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Thought leaders in the fields of geriatrics, cardiology, infectious diseases, internal medicine, pulmonology, critical care, family medicine, hospital-health systems, public health, and epidemiology convened at a roundtable to explore the direct and indirect consequences of influenza in older patients with multiple comorbidities. This monograph on the cardiovascular burden of influenza is Part 1 of a series resulting from the information shared and issues discussed during the roundtable.

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The Cardiovascular Burden of Influenza

Influenza's impact on the risk for pneumonia is well known, but did you know that influenza is also associated with an increased risk of acute myocardial infarction and stroke?

The relationship between infections and cardiovascular events has been described in the scientific literature for more than a century. In 1908, Sir William Osler proposed that acute infections were 1 of the 4 major factors causing atherosclerosis, the others being “the normal wear and tear of life, . . . the intoxications [including smoking, diabetes mellitus, obesity], and those combinations of circumstances which keep the blood tension high.”¹

More recently, a number of studies have established that atherosclerosis, the underlying mechanism for cardiovascular diseases (CVD), is an active inflammatory disease.² Atherosclerosis has a slow progression over many years, with inflammation playing a role in every stage of the atherosclerotic process, from the early binding of leukocytes (particularly monocytes and lymphocytes) to damaged endothelium, to the progression of atherosclerotic lesions, to destabilization of advanced plaques leading to thrombus formation and acute coronary syndromes (ACS) or sudden cardiac death.²⁻⁸

EVIDENCE THAT INFLUENZA CAN TRIGGER CARDIOVASCULAR DISEASE

The existence of a relationship between influenza and myocardial infarction was first suggested following the influenza epidemics in Europe and the United States (US) in the early 1900s, when a review of mortality data from 35 cities from 1917 through 1929 showed that deaths due to heart disease rose during almost all influenza epidemics.⁹

In the past 30 years, the evidence that influenza can trigger an adverse cardiac-related outcome has grown. Some studies have dem-

onstrated a close temporal relationship between winter peaks of acute respiratory infections and cardiovascular events.^{10,11} In the first of these analyses, a clear seasonal distribution of cases of acute myocardial infarction (AMI) was seen among nearly 260,000 cases reported to a national registry in the US, with about 53% more cases reported in winter than during the summer.¹⁰ The pattern was consistent across age groups (<55, 55–64, 65–74, and ≥75 years of age), geographic areas, and sexes. The second analysis found that, over a 40-year period in the US, peak months for mortality due to AMI and stroke coincided with peaks in pneumonia and influenza.¹¹

In the case of organic heart diseases there was a peak, corresponding in time with the influenza peak, for practically every epidemic.

– Selwyn D. Collins, Senior Statistician,
United States Public Health Service,
November 1932⁹

A similar association between influenza and AMI-related deaths and hospitalizations was seen in another study conducted in both temperate (England and Wales) and subtropical climates (Hong Kong), even after adjusting for seasonality and environment.¹²

Patients had recently sought medical care for influenza or another acute respiratory infection in more than one third of cases of first AMI analyzed in England and Wales.¹³

