1. Introduction

Ischemic heart disease (IHD) and stroke have been the world's leading causes of death for over 15 years [1]. Prominent 'traditional' risk factors for cardiovascular disease (CVD) such as hypertension, smoking, diabetes and obesity have been the focus of extensive epidemiological research and subsequent public health action [2]. Additional research has focused on a more diverse range of acute triggers including; emotional stress, physical exertion, air pollution and acute infections [3]. Here we consider the effect of acute respiratory infections (ARIs).

Population-level studies in a range of geographical settings show that patterns of CVD mortality and acute cardiovascular events mirror the seasonality of some ARIs, and persists after controlling for long-term incidence trends, seasonality and environmental conditions [4,5]. While the findings from these population-level studies suggest a link between ARIs and cardiovascular complications, stronger evidence comes from individual-level observational studies.

2. Observational research studies of the association between ARIs and acute cardiovascular events

Observational research using large electronic health record databases affords large sample sizes, and their longitudinal nature allows for a self-controlled case series (SCCS) study design. In SCCS studies, cases act as their own controls, accounting for fixed confounders, during periods of non-exposure – this is particularly useful when investigating associations between transient exposures and acute events. Results from SCCS studies have generally estimated a two to six-fold increase in risk of cardiovascular complications – particularly myocardial infarction (MI) and stroke – following an ARI [6-8]. Meta-analysis, limited to case-control studies, identified ARIs were more likely to have occurred among MI patients, with a pooled odds ratio (OR) of 2.01, 95% confidence interval (CI) 1.47-2.76 [9].

SCSS studies have split follow-up time, from ARI symptom onset or diagnosis to cardiovascular event, by days which thereby identified the length of risk. The results suggest risk lasts for up to one month following infection, with the highest risk in the first week after infection [6-8].

Risk is dependent on several factors. The severity of infection will impact the likelihood of cardiovascular complications; an international multicenter cohort study in patients with community acquired pneumonia (CAP) identified composite acute cardiovascular events were more likely following severe infection (OR 1.74, 95% CI 1.15-2.63), with a particularly high OR seen for MI (OR 4.33, 95% CI 1.55-12.1) [10]. Case-control and SCCS studies have largely used broad clinical definitions of ARI. Studies which use a microbiological definition identified an increased risk of cardiovascular complications after influenza virus and *Streptococcus pneumoniae* infection [7,8]. Host health will additionally modify risk; the majority of studies have been conducted among older adults with pre-existing diagnosed CVD [6,8,9]. ARIs can trigger acute cardiovascular events in people without known CVD [6], although it is likely that at least some of these events occur in people with undiagnosed atherosclerosis.

3. Potential mechanisms

Systemic inflammatory processes triggered by ARIs include release of pro-inflammatory cytokines which are key mediators of atherosclerosis and may directly impact plaque rupture through local inflammation [11]. Furthermore, infections induce pro-coagulant and hemodynamic effects which predispose to ischemia and thrombosis [11,12]. While animal models of severe pneumonia show that *S. pneumoniae* can invade the myocardium leading to cardiac injury and scarring [13], there have been few echocardiographic studies

during severe pneumonia in humans. Autopsy studies suggest that myocardial injury, which is relatively rare in uncomplicated infections [14], may occur more often in fatal influenza [15].

4. The role of influenza and pneumococcal vaccinations in reducing cardiovascular risk

Both randomized controlled trials (RCTs) and observational studies demonstrate some CVD benefits of influenza vaccine. A meta-analysis of five small RCTs identified influenza vaccine reduced the risk of cardiovascular events within one year of follow-up (relative risk (RR) 0.64, 95% CI 0.49-0.84) [16]. A subgroup meta-analysis of three RCTs in patients with IHD found risk reduction predominantly in people with recent acute coronary syndrome compared to stable IHD [16]. Recent observational research studies have demonstrated similar findings; in a SCCS study among heart failure patients, influenza vaccination was associated with a lower risk of hospitalization due to CVD (incidence rate ratio 0.73, 95% CI 0.71-0.76) [17].

The effects of pneumococcal vaccination on cardiovascular outcomes are less clear. Meta-analysis investigating the effect of pneumococcal vaccination on cardiovascular outcomes identified no RCTs, while results from observational studies were mixed [18]. In people aged ≥65 years, vaccination was associated with a lower risk of MI (RR 0.90, 95% CI 0.82-1.00), but no reduction in risk was identified among patients of all ages with high cardiovascular risk [18].

