COVID-19 by inhalation of the virus affect number of organs in the body (left picture). Organ damage is determined by the balance between the activation of hazardous mechanisms and protective mechanisms. ADMA, asymmetrical dimethylarginine; AngII, angiotensin II; Angpt-2, angiotensin-2; CAT, catalase; EDHF, endothelium-derived hyperpolarizing factor; eNOS, endothelial nitric oxide synthase; ET-1, endothelin 1; GCH1, GTP cyclohydrolase 1; H₂S, hydrogen sulfide; HO-1, heme oxygenase-1; ICAM1, intercellular adhesion molecule 1; KLF2, krüppel-like factor 2; NO, nitric oxide; Nrf2, nuclear factor erythroid 2-related factor 2; PAI-1, plasminogen activator inhibitor 1; PGI₂, prostaglandin I₂; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; SOD, superoxide dismutase; TF, tissue factor; Thbd, thrombomodulin; Tie-2, tyrosine-protein kinase receptor; t-PA, tissue plasminogen activator; Tx-A2, thromboxane A2; u-PA, urokinase plasminogen activator; VCAM1, vascular cell adhesion molecule 1; vWF, von Willebrand factor. Modified from Xu *et al.*¹⁹

Mechanisms of cardiovascular events after infection

Various mechanisms activated in acute and chronic infections may trigger or worsen CV events.²⁶ In that regard, Chlamydia species or viruses, notably Herpes, may infect CV tissues and in turn potentiate atherogenesis.^{27,28} However, a series of well-conducted randomized antibiotic trials using agents targeting Chlamydia revealed neutral results.²⁹ While viral nucleic acid and proteins can localize within atherosclerotic plaques, their causal role in atherogenesis, either through direct infection of arterial tissues or leukocytes within atheromata, is uncertain.^{26,30} Thus, chronic viral presence as a cause or facilitator of atherosclerotic plaques, while intriguing, remains unsubstantiated.

The relationship of acute infections to CV events also remains inconclusive. For example, in SARS-CoV-2, the angiotensin-converting enzyme-2 receptor for this virus appears expressed primarily in pericytes of the myocardial microvasculature rather than myocardial cells themselves. Nevertheless, scant evidence supports direct infection of endothelial cells by SARS-CoV-2, and the receptor for virus entry does not appear abundant in intrinsic vascular cells or in cardiomyocytes.

While direct cardiac tissue infection remains rather uncertain as a cause of CV events associated with acute or chronic infections, ample evidence supports indirect effects.^{31,32} Most infections will elicit local and systemic release of cytokines as well as protein mediators of inflammation, immunity and thrombus formation.^{31,32} Moreover, pathogen-associated molecular patterns derived from bacteria or viruses can activate molecular pathways in CV cells. For example, bacterial lipopolysaccharides, the principal endotoxins of Gram-negative bacteria, elicit the expression of cytokines such as tumour necrosis factor- α or various ILs, among them IL-1 and IL-6, primarily via their ligation of Toll-like receptor 4 that is expressed in macrophages.³¹ IL-1 refers to two cytokines, IL-1 α and IL-1 β , which signal through a common receptor, IL-1 receptor type I³² that may mediate inflammatory changes in target cells, among them production of matrix metalloproteases capable of digesting components of the plaque's protective fibrous cap.

Age and pre-existing CVD are important risk factors for death during and after acute viral infections. For example, between 2013 and 2017, the influenza-attributable excess death rate in Italy varied by virus strain and season, but consistently the death rate in those over 65 was five times that in younger persons, possibly because of the presence of occult or manifest CVD in the elderly.³³ In a meta-analysis of over 9000 individuals, influenza was associated with a 5.4% risk of death in patients with history of acute coronary syndromes (ACS), while vaccine against influenza was associated with a lower risk of death by 45%.³⁴

Prevention of cardiovascular events through vaccination

Vaccination is pivotal in preventing viral and bacterial infections and thus their potentially adverse CV sequelae.^{35–37}

Vaccines against viruses

Influenza vaccines reduce the risk of infection with influenza viruses by up to 60% and early trials supported evidence for a reduction in CV complications following the infection.^{38–40} Vaccinated individuals exhibit a 30% reduction in MACE,⁴¹ although observational studies appear to overestimate the benefit compared to randomized controlled trials (RCTs).^{42,43} Notably, most previous RCTs studied inactivated influenza vaccines.

Large meta-analyses, observational studies, and a randomized trial yielded similar results, with vaccination resulting in fewer MACE compared to no vaccination or to placebo.^{35–37}

Both observational studies and RCTs have evaluated influenza vaccination in patients who had suffered an acute myocardial infarction (AMI) and were vaccinated during the index hospitalization and documented even under these circumstances an up to 41% reduction in CV mortality (*Table 1, Figure 2*).⁴⁷ However, it has to be noted that the Influenza Vaccination after Myocardial Infarction (IAMI) trial was underpowered as it was stopped early due to the COVID-19 pandemic.

