If there were a vaccine against acute myocardial infarction, would you use it?

C Raina MacIntyre^{*,1,2} & Aye M Moa¹

¹School of Public Health & Community Medicine, The University of New South Wales, UNSW Sydney, NSW 2052, Australia

²College of Public Service & Community Solutions, Arizona State University, Phoenix, AZ 85004, USA

* Author for correspondence: r.macintyre@unsw.edu.au

“Coronary artery disease is an inflammatory condition, and influenza more than any other infection has been strongly associated with triggering of acute coronary events”

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Cardiovascular disease (CVD) is the leading cause of death globally and is rising in many countries. The WHO estimates that 18 million people die annually from CVD and the majority of these are a result of heart attack and stroke [1]. The association between CVD and influenza has long been recognized, with a peak in CVD mortality during the winter months, corresponding with peaks of influenza activity [2]. Coronary artery disease is an inflammatory condition, and influenza more than any other infection has been strongly associated with triggering of acute coronary events [3]. The postulated mechanism is that influenza causes systemic inflammation and release of various cytokines, which result in a prothrombotic state, disruption of coronary artery endothelium and acute thrombus formation in a diseased artery which may not otherwise be critically stenosed [3]. The infection also acts by causing hypoxia, tachycardia, vasoconstriction and direct effects on the myocardium, the combined effect of which may precipitate acute myocardial infarction (AMI) [3].

Influenza & AMI

A number of studies show that influenza is associated with AMI [4–7]. In a meta-analysis of available case–control studies, we showed that influenza infection doubles the risk of AMI [4]. In a prospective study, we tested patients admitted with AMI for influenza and found that almost 10% of AMI patients had undiagnosed, unrecognized influenza infection as an antecedent event [5]. An influenza infection may occur up to a week prior to AMI, and the diagnosis may not be considered when a patient presents with an acute coronary event.

Other infections & AMI

A 17-fold increase in risks of developing angiographically confirmed MI was reported by a recent study within 1–7 days following of self-reported respiratory infection of any cause. An increased relative risk of 13.5 (95% CI: 10.2–17.7) was observed in cases even with mild upper respiratory tract infection [8].

A review of observational studies showed consistent association between AMI and either influenza or other respiratory infection, with the association being most consistently significant for influenza [6].

Apart from respiratory infections, a few studies have shown an association between cardiovascular events/AMI following herpes zoster (HZ) infection, which is a reactivation of varicella zoster virus. The rate of MI reported showed an increase of 1.7-fold within a week after diagnosis of HZ infection in a self-controlled case series conducted in the USA of older adults of 65 years of age and over [9]. An increased risk (59%) of developing MI was reported in HZ cases compared to controls in a large population-based study in Korea [10]. Therefore, MI is a documented association with infections.

CVD & influenza vaccine

If influenza precipitates AMI, then it logically follows that vaccination against influenza may have a protective effect. There is, in fact a large body of evidence from both randomized controlled clinical trial (RCT) and observational studies which suggest that influenza vaccine protects against AMI [4]. We were the first to calculate vaccine effectiveness against AMI and found that influenza vaccine effectiveness was 45% against AMI [5]. The pooled vaccine effectiveness against AMI calculated from all available studies is 29% [4]. From observational studies, it is estimated that influenza vaccine could provide vaccine effectiveness of 15–45% against MI [3,11]. In addition, the vaccine effectiveness is more evident in AMI patients with early seasonal influenza vaccination compared with midseason vaccination (21 vs 12%) in a large matched case–control study conducted in the UK [11].

Given the high burden of CVD worldwide, a vaccine effectiveness of this range can have a substantial population health benefit in preventing AMI [5]. Influenza vaccine is postulated to prevent AMI by preventing influenza infection and the resulting pathological mechanisms outlined above. There is also evidence that influenza vaccine results in antibodies which cross-react with bradykinin receptors, as yet another protective mechanism [12].

Compelling evidence continues to accumulate, with many studies reporting the benefits of influenza vaccine on cardiovascular events and its relative reduction in patients with AMI [13,14]. Pooled data from small randomized controlled trials show a relative reduction of 50% in cardiovascular deaths and 43% in cardiovascular events, with 54% protection for patients who have an acute coronary syndrome within 12 months [15]. However, small sample sizes of the available RCTs, as well as variable study outcomes reported in these studies are a limitation. We have already argued the need for a large randomized controlled trial to better inform policy and practice [16]. Currently, a multicenter, registry-based randomized clinical trial is underway with over 4000 participants to determine the effect of influenza vaccine to all-cause death and cardiovascular events at 1-year period after in-house influenza vaccination compared with placebo [17]. The study finding could provide valuable information on the efficacy of influenza vaccine against MI in the target population.

We showed that the effectiveness of influenza vaccine as a coronary prevention of 15–45% against AMI, makes it comparable to accepted strategies such as smoking cessation (32–43% efficacy), use of statins (19–30% efficacy) and use of antihypertensive drugs (17–25% efficacy) [3]. A paradigm shift is required to view influenza vaccination as another available strategy for secondary prevention of AMI in addition to accepted measures such as statins.

Influenza vaccine versus other measures for AMI prevention

Another interesting association between influenza and AMI includes the use of statins. Statins are widely used for the secondary prevention of coronary heart diseases. Recent studies have suggested an interaction between influenza vaccine and statins which reduce the benefits of vaccination [18,19]. The role of confounding in these studies is unclear and more research is required to understand this relationship. However, statins have also been proposed as a protective therapy during pandemic influenza due to their anti-inflammatory properties [20]. In addition, a reduced risk of MI was also reported in patients who take regular cardiac medications [8]. An additive effect of annual influenza vaccination plus other cardiovascular preventive strategies for both primary and secondary prevention of cardiovascular events may be seen in populations at high risk for AMI. More in-depth research is needed to investigate the cumulative benefit of vaccination with accepted preventive strategies for AMI.

Conclusion

Influenza vaccine is safe, effective and relatively cheap. It has already shown to be highly cost-effective, even without considering the prevention of AMI [21]. Cost–effectiveness studies which include AMI prevention need to be conducted. There is enough evidence available to guide policy and most immunization policies do in fact recommend influenza vaccination for patients with CVD. Despite influenza vaccine being recommended in many countries for patients with CVD [22], it has not made its way into practice as a routine measure to protect patients at risk, with vaccination rates in patients with CVD being low [23]. It has been shown that clinicians in general have a low awareness of adult vaccination and are not strong advocates for vaccination in adults [24,25]. Improved clinician awareness of the benefits of influenza vaccine in prevention of CVD events is needed to take advantage of vaccination as low-hanging fruit for prevention of AMI.

Future perspective

The intersection of communicable and noncommunicable diseases is becoming more apparent with time, not only in inflammatory conditions, but also in cancer and diabetes. Vaccines for noncommunicable diseases such as diabetes

are in development and there is strong evidence for influenza vaccine as an adjunct to conventional coronary prevention strategies. In the future, RCTs of combination strategies such as statins and influenza vaccination, will progress, and the evidence base will accumulate to drive policy, practice and prevention of CVD. Influenza vaccination may become a standard, accepted intervention for CVD prevention.

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