In most high-income countries universal influenza and pneumococcal vaccination is recommended for adults aged ≥60-65 years. Adults under these ages are recommended to receive vaccination when they fall into a clinical risk group who are more likely to experience complications following infection such as those with IHD [19].

5. The effect of antiviral drugs on cardiovascular events

Only a small number of studies have investigated cardiovascular complications following antiviral use. A meta-analysis of six RCTs on the effect of oseltamivir versus placebo among influenza infected adults found that antiviral use was associated with a decrease in adverse cardiac events (RR 0.49, 95% CI 0.25-0.97) [20]. Conversely, results of one RCT suggested that, compared to placebo, oseltamivir may increase QTc prolongations during treatment periods (risk difference 4.0%, 95% CI 0.71-7.30) [20]. Another meta-analysis of 11 RCTs investigating the effect of zanamivir use in influenza-infected adults found no difference (RR 0.98, 95% CI 0.50-1.91) in adverse events affecting the ‘cardiovascular body system’ [20].

The association between oseltamivir and cardiovascular complications also been explored in observational research. A historical cohort study among adult US military health beneficiaries with CVD identified a reduction in the incidence of recurrent cardiovascular events within 30 days among the oseltamivir treatment group (OR 0.42, 0.35-0.50) [21]. In another historical cohort study, oseltamivir use resulted in a 28% (HR 0.72, 95% CI 0.62-0.82) reduction in stroke and transient ischaemic attack risk during the subsequent six months [22].

Antiviral drugs are recommended for influenza prophylaxis and treatment. Prophylactic use may occur if antigenic mismatch between seasonal vaccine strains and circulating strains occurs, or as post-exposure prophylaxis, particularly to control outbreaks in residential care communities. Antiviral treatment within 48 hours of symptom onset during influenza seasons in certain clinical risk groups (i.e. IHD) and immunosuppressed adults aged ≥65 years is also recommended [19].

6. Future research directions

More research focused on who is at risk of cardiovascular complications triggered by ARIs is needed. Predicting future CVD, particularly in people with different combinations of co-morbid conditions, will assist in providing targeted personalized interventions. Any expansion to current vaccine recommendations resulting from new patient groups being identified as high risk for cardiovascular complications following ARI will require effectiveness and cost-effectiveness studies.

In addition, vaccine uptake among those currently recommended to receive it is suboptimal: across Europe, influenza vaccination coverage remains well below the 75% target level among at-risk groups [19]. Identifying the optimum vaccine target groups whom vaccination campaigns should be aimed at, as well as understanding healthcare barriers and facilitators to uptake should be prioritized. The timing and dose of vaccines are also important research considerations. One SCCS study identified a significant reduction in the incidence of MI within 60 days of vaccination, particularly in the first two weeks [23]. Some RCTs have investigated the impact of high dose influenza vaccine; compared to standard dose vaccine, use of high dose vaccine in people with high cardiovascular risk resulted in a greater reduction of cardiovascular complications [16]. A large RCT with nearly 10,000 CVD patients is currently underway to determine whether high dose influenza vaccine will reduce all-cause mortality and cardiovascular hospitalizations [24].

While prevention of ARIs themselves is likely to result in the greatest clinical and public health benefit, treatment during the acute phase of infection could also prevent cardiovascular complications. A better understanding of the cardiovascular effects of antivirals is needed e.g. from RCTs with the primary outcome of cardiovascular complications. Some observational studies have investigated whether other drugs including statins, corticosteroids and antiplatelet agents may potentially reduce risk of CVD events during acute infections [25-27]. Further research is needed on the effectiveness, timing and target populations for any such treatments. Observational research suggests cardiac biomarkers provide one method to identify patients with ARI who are at high risk of cardiovascular complications [28]. This cohort study identified hospitalized CAP patients who had blood samples taken at several time points during the first 30 days of admission and showed multiple biomarkers were higher among patients who had a cardiovascular event. People with high overall vascular risk score, such as Framingham or QRISK, are another group who could be targeted for early intervention.

7. Conclusions

Understanding and addressing interactions between diseases, such as ARIs and CVD, is increasingly important as the global population ages and multimorbidity increases. Among ARIs, much focus has been given to influenza due to its severity but also because it is one of the only respiratory infections for which there is effective prevention and treatment. This focus is supported by findings from observational studies which confirm an association between laboratory-confirmed ARIs and cardiovascular complications. However, where infections other than preventable and treatable influenza or *S. pneumoniae* result in cardiovascular complications, other approaches to avert these outcomes are required.

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