The largest published randomized placebo-controlled study to date on influenza vaccines was the IVVE study with >5000 individuals enrolled.⁴⁵ The IVVE study was conducted in patients with stable heart failure, of which 30% had ischaemic aetiology. The study was neutral for its primary endpoint, but there was a reduction in secondary outcomes including pneumonia and hospitalizations.⁴⁵ However, non-fatal myocardial infarction, non-fatal stroke, all-cause hospitalization, and hospitalization for heart failure were not significantly reduced (*Table 1*).⁴⁵

High-dose influenza vaccine was compared to standard-dose vaccine in the Influenza Vaccine to Effectively Stop Cardio Thoracic Events and Decompensated Heart Failure (INVESTED) trial in 5260 patients with high CV risk (*Table 1*). High-dose vaccine did not reduce cardiopulmonary hospitalizations or death compared with standard dose vaccine. The authors suggested that the very high number of events in this high-risk population may have diluted a potential benefit of high-dose vaccine. In contrast, high-dose vaccine compared with standard dose was associated with reduced CV and respiratory events in lower-risk elderly patients.⁴⁸

The ongoing DANFLU-2 trial (A Pragmatic Randomized Trial to evaluate the Effectiveness of High-Dose Quadrivalent Influenza Vaccine vs Standard-Dose Quadrivalent Influenza Vaccine in Older Adults, ClinicalTrials.gov: ID NCT05517174) is co-powered to assess CV events and will address this hypothesis (*Table 1*). Results from the corresponding feasibility study DANFLU-1 have already been published (*Table 1*).^{46,49} The DANFLU-2 trial has in the meantime recruited over 300 000 individuals randomized 1:1 to either high- or low-dose quadrivalent influenza vaccines into a registry based, pragmatic trial with mortality and hospitalizations as primary endpoint and will be reported shortly.

The IAMI trial investigated whether influenza vaccination reduces CV events in patients with AMI.³⁷ In a *post hoc* analysis comparing early-season vs late-season vaccination, there was no significant difference in vaccine effectiveness against adverse CV outcomes at 1 year.³⁷ Both early and late vaccination resulted in similar reductions in all-cause death, myocardial infarction, or stent thrombosis compared to placebo.³⁷ Although the benefit on all-cause mortality appeared slightly greater with early vaccination, the difference was not statistically significant.³⁷

Herpes zoster or shingles has also been associated with CV complications including AMI, stroke and transient ischaemic attack, in particular during the first month following reactivation. A herpes zoster vaccine is more than 90% efficient in preventing the disease⁵⁰ and also associated with a strong, over 50% reduction in CV events.⁵¹

Respiratory syncytial virus mainly affects children and adults over 60 years of age, particularly those with comorbidities including CV conditions. Cardiac events can occur in 20% of individuals with a prior cardiac condition during an acute infection.⁵² In the elderly, the vaccine is 89% effective in preventing lung infections⁵³ and may also reduce subsequent cardiac events, but solid evidence is still missing. The DAN-RSV trial (Vaccine Effectiveness of a Bivalent RSV Prefusion F Protein-based Vaccine for Preventing RSV Hospitalizations in Older Adults, ClinicalTrials.gov: ID NCT06684743) is a pragmatic, open label

Table 1 An overview of influenza vaccine cardiovascular outcome trials

	INVESTED	IAMI	RC-IVVE	DANFLU-1	DANFLU-2
Trial title	Influenza Vaccine to Effectively Stop Cardio-Thoracic Events and Decompensated Heart Failure	Influenza Vaccination After Myocardial Infarction	Influenza Vaccine to Prevent Adverse Vascular Events	A Pragmatic Randomized Feasibility Trial of Influenza Vaccines	A Pragmatic Randomized Trial to Evaluate the Effectiveness of High-Dose Quadrivalent Influenza Vaccine vs Standard-Dose Quadrivalent Influenza Vaccine in Older Adults
Status	Completed	Completed Stopped early due to COVID-19 pandemic (underpowered)	Completed	Completed	Recruiting
Participants	5260	2571	5129	12 477	339 700
Groups	High dose vs standard dose influenza vaccine	Influenza vaccine vs placebo	Influenza vaccine vs placebo	High-dose quadrivalent influenza vaccine (QIV-HD), standard-dose quadrivalent influenza vaccine (QIV-SD) (feasibility study)	High-dose quadrivalent influenza vaccine (QIV-HD), standard-dose quadrivalent influenza vaccine (QIV-SD)
Primary Endpoint	Time to first occurrence of all-cause death or cardiopulmonary hospitalization up to 3 years	Composite endpoint of time to all-cause death, a new MI or stent thrombosis at 1 year	Composite of CV death, non-fatal MI, non-fatal stroke, and hospitalizations for heart failure at 6 months	Feasibility and relative vaccine effectiveness high-dose flu vaccine can reduce the number of hospital admissions due to flu, pneumonia, and cardiovascular disease in comparison to a standard-dose flu vaccine	Primary outcome: Hospitalization for influenza or pneumonia Secondary outcomes: Hospitalization for any cardio-respiratory disease, all-cause hospitalization, all-cause mortality, hospitalization for influenza, hospitalization for pneumonia
Region	North America (United States and Canada)	Europe, Australia, Asia	Asia, Middle East, Africa	Denmark	Denmark
Number of Sites	190	30	10	Registry study, 1 main center	Registry
Results	High-dose trivalent inactivated influenza vaccine vs standard-dose quadrivalent inactivated influenza vaccine did not significantly reduce all-cause mortality or cardiopulmonary hospitalizations in patients with high-risk CVD	Influenza vaccination early after MI or in high-risk CAD resulted in a lower risk of all-cause death, MI, or stent thrombosis, and a lower risk of all-cause death and CV death at 12 months vs placebo	Prespecified co-primary outcomes were not statistically significant	Lower incidence of hospitalization for influenza or pneumonia and all-cause mortality in the QIV-HD group compared to the QIV-SD group (feasibility study, not powered to assess outcomes)	Recruiting
Reference	Vardeny et al. ⁴⁴	Fröbert et al. ³⁷	Loeb et al. ⁴⁵	Johansen et al. ⁴⁶	https://clinicaltrials.gov/study/NCT05517174
Journal	JAMA, 2021	Circulation, 2021	Lancet Global Health, 2022	NEJM Evidence, 2023	NA

