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FULL TITLE: Influenza vaccination: a simple, safe, and effective treatment for patients with ischaemic heart disease and heart failure

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Annual influenza epidemics are estimated to cause between 290 000 - 650 000 respiratory deaths per year – however, this estimate does not include cardiovascular (CV) deaths.(1) Influenza infection is associated with increased risk of CV events, particularly among individuals at high CV risk.(2, 3) Multiple pathophysiological mechanisms have been proposed to explain the associated increase in CV outcomes in individuals with influenza infection, such as atherosclerotic plaque rupture and an increased risk of atherothrombosis

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(secondary to the release of pro-inflammatory cytokines resulting in a pro-thrombotic milieu, influx of inflammatory cells, plaque destabilisation, and endothelial dysfunction), increased metabolic demand due to sympathetic activation (leading to tachycardia and hypoxaemia, exacerbating supply-demand mismatch), or by direct viral effect or triggering of myocarditis.(2, 4)

Influenza vaccination (IV) is widely acknowledged as the most effective way to prevent seasonal influenza, reduce disease severity, and lower the incidence of complications and deaths.(1) It is, therefore, intuitive that IV might reduce the risk of CV events in at-risk patients, although until recently randomized controlled trials (RCTs) specifically addressing this hypothesis were small and varied in quality. Prior meta-analyses assessing the influence of IV on CV events yielded conflicting results, partly due to the inclusion of small, non-randomized studies (which are more susceptible to biases and unmeasurable confounders) and the heterogeneity in populations studied, follow-up intervals, and outcome measures.

Modin et al conducted a contemporary and comprehensive systematic review and meta-analysis examining the effect of IV on CV outcomes in patients with high CV risk, defined as patients with ischaemic heart disease (IHD) and/or heart failure (HF).(5) The meta-analysis included six RCTs with a total of 9340 patients (4211 with IHD, 5129 with HF). Five of the six trials included patients with IHD, while the recently published Influenza Vaccine to Prevent Adverse Vascular Events (IVVE) trial included patients with HF.(6) The follow-up duration ranged from 10 to 36 months. The primary major adverse cardiovascular event (MACE) endpoint was a composite of CV death, acute coronary syndrome (ACS), stent thrombosis, coronary revascularization, and stroke or HF hospitalization. If a trial did not report a composite endpoint including all these events, a composite endpoint most closely

resembling the primary MACE endpoint was used. In this pooled meta-analysis, IV led to a reduction in MACE (15.5 vs. 18.4%; HR 0.74, 95% CI 0.63-0.88, p<0.001) (*Figure 1*). Additionally, there was a reduction in the secondary endpoints of CV mortality (HR 0.63, 0.42-0.95, p=0.028) and all-cause mortality (HR 0.72, 0.54-0.95, p=0.023). The six RCTs included spanned multiple geographical regions (Africa, Asia, Australia, Europe, Middle East, South America) which enhances the generalizability of the findings, although North America was not represented in any of the trials identified in the systematic review.

The largest trial of patients with IHD included in this analysis was the Influenza Vaccination After Myocardial Infarction (IAMI) trial which randomised 2532 patients after myocardial infarction (MI) or with high risk stable coronary artery disease to IV or placebo.(7) Almost all (99.7%) patients had been admitted with an ACS, representing a cohort with increased risk for recurrent CV events. Treatment was administered within 72 hours of coronary angiography or admission. The trial was prematurely terminated due to the coronavirus disease 2019 (COVID-19) pandemic, leading to only half of the planned recruitment target being met. Nevertheless, the intervention group showed a reduction in the primary outcome of all-cause mortality, MI or stent thrombosis over 12 months compared to the control group (5.3 vs. 7.2%; HR 0.72 [95% CI, 0.52–0.99]; p=0.040), primarily driven by a reduction in all-cause mortality (2.9 vs. 4.9%; HR 0.59 [95% CI, 0.39–0.89]; p=0.010).(7) In contrast, the IVVE trial recruited 5129 patients with symptomatic HF, 2020 (39%) of whom had HF with preserved ejection fraction (ejection fraction >40%). Despite IVVE's recruitment from exclusively low- and middle-income countries, patients were on relatively good disease-modifying therapies at baseline. Reflective of the enrolling countries, the proportion of patients with IHD (30%) or prior MI (21%) was low.(6) IVVE also actively recruited during the COVID-19 pandemic, and follow-up was consequently terminated early in 7 of the 10

