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NEWS

Sixfold Higher Risk of Acute MI in the Week After Flu Diagnosis

The flu vaccine has been overlooked as a way to reduce complications from flu in high-risk patients and those with CVD, says one expert.

By **Michael O'Riordan** *January 24, 2018*

The flu tends to send individuals to bed with a cough, sore throat, and fever-like chills, but now yet another study has shown influenza can also be a trigger for devastating cardiovascular events.

Experts say the new data should remind cardiologists, who tend to be more enamored of new drugs or devices than simple, established approaches, to remind their patients what's at stake if they skip their annual flu vaccine.

In an analysis of people hospitalized with acute MI who had a positive test for influenza, patients were significantly more likely to be hospitalized for an acute cardiac event in the 7 days after the detection of influenza than at any other time point, report investigators.

“The risk of acute MI is greatest in the week after the detection of influenza, and it’s elevated by more than sixfold compared to the patient’s baseline risk,” lead investigator Jeff Kwong, MD (Institute for Clinical Evaluative Sciences, Toronto, ON) told TCTMD. “After that first week, [the risk] does seem to go back down to baseline.”

Kwong added that previous analyses have shown there is an increased risk of cardiovascular mortality during flu season, while others have shown there is an association between acute respiratory infections or influenza-like illnesses and acute cardiovascular events. In those studies, however, the diagnosis of acute respiratory infection was not sensitive nor specific for influenza.

“Ours is the first to show that this is lab-detected influenza,” said Kwong. “We know definitively that this is an influenza virus infection in these patients with acute MI.”

Mohammad Madjid, MD (Texas Heart Institute, Houston), who has extensively studied the link between cardiovascular disease and influenza, said the results aren’t surprising, but praised the analysis for its unique confirmation of infection.

“In every flu epidemic—except for 1918, the Spanish flu, which was completely different—twice the number of people die from cardiovascular causes than pneumonia or influenza,” Madjid told TCTMD. The present study, he said, confirms that “flu is a killer” and that individuals at higher risk for heart disease, such as the elderly and those with cardiovascular risk factors, or those with known coronary artery disease, are at risk of developing potentially fatal complications, such as acute MI, with the onset of flu.

“It’s a message for the public—everybody should get the influenza vaccine unless they have a contraindication,” said Madjid.

Jacob Udell, MD (University Health Network, Toronto, Canada), who has also studied the link between influenza and cardiovascular events, said the “elephant in the room” with

previous analyses has been their reliance on a clinical rather than laboratory-confirmed diagnosis of influenza infection.

The present study, with its focus on the first 7 days after influenza diagnosis, confirms that the flu is "a strong, temporally associated trigger for the onset of heart attacks," said Udell. "That time-related course is extremely tight."

Influenza 'Tips Over' CVD-Susceptible Patients

In the study, which was published today in the New England Journal of Medicine, investigators identified 364 hospitalizations for acute MI that occurred 1 year before and 1 year after a confirmed diagnosis of influenza. The risk interval was defined as the first 7 days after the respiratory specimen was obtained and influenza confirmed, while the control interval was classified as the 52 weeks before the flu confirmation and the 51 weeks after the end of the risk interval.

Overall, there were 20 admissions for acute MI during the risk interval and 344 admissions during the control period, or 20 admissions per week in the risk interval and 3.3 admissions per week in the control interval. As Kwong noted, admission to hospital for acute MI during the risk interval was six times greater compared with admissions during the control period (incidence ratio 6.05; 95% CI 3.86-9.50). There was no significant increase in the risk of acute MI after day 7.

The researchers also report that the incidence of acute MI was significantly higher in the 7 days after a laboratory-confirmed diagnosis of influenza B, influenza A, respiratory syncytial virus, and other viruses.

"For people who are already susceptible to coronary events, influenza can lead to acute inflammation, vasoconstriction, and platelet activation," said Kwong in reference to the potential mechanisms linking the flu with acute MI. "In general, influenza can cause metabolic stress, and all of these things can tip somebody over to having a coronary event."

Regarding the potential mechanisms, Madjid also highlighted the proinflammatory role influenza can play. In a previous study of atherosclerotic apoE-deficient mice infected with the influenza virus, he and other researchers observed a significant increase in macrophages and inflammatory cells within the vascular walls of the rodents' arteries. The peak inflammatory

changes occurred 7 to 10 days after the influenza infection, which lines up with the present study.

The hypothesis that influenza might trigger acute cardiovascular events has been around since 1932, although much greater attention has been paid to its role in acute cardiovascular events in the past 15 years. Among other studies, a 2013 meta-analysis led by Udell and published in JAMA, which included six randomized trials involving 6,735 patients, showed the use of the influenza vaccine was associated with a significantly lower risk of major cardiovascular events.

Vaccination for CVD Prevention

Kwong told TCTMD he believes there is still a need for randomized controlled clinical trials to determine whether widespread use of the flu vaccine could prevent cardiovascular events. That said, the study shows there is a very strong association between influenza and acute MI, and "if you can prevent the infection from happening in the first place, then we should be preventing some proportion of these MIs from happening," said Kwong.

Madjid is a big believer in vaccination, particularly for its cardiovascular benefits. As early as 2003, he called on professional societies to endorse the Centers for Disease Control and Prevention's recommendation that everybody over age 50 and those with cardiovascular disease be vaccinated. Currently, the American College of Cardiology and American Heart Association recommend annual influenza vaccination as secondary prevention for individuals with coronary and other atherosclerotic vascular disease (Class I, Level B).

"It's been proven—we have randomized trial data," said Madjid. Despite this, uptake remains low, he added. Currently, only about 60% of patients with known coronary heart disease are vaccinated each year. "It's very shameful," he said. "In fact, overall uptake of flu vaccine over the past 10 or 15 years hasn't changed at all in the United States."

Part of the problem, Madjid said, is that cardiologists tend to get excited over the latest drugs and technology but ignore simple solutions. "We have failed to promote influenza vaccination, which is very cheap and very safe and proven to work," he said. Madjid stressed that it's every physician's obligation, whether

they're a cardiologist or primary care doctor, to recommend their patients get vaccinated.

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>
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To TCTMD, Udell acknowledged that members of the general public are somewhat reluctant to get an annual vaccination. The flu vaccine doesn't protect everybody, but protection rates are even lower in the elderly and people with compromised immune systems, such as those with cardiac conditions and diabetes. For this reason, these individuals might feel it's not worth it to get a flu shot, said Udell.

"I don't think it's good enough to convince the public the flu is more than the sniffles," said Udell. "The whole point of what we're working on is a heart attack vaccine. I'd hope that would be profoundly convincing to people, that this minor thing with so little risk can have such a profound effect on protecting you.

Udell hopes that the ongoing INVESTED study will provide such convincing data. The National Institutes of Health-funded trial is testing whether a high-dose influenza vaccine will reduce cardiopulmonary events to a greater extent than a standard-dose vaccine in 9,300 high-risk patients with a history of MI or heart failure. As one of the INVESTED investigators, Udell said the trial is being conducted over four flu seasons, in order better their chances of matching the influenza vaccine to the virus and to ensure they are following patients during a strong flu season.

Sources

Kwong JC, Schwartz KL, Campitelli MA, et al. Acute myocardial infarction after laboratory-confirmed influenza infection. N Engl J Med 2018;378;345-353.

Disclosures

Kwong reports grants from Canadian Institutes of Health Research during the conduct of the study, as well as grants from Canadian Institutes of Health Research and University of Toronto Department of Family and Community Medicine outside the submitted work.

Madjid reports no conflicts of interest.

Udell is a site investigator for the INVESTED trial.