CAD, coronary artery disease; CV, cardiovascular; CVD, cardiovascular disease; MI, myocardial infarction. Modified from Behrouzi et al.³⁴

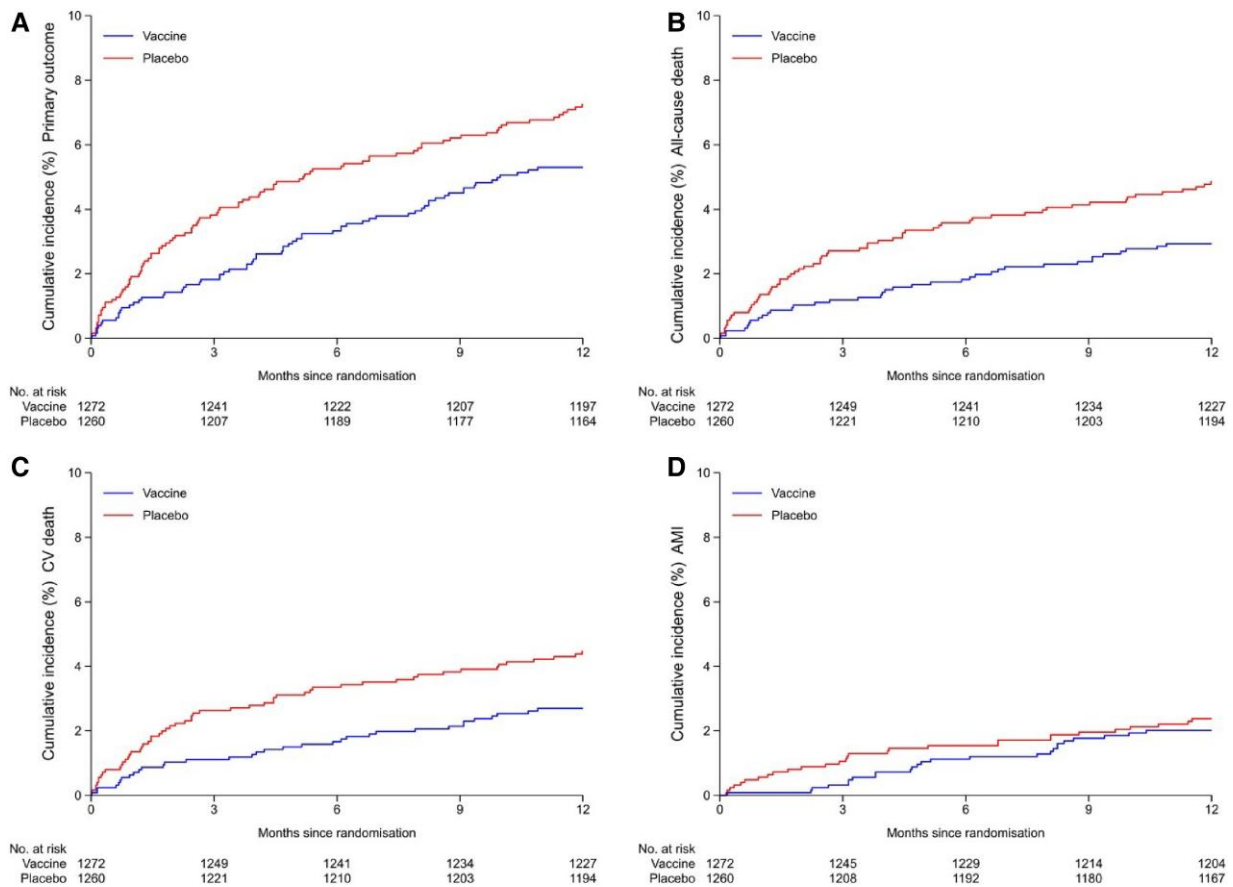


Figure 2 Reduction of cardiovascular events through influenza vaccination after myocardial infarction. Results from the IAMI trial: Kaplan–Meier event curves of the influenza vaccine and placebo groups for the primary composite endpoint of all-cause death, myocardial infarction, or stent thrombosis in a time-to-event analysis for (A) the primary outcome, (B) all-cause death, (C) cardiovascular death, and (D) myocardial infarction. The study was stopped early due to the COVID-19 pandemic and was underpowered as a consequence. AMI, acute myocardial infarction; CV, cardiovascular. From Fröbert et al.³⁷

trial that randomized over 130 000 elderly individuals 1:1 to either an RSV vaccine or no RSV vaccine with hospitalization as the primary endpoint. The results will be reported shortly.

Vaccines against SARS-CoV-2 are effective against infection, with efficacy varying depending on the type of the vaccine and the SARS-CoV-2 strain.⁵⁴ Overall, the available vaccines reduce the severity of infection, hospitalization and death.⁵⁴ Furthermore, patients with any CVD including heart failure have a much more severe course^{17,18,55} and an around 30% higher risk of developing long COVID.⁵⁶ Vaccination reduces the risk of long COVID by 43%.^{57,58}

Finally, human papillomavirus (HPV) infection is also associated with up to a four-fold risk for atherosclerotic CVD, CAD, and stroke.⁵⁹ An HPV vaccine appears effective in almost 100% of individuals⁶⁰ with one study showing normalization of the excess CV risk in vaccinated women.⁶¹ Further research is needed to evaluate if HPV also puts men at higher risk for CV complications.

Vaccines against bacteria

Vaccination with pneumococcal vaccine is 60%–70% effective in preventing an invasive disease course.⁶² Furthermore, a meta-analysis has shown that vaccination with the pneumococcal polysaccharide vaccine

led to a 10% reduction in any CV event including myocardial infarction in those aged ≥ 65 years.⁶³

Recommendations of the European Society of Cardiology, American College of Cardiology/American Heart Association guidelines

Chronic coronary syndromes

The 2024 ESC guidelines for the management of chronic coronary syndromes (CCS) recommend vaccination against influenza, pneumococcal disease and other widespread infections, e.g. COVID-19 in patients with CCS.⁶⁴ The 2023 AHA/ACC guideline for the management of patients with chronic coronary disease (CCD) state that ‘In patients with CCD, an annual influenza vaccination is recommended to reduce CV morbidity, CV death, and all-cause death.’⁶⁵ They further state: ‘In patients with CCD, COVID-19 vaccination is recommended per public health guidelines to reduce COVID-19 complications, and in patients with CCD, a pneumococcal vaccine is reasonable to reduce CV morbidity and mortality