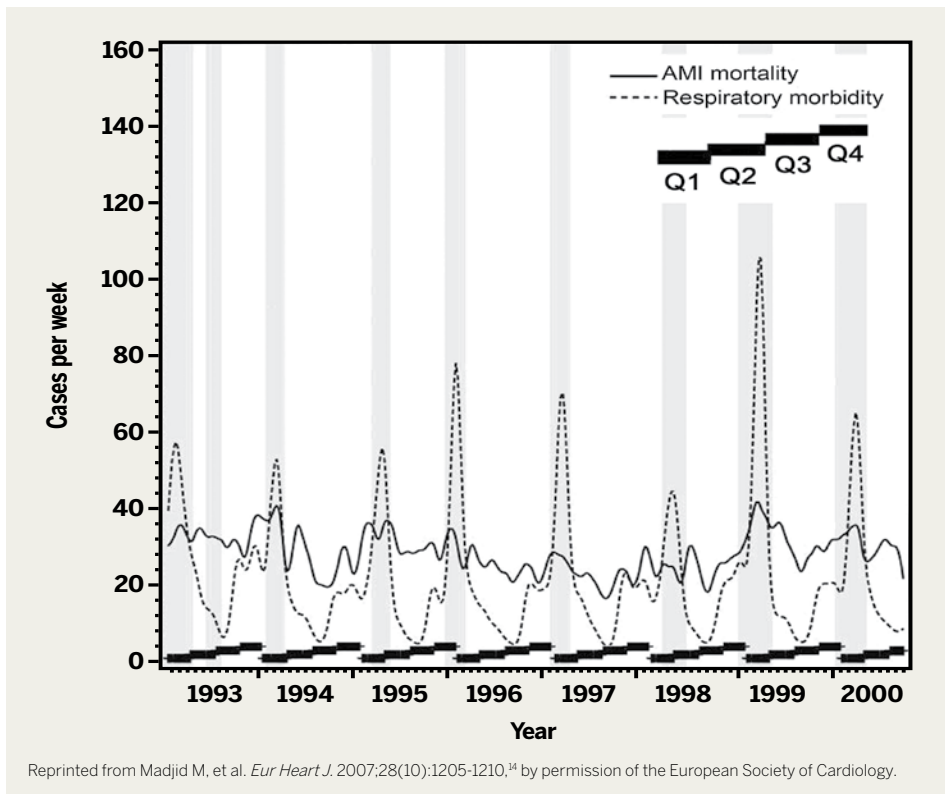


FIGURE 1. Deaths due to AMI and morbidity from acute respiratory disease (ARD) from 1993 to 2000. The solid line depicts AMI mortality while the dashed line indicates ARD morbidity. Gray columns indicate influenza epidemic periods. The thick black “ladders” at the bottom of each year’s plot indicate the 4 seasons in the order of winter (Q1), spring (Q2), summer (Q3), and fall (Q4). For almost every influenza epidemic, there was a rise in the number of coronary deaths.¹⁴

In a study of nearly 35,000 patients over an 8-year period, a surge in autopsy-confirmed deaths from coronary heart disease was shown to be associated with influenza epidemics and acute respiratory disease activity (Figure 1).¹⁴ The effect was seen in all age groups and in both sexes.

An important feature of this study was the use of autopsy results to determine the cause of death, which provided more accurate results than the more typically utilized death certificate statistics. For example, in cases where patients have been infected with influenza and subsequently suffered a fatal AMI, death is usually reported as due to cardiac causes; influenza is not listed on the death certificate. On the other hand, signs and symptoms of an AMI—for example, dyspnea, chest pain, and hypoxia—may be missed in patients who have influenza and influenza-related pneumonia.

An earlier case-control study based on data from the United Kingdom General Practice Research Database found that rates of first AMI and first stroke increased sharply during the first 3 days after the diagnosis of an acute respiratory syndrome.¹⁵ The rates also increased, but to a lesser degree, after acute

urinary tract infections. By contrast, there was no increase in risk after vaccination for influenza, tetanus, or pneumococcal disease. This study provided additional support for the concept that inflammation is an important

factor in atherosclerotic disease, and it also provided reassurance that vaccination *does not* itself increase the risk of vascular events.

POTENTIAL MECHANISMS FOR THE EFFECTS OF INFLUENZA ON ATHEROSCLEROSIS

Both in vitro and in vivo models have shown that influenza and other acute respiratory infections affect multiple inflammatory and coagulation pathways (Figure 2). In addition to eliciting systemic inflammatory responses (for example, a rise in inflammatory cytokines such as tumor necrosis factor- α and interleukin-6), influenza can also have direct inflammatory effects on atherosclerotic plaques and coronary arteries, triggering destabilization and eventual rupture of plaque.^{4,16} Plaque rupture is considered to be the underlying mechanism for more than half of acute coronary events.¹⁷

A study conducted in mice that are deficient in apolipoprotein-E, a well-established animal model of atherosclerosis in humans, showed that infection with influenza A virus leads to a marked increase in acute inflammation, proliferation of smooth muscle cells, and deposition of fibrin clots over the atherosclerotic plaques, but not in normal regions of the aorta.¹⁸

Other mechanisms by which influenza may trigger AMI include increased prothrombotic effects, hemodynamic stress (ie, fever, tachycardia, demand ischemia, hypoxemia, increased blood viscosity, and hypotension), and acute endothelial dysfunction.^{8,12,19}