countries involved due to a combination of administrative and supply issues, as well as the direct impact of the COVID-19 pandemic. Although numerically fewer patients experienced the primary endpoint of CV death, non-fatal MI, or non-fatal stroke with IV compared to placebo, this did not reach statistical significance (14·8 vs. 16·0%; HR 0·93 [95% CI 0·81–1·07]; p=0·30). Given the lower prevalence of ischemic aetiology or history of MI in IVVE, patients were likely at lower risk of risk of atherosclerotic CV events compared to those in IAMI. The difference in these two trial results and prevalence of IHD could, taken simplistically, imply a greater benefit in reduction of CV risk from IV for HF patients of ischemic aetiology, perhaps in keeping with some of the proposed pathophysiological mechanisms of increased CV events in influenza infection as highlighted by Modin et al. However, the complex influence and interaction of seasonal variation on influenza exposure and risk of CV events is important when interpreting this trial. A pre-specified sub-analysis of IVVE, focused on times of peak influenza circulation, demonstrated a reduction in the primary composite outcome (7·5 vs. 9·3%; HR 0·82 [95% CI 0·68–0·99]; p=0·038).

Undoubtedly, the COVID-19 pandemic added additional challenges to the two most recent and largest trials included in this meta-analysis (IAMI and IVVE). The IAMI trial's enrolment duration and size were curtailed due to the pandemic.(7) As a result, there may have been an underestimation of the effect of IV on the primary outcome and limited power to assess secondary outcomes, such as MI, due to a smaller number of events. Similarly, the IVVE trial had to terminate follow-up prematurely in seven of the ten countries, primarily due to national restrictions related to the pandemic.(6) Moreover, the spread of misinformation regarding vaccination during the COVID-19 pandemic might also have exacerbated recruitment and retention challenges faced by these trials. Public health interventions (e.g., social distancing, hand and cough hygiene, and face masks) may have

attenuated influenza infection rates and severity, potentially diminishing the comparative effectiveness of IV. Despite these challenges, these trials have not only provided valuable efficacy data but have also contributed to the extensive safety profile of IV, particularly for individuals with higher CV risk and older patients. Importantly, the IAMI trial demonstrated the safety of administering IV in patients at the time of acute atherothrombotic events, allowing for opportunistic vaccination of at-risk individuals while they are hospitalised. Furthermore, emerging evidence suggests that COVID-19 vaccination is associated with a reduced risk of MACE compared to unvaccinated individuals, albeit in non-randomized cohort studies.(8) The advancements in messenger ribonucleic acid (mRNA) and viral vector deoxyribonucleic acid (DNA) vaccines developed during the COVID-19 pandemic hold promise for the future of influenza prevention, potentially revolutionising the approach to influenza vaccine development.

International guidelines recommend IV for patients at high CV risk. The European Society of Cardiology (ESC) guidelines for chronic coronary syndromes strongly recommend annual IV (Class 1 recommendation).(9) Additionally, both the ESC and the American College of Cardiology/American Heart Association guidelines for HF state that IV should be considered (Class 2a recommendation).(10, 11) Despite these recommendations and public health endorsements, IV uptake among patients with CV disease varies significantly worldwide. In the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, the top predictor of IV was enrolling country, with highest rates in the Netherlands (77.5%), Great Britain (77.2%) and Belgium (67.5%) and lowest rates in Asia (2.6%), with intermediate rates in North America (52.8%).(12) The IVVE trial was conducted in countries with low baseline IV rates to ensure ethical administration of a placebo to patients with limited access to vaccination.(6) Despite

allowing cross-over, only 0.9% of patients in the placebo group received open-label IV outside the trial, highlighting the continued significance of geography as a major determinant of vaccination status. Vaccine hesitancy remains an important cause of low vaccine uptake. Proposed strategies to reduce barriers to IV include reinforcing existing guidelines, providing education to both patients and clinicians, combating misinformation, and incorporating IV into post-myocardial infarction checklists. This updated meta-analysis by Modin et al strengthens the evidence base supporting the use of IV in patients at higher CV risk, particularly in patients with a history of IHD, aligning closely with the aforementioned guideline positions and recommendations. IV holds the greatest potential for benefiting patients in low- and middle-income countries, where access to conventional secondary prevention therapies for IHD and contemporary HF therapies may be limited. The findings of this meta-analysis are welcomed and will contribute to the ongoing efforts in countering vaccine misinformation and promoting appropriate vaccine use, particularly in patients with higher CV risk.