and all-cause death.⁶⁵ The ACC/AHA guidelines recommend annual influenza vaccination in patients with ACS without a contraindication to reduce the risk of death and MACE.⁶⁶ Thus, international guidelines all recommend influenza vaccinations, particularly in the elderly. The US, but not the ESC guidelines, also recommend pneumococcal vaccination in this population.

Heart failure

The 2021 ESC Guidelines on the diagnosis and treatment of acute and chronic heart failure recommended that influenza and pneumococcal vaccinations should be considered to prevent heart failure hospitalizations.⁶⁷ The 2022 AHA/ACC guidelines for heart failure note that vaccination was associated with lower risk in observational and randomized trials and state that '*Patients with heart failure should learn to take medications as prescribed, restrict sodium intake, stay physically active, and get vaccinations.*'⁶⁸ The recommendations further state that '*In patients with heart failure, vaccinating against respiratory illnesses is reasonable to reduce mortality.*'⁶⁸ The 2022 AHA/ACC guidelines do further note that '*patients with heart failure are uniquely susceptible to poor outcomes in the setting of SARS-CoV-2 infection and should be vaccinated against COVID-19.*'⁶⁸

Cardiovascular risks of vaccination

Acute reactions to vaccines

Serious adverse reactions to most vaccinations are very rare with reported incidences below 10 per 100,000,⁶⁹ but are more common among younger individuals.⁶⁹ These adverse reactions include myocarditis and pericarditis as well as even less commonly anaphylaxis, immune thrombocytopenia, and encephalitis/meningitis.⁶⁹ On the other hand, flu-like symptoms and especially local vaccine adverse reactions may often occur. After influenza vaccination, about 25% experience injection site pain. While in a placebo-controlled trial such local reactions were more common after influenza vaccination in the active arm, serious adverse events were similar in both type and incidence and in the placebo groups.³⁷ Mild to moderate adverse reactions after an influenza vaccine have been related to a reduced risk of cardiopulmonary hospitalization and all-cause mortality in patients with a CVD. Rare anaphylactic reactions to vaccines should be promptly treated as any other anaphylactic reactions. The same holds true for other severe reactions to vaccines. There are no proven specific treatments for vaccine-related serious adverse reactions and as such treatment is mainly symptomatic in nature.