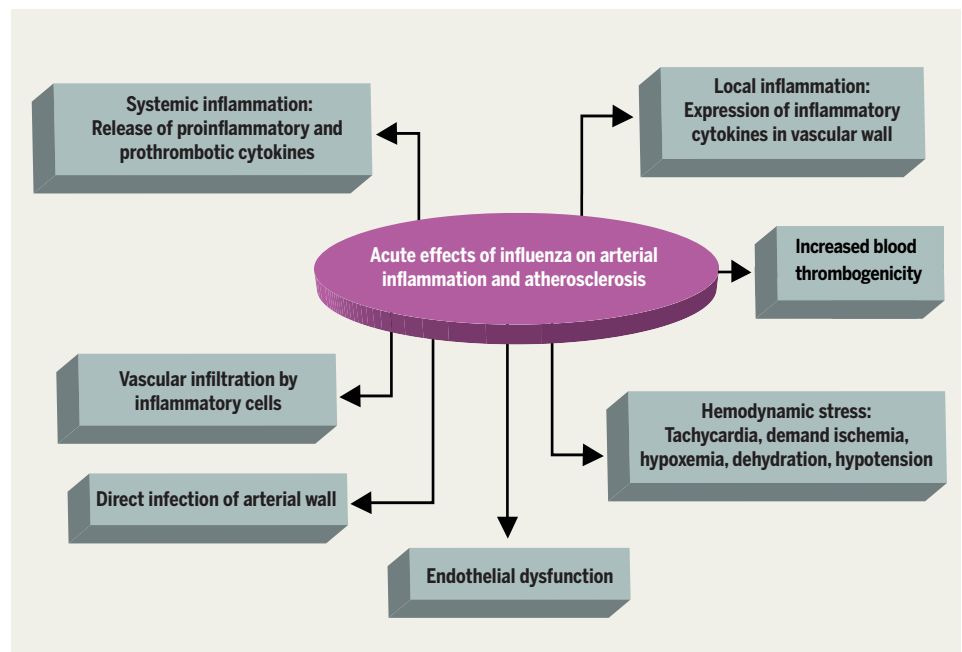


FIGURE 2. Potential mechanisms by which influenza may affect atherosclerosis.^{4,8,12,16,18,19}

Studies in mice have demonstrated the presence of influenza virus, its antigens, and its viral RNA in the hearts and aortas of normal and atherosclerotic mice after influenza infection, suggesting that influenza virus plays a direct role in the pathogenesis of cardiovascular disease.²⁰

THE ROLE OF INFLUENZA VACCINATION IN DECREASING CARDIOVASCULAR EVENTS

If influenza can cause CVD and AMI, a key question is whether preventing influenza—particularly by means of vaccination—can help to prevent those cardiovascular events. Studies currently under way in Canada are using polymerase chain reaction to determine whether and how often influenza viruses trigger acute cardiac events.

A number of published studies suggest that influenza vaccination does play a protective role. A case-control study found that in patients with established coronary atherosclerosis and a history of previous AMI, influenza vaccination was associated with an average 67% relative (24% absolute) reduction in the risk of a recurrent MI ($P=0.017$).²¹ The randomized, prospective, controlled Flu Vaccination Acute Coronary Syndromes (FLUVACS) study in patients hospitalized for AMI or planned angioplasty showed a reduced incidence of the primary end point, cardiovascular death, at 6 months and 12 months in those immunized against influenza compared with controls.^{22,23} Similarly, influenza vaccination significantly reduced the risk of secondary coronary ischemic events (40% relative risk reduction, 4% absolute risk reduction; $P=0.047$) at 12 months in patients with known coronary artery disease in a randomized, double-blind, placebo-controlled study.²⁴

The effects of influenza vaccine on cardiovascular outcomes in patients with ACS were examined in a prospective, randomized open study with a blinded end point.²⁵ Major adverse cardiovascular events (MACE)—including death, hospitalization from ACS, hospitalization from heart failure, and hospitalization from stroke—occurred less frequently in the vaccine group than in the control group (9.5% vs 19.3%, adjusted hazard ratio [HR] 0.67 [0.51–0.86], $P=0.005$). There was no significant difference in the incidence of cardiovascular death between the vaccine and control groups. The beneficial effects of influenza vaccine persisted after adjustment for variables affecting MACE and in every subgroup of patients (**Table 1**).²⁵

TABLE 1. Results of a study to evaluate the effects of influenza vaccine on cardiovascular outcomes in patients with ACS^{a,25}