Conflict of interest

R.T.C. has received consultancy honoraria from Bayer and speaking honoraria from AstraZeneca.

M.M.Y.L. has received research grants through his institution, the University of Glasgow, from AstraZeneca, Boehringer Ingelheim and Roche Diagnostics; is a member of a Trial Steering Committee for Cytokinetics, and Clinical Endpoints Committee for Bayer.

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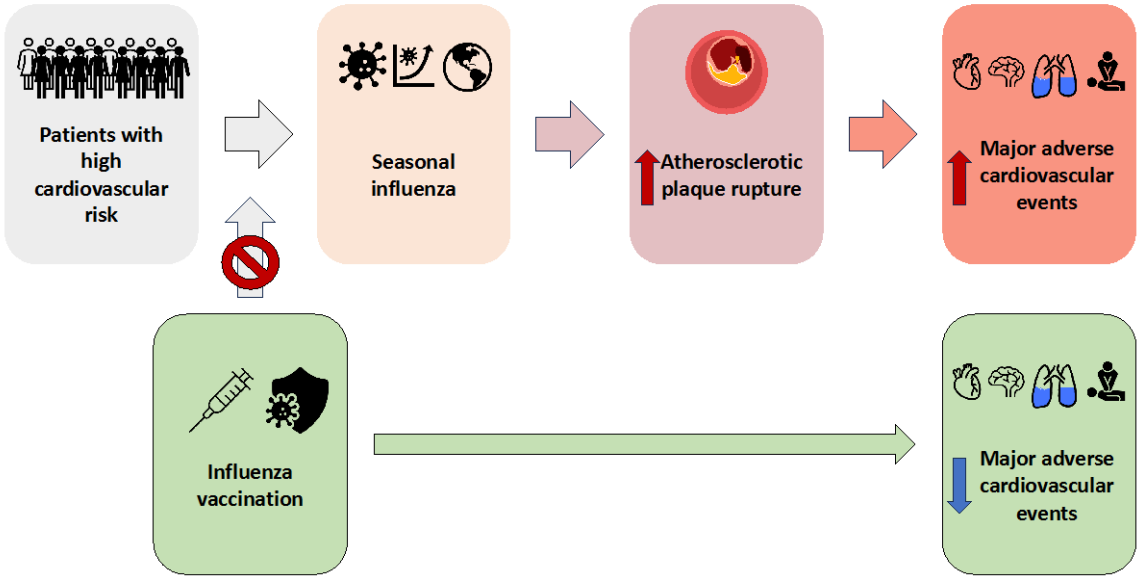
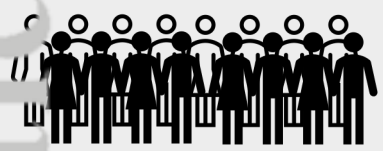
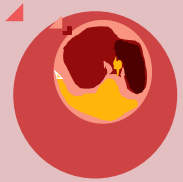
Figure 1 Influenza vaccination and effect on major adverse cardiovascular events in patients with high cardiovascular risk



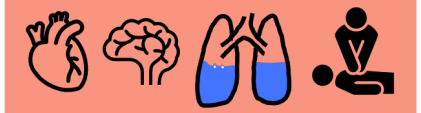


Patients with high cardiovascular risk

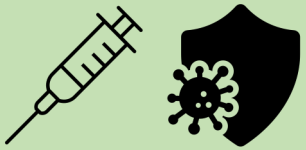
Seasonal influenza



Atherosclerotic plaque rupture



Major adverse cardiovascular events



Influenza vaccination

Major adverse cardiovascular events