Myocarditis after SARS-CoV-2 vaccine

A recent consensus document comprehensively summarized the risks of developing myocarditis after SARS-CoV-2 vaccine.¹ Overall, younger individuals have a higher risk of myocarditis in the context of a vaccination against COVID-19 compared to older ones, who may need vaccination more.¹ Also, myocarditis is more common in young men¹ than in young females, similar to the prevalence of classic myocarditis.⁷⁰ It merits emphasis that the risk of developing myocarditis from COVID-19 is 6 times higher than developing myocarditis from the vaccine.^{1,71} Most cases are mild and resolve spontaneously, though rare instances of severe cases have been reported.¹

The mechanisms of myocarditis following vaccination are not well understood. Circulating spike proteins have been described in patients with myocarditis.^{1,72} In another study anti-IL-1RA antibodies were elevated in 75% of 14–21-year-old myocarditis patients.⁷³ In contrast, other studies on antibody reaction to the vaccines have demonstrated

a robust anti-viral antibody response, but no increase in overall auto-antibody reactivity compared to control groups.⁷⁴ Similar to other forms of myocarditis, innate immune cells in the heart following rechallenge with antigen through a second dose of vaccine may activate a robust TLR4 and inflammasome mediated, IL-1 β pathway driving myocarditis through trained immunity.⁷⁵

Management of vaccine-associated myocarditis

If myocarditis is suspected based on cardiac symptoms such as chest pain within a few weeks of vaccination, testing should include an ECG, troponin, serum natriuretic peptides (BNP or NT-proBNP), and echocardiography.¹ Abnormal results that suggest cardiac injury should prompt cardiac magnetic resonance imaging in haemodynamically stable patients.¹ In rare cases with clinically significant arrhythmias or cardiogenic shock, endomyocardial biopsy may be useful to confirm myocarditis and exclude more clinically aggressive forms such as giant cell myocarditis.^{1,76}

Heart failure and arrhythmias associated with COVID-19 vaccination should be treated according to the respective guidelines.^{67,77,78} Anti-inflammatory treatments have uncertain value especially in mild cases that often resolve within a few days to weeks. Colchicine may be considered for patients with pericarditis and chest pain and in the context of myopericarditis with normal left ventricular function. As for other forms of myocarditis, exercise cessation is advised for 3–6 months after an episode of vaccine-associated myocarditis.^{1,79}

Advice on when, how and who to vaccinate

When, how, and whom to vaccinate remain crucial concerns in daily practice and do require special care and attention (Table 2).

Influenza vaccination

In the United States and China, health authorities recommend a routine annual influenza vaccination for all individuals ≥ 6 months of age who do not have contraindications.^{80,81} In Europe, vaccination recommendations vary according to countries, but are generally limited to persons aged 65 years or older or to those at increased risk of severe disease and influenza-related complications. Vaccination is especially important for people at higher risk of serious influenza complications, e.g. individuals with specific chronic medical conditions, pregnant women, the elderly and healthcare workers.⁸² A number of European countries have initiated programmes to vaccinate children aged 6–59 months.⁸² Recommendations for healthcare professionals vary substantially.

The ESC guidelines recommend annual influenza vaccination for patients with established CVD.⁶⁷ This has been particularly reinforced in the last guidelines on heart failure⁶⁷ and CAD^{83,84} as the vaccination against influenza has been well established as particularly safe. In CAD, the ESC guidelines recommend an annual influenza vaccination in patients with stable atherosclerotic CVD.^{61,67} Furthermore, the ACC/AHA guidelines recommend annual influenza vaccination in patients with ACS without a contraindication to reduce the risk of death and MACE.⁶⁶ Vaccine is associated with a reduction of AMI, an improved prognosis in patients with heart failure, and decreased CV risk in adults aged 65 years and older, as reported in several consistent meta-analyses.⁸⁵ Above all, influenza vaccination given early after an AMI³⁷ or in high-risk CAD³⁸ decreases all-cause and CV death at 1 year. These results driven by consistent large trials led to

Table 2 When to vaccinate? Patients with chronic cardiovascular disease, heart failure and coronary artery disease

Pathogen	Before winter, annually	Specific pluriannual schedule	Possible in acute conditions (e.g. acute HF)	Possibility of simultaneous vaccination
Influenza	X		X	X
Pneumococcus		X 5–10 years	X	X
COVID-19	?		X	X
RSV	?	2 years?	?	X
Herpes zoster		X		
DT-polio		X ^a		

DT, diphtheria, tetanus; HF, heart failure; RSV, respiratory syncytial virus.

'X' indicates timepoints, when vaccine should occur. Empty cells correspond to timepoints, when the vaccine does not have to occur.