End points	Vaccine (n=221)	Control (n=218)	Adjusted HR (95% CI)	P-value (adjusted HR)	Number needed to treat
MACE ^b , n (%)	21 (9.5)	42 (19.3)	0.67 (0.51-0.86)	0.005	11
Death (total), n (%)	6 (2.7)	12 (5.5)	0.62 (0.34-1.12)	0.113	36
Hospitalization for ACS ^a , n (%)	10 (4.5)	23 (10.6)	0.68 (0.47-0.98)	0.039	17
Hospitalization for HF ^c , n (%)	4 (1.8)	10 (4.6)	0.62 (0.19-2.04)	0.136	36
Hospitalization for stroke, n (%)	1 (0.5)	0	—		

Hazard ratios were adjusted for age, sex, serum creatinine, treatment with angiotensin-converting enzyme inhibitors, and coronary revascularization. The number needed to treat is the number of adults who must be immunized against influenza in order to prevent 1 additional incident of the undesired outcome.
^a ACS, acute coronary syndrome; ^b MACE, major adverse cardiovascular events; ^c HF, heart failure.
 Reprinted from Phrommintikul A, et al. *Eur Heart J*. 2011;32(14):1730-1735,²⁵ by permission of the European Society of Cardiology.

A case-control study conducted during consecutive winter seasons (2008–2010) at a tertiary referral hospital in the southern hemisphere found that influenza vaccination was significantly protective. Vaccine effectiveness against AMI was estimated as 45% in patients 40–64 years of age and 33% in those ≥65 years of age, suggesting that there is a potential population health benefit of vaccination in adults at risk of ischemic heart disease.²⁶

... influenza vaccination may provide additional benefits over preventing influenza infection and reducing the risk of atherosclerotic progression.

—Arintaya Phrommintikul and Wanwarang Wongcharoen, Faculty of Medicine, Chiang Mai University, Thailand, 2012²⁷

In patients ≥40 years of age in a case-control study using data from the United Kingdom General Practice Research Database, influenza vaccination within the previous year was associated with a 19% reduction in the rate of first AMI.²⁸ A systematic review, as well as an observational study, also suggest that influenza vaccination can offer protection against cardiac events.^{29,30} However, some researchers call for additional large, well-controlled observational studies to confirm the efficacy of influenza vaccines, and point to the need for even more immunogenic

vaccines for seniors as well as other strategies to better protect this and other high-risk groups against influenza.³¹

THE NEED TO INCREASE INFLUENZA VACCINATION EFFORTS IN PATIENTS WITH HIGH-RISK CONDITIONS

Both the American Heart Association (AHA) and the American College of Cardiology (ACC) recommend seasonal influenza vaccination for preventing cardiovascular events in all patients with coronary heart disease and their household contacts (AHA/ACC Recommendation Class I, Evidence Level B).³² However, influenza vaccine coverage among cardiac patients is far from optimal, and rates are even lower among patients' household contacts, according to a random, nationwide telephone survey of more than 1000 adults ≥18 years of age.³³

Of those interviewed about their knowledge, attitudes, and behaviors regarding influenza vaccination, 11% had histories of heart disease or stroke, and nearly half were at least 65 years of age. Overall, 57% of those surveyed had received influenza vaccine in the previous influenza season, and 68% had received or intended to receive vaccine during the current season.³³

Vaccination rates increased with age, from 48% of those 18–49 years of age to 68% of those 50–64 years of age and 75% of those ≥65 years of age. Only 58% of spouses and 33% of children ≤17 years of age in the household had been vaccinated. Many patients were unaware of or denied their

Table 2. Reasons given by patients with cardiovascular disease for not receiving influenza vaccine: results of a random nationwide telephone survey of US adults³³

Reason	Percentage of respondents
I am not in a high-risk group	24
I am afraid that I could catch the flu from the shot	18
I am careful about hand-washing and avoiding sick people	8
I had a bad reaction before	8
I hate needles	6
I do not want to pay for the shot	4
My doctor did not recommend it	4
A dirty needle could give me something worse than the flu	4
I am allergic to eggs	4
I bleed easily	2
Other	18
Total	100

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own high-risk status; some said they were afraid of “catching” influenza from the vaccine (**Table 2**).

KEY MESSAGES¹⁹

- Acute respiratory tract infections, including influenza, are associated with acute cardiovascular events.
- Vaccination against influenza may help prevent the infection-associated increase in acute coronary syndrome.
- The potentially dire cardiovascular effects of influenza should be an urgent call to action for health care providers: Ensure that your patients are vaccinated against influenza!

As the evidence mounts that influenza infection may be a factor in the pathogenesis of cardiovascular disease, immunization against influenza takes on even greater importance. Health care providers must take an active role in ensuring that their patients receive influenza vaccine.

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