^aSimilar to the general population, regardless of comorbidities.

propose influenza vaccination for all patients admitted for ACS, preferentially during index hospitalization.

Obviously, a licensed and age-appropriate vaccine should be used, following national or local approvals. Studies have been designed to compare high doses vs low doses of influenza vaccines, but no specific recommendations have been proposed until now. Depending on the seasons and industrial developments, the following types of vaccines are available: inactivated influenza vaccines, recombinant influenza vaccine, and live attenuated influenza vaccine.

Pneumococcal vaccination

Recommendations for pneumococcal vaccine allow some flexibility. Indeed, patients can be eligible to receive both pneumococcal conjugated and polysaccharide vaccines (PCV13 and PPSV23, respectively), sequentially, or only PPSV23 in specific conditions, and soon new vaccines with only one dose will become available.⁶² PCV13 contains 13 pneumococcal serotypes, whereas the 23-valent unconjugated polysaccharide vaccine PPSV23 contains 23 pneumococcal serotypes.⁶² The combination of the two vaccines (PCV13 and PPSV23) makes it possible to obtain a higher immune response than the use of PPSV23 alone.⁶² Persons vaccinated using the previous sequence may receive a repeat injection of PPSV23 after 5 years.⁶² Persons vaccinated for more than 1 year with PPSV23 will receive PCV13 and a revaccination with PPSV23 at least 5 years after the last PPSV23.⁶² The necessity of subsequent revaccination is not currently established but is advised by infectious disease specialists.⁶²

In the United States and the United Kingdom, health authorities recommend pneumococcal vaccination in patients older than 65 years. It is also recommended after 65 years and earlier in high-risk immunocompetent patients, such as those with chronic CVD (except hypertension). Based on expert opinion, the ESC guidelines recommend pneumococcal vaccination in patients with heart failure.⁶⁷

COVID-19 vaccination

Most countries recommend COVID-19 vaccination in patients with chronic diseases, including CV conditions. The COVID-19 epidemiology is changing fast and new recommendations should be considered, not only regarding the patients prioritized, but also regarding novel vaccines and the virus types circulating within a specific population. The utility of RNA vaccines compared to more classical technologies remains a matter of debate.

General recommendations are well supported also for patients with CVD. All patients irrespectively of age, sex, or comorbidities should follow the recommendations given for the general population. Patients older than 65 years and patients with comorbidities, especially heart failure and CAD, but also diabetes or other immunocompromised situations, should be more strictly advised to get protected.

Other vaccines

Other vaccines are currently under evaluation by national or local health authorities, including vaccines against RSV or herpes zoster. In that regard, a randomized controlled trial studying RSV vaccine in 130 000 individuals is currently underway (DAN-RSV). These approaches will have to be evaluated in the context of CVD prevention. Specific sequential or simultaneous schedules have to be evaluated and the hope is to propose combined vaccines, for instance a 'winter' vaccine grouping protection against several viruses to simplify administration.

In practice

Based on the overall increasing evidence for the effectiveness of influenza vaccination in reducing CV events,⁸⁶ the influenza vaccine carries a class IA recommendation in the ESC guidelines.⁶⁷ Similar to statins, this intervention is effective, safe, and inexpensive and it has a substantial impact on this vulnerable population. Classically, vaccination is considered the responsibility of primary care physicians. However, this strategy does not appear to be optimal given the low current vaccination rates, suggesting that other health providers should be involved in the future. Every opportunity should be taken to vaccinate patients either during a routine visit or hospitalization, even for acute conditions. The first step to improve vaccination coverage is to improve informing patients, families and healthcare providers about evidence-based important benefits and low risks of the intervention. Implementation research is underway to study the most effective means to improve vaccination coverage nationwide.⁸⁷ In that regard, a study in Denmark evaluated a governmental letter system to deliver electronic letters to individuals aged ≥ 65 years to inform them about the benefits of the influenza vaccine.^{87,88} Overall, the magnitude of effectiveness of this intervention was modest,⁸⁸ highlighting that offering vaccination during direct patient contact should become a priority in the clinical setting.

Table 3 Vaccinations in pregnancy (indicated and contraindicated vaccination for pregnant individuals overall)

Advised	Not advised
Influenza	Bacillus Calmette-Guérin (BCG)
Whooping cough	Measles, mumps and rubella (MMR)
COVID-19	Oral polio
Respiratory syncytial virus	Oral typhoid
	Yellow fever

Special risk groups and vulnerable populations

An infection specialist should always be consulted before considering vaccinating a patient with a suppressed immune system. Live vaccines are in general contraindicated in immunocompromised patients and inactivated, nonconjugated vaccines may not induce sufficient antibody production. Recent acute cardiac illness does, however, not seem to be of concern regarding vaccination. A large, randomized clinical trial has proven that influenza vaccination is safe and reduces total and CV mortality when given within 72 h of an AMI. This effect seems to be especially pronounced in non-ST-elevation myocardial infarction patients with more comorbidities compared to ST-elevation myocardial infarction patients.³⁷ It thus seems safe and practical to introduce a potential vaccination programme already during the in-hospital phase of an acute cardiac condition—although only proven safe and effective for patients with a myocardial infarction.

Vaccination during pregnancy

Inactivated vaccines, not containing a live version of the virus they are protecting against, are generally safe during pregnancy (Table 3).⁸⁹ In contrast, live virus vaccines such as measles, mumps and rubella (MMR) and chickenpox are generally contraindicated as they can cross the placenta and infect the fetus. However, there is no evidence that any live vaccine may cause birth defects. Live vaccines should therefore be given before or after pregnancy, the latter right after delivery, even during lactation, if indicated.⁹⁰

Some vaccines, such as the tetanus vaccine, are safe during pregnancy if necessary (Table 2).

Congenital heart disease

Patients with moderate to severe and/or cyanotic CHD and those with pulmonary arterial hypertension are advised to have annual influenza vaccination in the fall. There have been no reports of particular concerns regarding COVID-19 vaccination in CHD patients.

Patients with functional asplenia syndrome, commonly -but not exclusively- present with right atrial isomerism (duplication of right-sided structures and associated 'asplenia'), should receive pneumococcal vaccination (PPV23) after the age of 2, and have it repeated every 5 years thereafter. Patients with 22q deletion (DiGeorge syndrome), a congenital disorder characterized by cellular immune deficiency, should generally avoid live vaccines.⁹¹

Table 4 Advised vaccinations before transplant

Measles, mumps and rubella (MMR)
Varicella
Herpes zoster
Rotavirus
SARS-CoV-2
Influenza
Pneumococcus
Tetanus, pertussis
Hepatitis A and B
Human papillomavirus

It remains unclear as to whether thymectomy, often performed during neonatal cardiac surgery, is a contraindication for live vaccines.⁹² Patients should consult with their CHD Team. Regarding thymectomy, there is often poor documentation in the surgical notes, a practice that must improve as it may have implications on patients.

Vaccination and heart transplantation

Heart transplant recipients represent a unique population with heightened susceptibility to infections due to immunosuppression. Vaccination plays a critical role in preventing diseases and reducing the risk of infectious complications post-transplantation. In a large Swiss cohort study of solid organ transplant recipients, 11.9% experienced vaccination preventable infections.⁹³ Importantly, there was significant morbidity and mortality associated with these infections.⁹³ Despite this, only around 60% of all transplant candidates undergo pneumococcal vaccination⁹⁴ highlighting the need for optimized immunization strategies. Also, a nationwide cohort study in Denmark of solid organ transplant recipients undergoing influenza vaccine reported a reduced risk of all-cause pneumonia admission (adjusted hazard ratio [HR] 0.83; 95% CI 0.69–0.99; $P = .035$) and all-cause mortality (adjusted HR 0.60; 95% CI 0.47–0.76; $P = .001$) in vaccinated individuals.⁹⁵ The investigators also pointed out that overall vaccination coverage was low (48%) and that vaccination should become a priority in the care of transplant recipients given its benefits.⁹⁵ Current International Society for Heart and Lung Transplantation (ISHLT) guidelines recommend completion of live virus vaccination, including MMR, varicella, herpes zoster and rotavirus, at least 4 weeks prior to transplantation⁹⁶ (Table 4). Inactivated vaccines including SARS-CoV-2, influenza, pneumococcal, tetanus, pertussis, hepatitis A and B, and HPV vaccines, should be completed at least 2 weeks before transplantation (Table 4).^{96–98} Unfortunately, in these often severely ill patients with secondary organ failure, the response to many vaccines is impaired.⁹⁹ Although live attenuated vaccines are generally avoided after transplantation, small studies in paediatric patients after liver transplantation showed good safety profile and efficacy with live attenuated vaccines for MMR and varicella zoster.^{100,101} After transplantation, vaccination is usually not performed within the first 3 to 6 months.⁹⁶

During the SARS-CoV-2 pandemic and with influenza vaccination, seroconversion was achieved as early as 1 month after transplantation, if no induction therapy with a B or T-cell-depleting agent has been

carried out.^{102,103} Even after vaccination, heart transplant recipients should continue to adhere to infection prevention measures recommended by health authorities, such as wearing masks, practising hand hygiene, and avoiding crowded settings, due to their increased vulnerability to infections and decreased seroresponsiveness. Especially steroids, high doses of mycophenolate mofetil and belatacept in maintenance immunosuppressive regimens have been associated with a lower rate of antibody response to vaccination.^{58,103} To ensure an adequate protection from infections, vaccination strategies are also crucial for close contacts.⁹⁹

Influenza in heart transplantation

Influenza vaccine with inactivated virus is safe and effective without increasing the risk of either rejection episodes or infections.¹⁰² Health authorities recommend for an annual vaccination that can be administered as early as 1 month after transplantation to ensure adequate vaccination during influenza season. The response in transplant recipients is reported to be lower compared with healthy subjects, with 70% of patients having virus specific IgGs.^{104,105}

Human papillomavirus in heart transplantation

Transplant recipients are at increased risk of HPV-related malignancies. The HPV vaccine should be administered without any age or sex restrictions, if possible, pre-transplantation.¹⁰⁶ Vaccination after transplantation can still be beneficial, and it should be considered as part of post-transplant care. The HPV vaccine is available in several formulations, including bivalent, quadrivalent, and nonavalent vaccines. Theoretically, it is advised to consider the nonavalent vaccine as the first choice in solid organ transplant recipients due to its broad coverage of HPV genotypes.¹⁰⁶

Pneumococcus in heart transplantation

Pneumococcal vaccination should be administered to heart transplant recipients as part of routine care prior to or 3 months at the earliest after heart transplantation and is as safe as it is in non-transplanted patients.¹⁰⁷ Adult heart transplant recipients should receive both the pneumococcal conjugate vaccine and the pneumococcal polysaccharide vaccine (PPSV23) to provide comprehensive protection against pneumococcal disease.¹⁰⁷

SARS-CoV-2 in heart transplantation

The ISHLT COVID-19 Task Force advises to delay the SARS-CoV-2 vaccination for at least 1 month after heart transplantation and at least 3 months from the use of T-cell depleting agents or specific B-cell depletion agents.¹⁰³ In general, detectable antibodies against the receptor-binding domain of the spike protein of the SARS-CoV-2 are demonstrated in 10% to 57% and cellular response in 10% to 70% of heart transplant recipients following two doses of mRNA vaccines.¹⁰⁸ Increased intensity of immunosuppression, use of antimetabolites such as mycophenolate, and agents that inhibit B-cell response are associated with reduced immunogenicity. Despite suboptimal seroconversion rates, vaccination was associated with reduced risk of death from COVID-19 when compared to unvaccinated transplant recipients.¹⁰⁸ The third dose of mRNA vaccination in transplant recipients is associated with an increase in detectable humoral response ranging from 55% to 68%.^{109–111} However, specific heart transplant data in

this setting have been sparse as previous studies included only up to 96 heart transplant patients.¹¹²

Further direction in heart transplantation

Novel vaccine formulations, including high-dose influenza vaccines and adjuvanted vaccines, have demonstrated enhanced immunogenicity in immunocompromised individuals, potentially addressing the diminished vaccine response observed in heart transplant recipients. Furthermore, the development of mRNA vaccines has revolutionized vaccine delivery, offering the prospect of improved efficacy and safety profiles.

Limited data on vaccine effectiveness and safety in this specific population underscore the need for further research to guide evidence-based recommendations. Additionally, logistical challenges, such as vaccine availability, accessibility, and vaccine hesitancy among transplant recipients, their relatives and healthcare providers, pose significant hurdles to achieving high vaccination coverage rates. By optimizing vaccination practices, we can mitigate the burden of vaccine-preventable infections and improve long-term outcomes in this vulnerable population.

Existing knowledge gaps

Influenza vaccination demonstrates a significant protective effect in the acute post-myocardial infarction period supported by the IAMI trial and a meta-analysis of other RCT,^{34,47} but only a modest benefit in stable CAD and stable heart failure, as demonstrated in IVVE, and indirectly in the INVESTED and DANFLU-1 trials.

Its protective effect on hard outcomes after myocardial infarction exceeds its impact on influenza infection alone and appears to persist beyond the influenza season. This raises important research questions: What are the additional effects/mechanisms of influenza vaccine in addition to preventing respiratory infection? Should influenza vaccination be administered year-round? Should myocardial infarction patients receive a booster, if vaccinated earlier in the season? Additionally, emerging evidence suggests that influenza and other vaccines may reduce inflammation through trained immunity mechanisms.^{113,114} Additional evidence from randomized, placebo-controlled trials is necessary for other types of vaccines such as herpes zoster to assess the potential benefits of vaccination against the most common viruses linked to CV events. Furthermore, mechanistic studies are needed to gain deeper insight into why these types of vaccines reduce the risk of MACE.

Summary and outlook

Vaccination has been among the greatest achievements of science-based medicine and has prevented millions of patients from infections and premature death. Beyond prevention of infection and its sequelae, vaccinations have profound effects on the CV risk and as such should be considered the fourth pillar of medical CV prevention besides antihypertensives, lipid-lowering drugs and medications that treat diabetes. International guidelines support such a concept and recommend vaccination in patients at risk for MACE such as those with CAD and heart failure.

Nevertheless, several knowledge gaps remain. While evidence of influenza, SARS-CoV-2 and pneumococcus is reasonably solid, more data are required for other vaccinations. Furthermore, while there are trials and large registries for common CV conditions, less is known in patients with rarer diseases. Thus, further trials are needed with some vaccinations and in CV patient populations other than those with CAD and/or heart failure.

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Supplementary data

Supplementary data are not available at *European Heart Journal* online.

Declarations

Disclosure of Interest

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Data Availability

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