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Cardiovascular Therapeutics

Influenza Vaccine for Cardiovascular Risk Reduction

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Cardiovascular disease is a leading cause of morbidity and mortality. Individuals with underlying cardiovascular disease are at high risk for adverse outcomes from influenza infections. Although additional studies are needed, current evidence suggests the influenza vaccine may reduce the risk of cardiovascular death and coronary events. In addition to their overall efforts to encourage influenza vaccination for all eligible persons, pharmacists should pay special attention to these high-risk individuals.

Cardiovascular disease (CVD) continues to be a major public health problem in the United States affecting an estimated 1 in 3 adults.[1] Approximately 17 million individuals have coronary heart disease (CHD), resulting in over 1.5 million acute myocardial infarctions (AMI) annually. The prevalence increases with advancing age such that 25% of men and 16% of women aged 60 years or older have CHD.[2] Each year an estimated 380,000 individuals die in the United States from CHD, which continues to be the number one cause of death for both men and women.

Influenza results in more than 35,000 deaths and 225,000 hospitalizations in the United States annually.[3] For persons with underlying CVD or diabetes, the risk of death and serious complications from influenza is especially high.[4,5] Additionally, cardiovascular-related death is the leading cause of mortality during influenza season.[6-8] Numerous studies have suggested a link between influenza and increased risk of cardiovascular events. For example, a systematic review of 39 studies found evidence that influenza may serve as a trigger for AMI.[9] These studies have led to greater efforts to promote influenza vaccine for persons with known CVD. This article will discuss recent studies examining the possible cardioprotective effect of the influenza vaccine and the role of the pharmacist.

EFFICACY OF INFLUENZA VACCINE FOR CARDIOVASCULAR PREVENTION

In recent years, a number of observational and small clinical studies have examined the potential efficacy of influenza vaccination for reducing cardiovascular risk and have shown mixed results. Many of these studies have lacked adequate power due to small sample sizes and low event rates. To overcome these limitations, a larger meta-analysis was conducted to examine the efficacy of the influenza vaccine in reducing CVD.[10] The analysis was limited to prospective randomized studies with 2 groups, vaccinated and unvaccinated. After an extensive review of the quality of the available studies, the final analysis included data from 5 studies with a total of 292,383 patients. The study compared patients who did and did not receive the influenza vaccination for 3 primary endpoints: AMI, all-cause mortality, and major adverse cardiac events (MACEs).

Findings from this analysis can be summarized as follows: For AMI, data from 4 studies were included comparing165,791 vaccinated patients and 121,990 unvaccinated patients. There was a reduction in AMI among vaccinated patients (odds ratio [OR], 0.731; 95% CI, 0.574-0.931). For all-cause mortality, data from 5 studies were included with a total of 169,203 vaccinated and 123,481 unvaccinated patients. A reduction in mortality was observed among those vaccinated (OR, 0.606; 95% CI, 0.571-0.643). Last, MACEs were evaluated from 2 studies including 546 vaccinated patients and 551 unvaccinated patients. A reduction in events was observed among the vaccinated patients (OR, 0.467; 95% CI, 0.294-0.742). As with all meta-analyses, the findings are limited by possible publication bias and unknown confounders.

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The findings of lower MACEs after vaccination are consistent with those of another observational study from a large clinical database consisting of prospectively collected data.[11] The study population included participants in 2 randomized placebo-controlled trials: the Ongoing Telmisartan Alone and in Combination With Ramipril Global EndPoint Trial (ONTARGET) and the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSCEND) trial.[12-14] The study included a total of 31,546 participants from 40 countries, age 55 years and older, with known vascular disease or diabetes and documented end-organ damage. Immunization status was obtained through self-reported questionnaires. During 3 influenza seasons between 2004 and 2006, the study found a 30% to 50% lower risk of MACE. Conversely, from 2003 to 2004, no reduction was seen; however, there was an incomplete match between circulating influenza and the vaccine antigen for this year.

The impact of the influenza vaccination on CVD was also evaluated in a randomized controlled pilot trial, the FLU Vaccination in Acute Coronary Syndromes (FLUVACS).[15,16] This trial evaluated 301 patients hospitalized for either AMI or planned angioplasty/stenting. Patients were randomly assigned to receive influenza vaccination or to remain unvaccinated. At the 1-year follow-up, the rates of cardiovascular death were 2% for the vaccinated group versus 8% for the unvaccinated group (relative risk [RR], 0.25; 95% CI, 0.07-0.86). A composite endpoint (cardiovascular death, nonfatal AMI, or severe ischemia) was also lower with vaccination (11% vs 23%) (RR, 0.59; 95% CI, 0.30-0.86).

Most recently, the potential benefits of influenza vaccine were reported from a case-control study conducted in Australia from 2008 to 2010.[17] The study included 275 hospitalized patients with MI and 284 outpatient controls. Influenza vaccination was found to significantly reduce the risk of AMI (OR, 0.55; 95% CI, 0.35-0.85). The observed 45% reduction in risk was maintained after adjustment for multiple potential confounders.

MECHANISMS FOR INFLUENZA INCREASING CARDIOVASCULAR RISK

Atherosclerosis involves a progressive chronic inflammation of the arteries. The underlying mechanisms through which influenza might cause cardiovascular-related morbidity are still unclear. Similarly, it is not known which mechanisms may explain the apparent protective effect of the vaccine. Multiple hypotheses have been suggested.[10,18-22] Influenza may enhance the inflammatory process through cellular or humoral autoimmune mechanisms. This process may be facilitated through the production of autoantibodies against modified low-density lipoprotein or direct vessel wall colonization causing local autoimmune reactions. Increased macrophage infiltration and impairment of the anti-inflammatory properties of high-density lipoprotein may also occur. Others have suggested the influenza virus may cause smooth muscle proliferation, endothelial dysfunction, plaque rupture, platelet aggregation, and thrombus formation. Finally, the fever-induced tachycardia and metabolic abnormalities associated with dehydration, which often occur during acute influenza, might also contribute to the increased risk of cardiovascular events.

RECOMMENDATIONS FOR INFLUENZA VACCINE TO REDUCE CARDIOVASCULAR RISK

A joint advisory from the American Heart Association (AHA) and American College of Cardiology (ACC) recommends influenza vaccine for the secondary prevention of coronary and other atherosclerotic vascular diseases.[3] The AHA/ACC advisory recommends that all persons in the United States with a history of CVD receive an inactivated form of the annual influenza vaccine. This is consistent with guidelines from the Centers for Disease Control and Prevention (CDC) that recommend influenza vaccine for populations at high risk including adults with CVD.[23] The Healthy People 2020 guidelines have set national goals for influenza vaccination rates at 90% for high-risk individuals who are 18 to 64 years of age.[24]

PRACTICAL CONSIDERATIONS FOR PHARMACISTS

Despite the strong recommendations for immunization, particularly for those considered to be high risk, vaccination rates remain low. From 2008 to 2009, only 38.6% of high-risk patients were immunized.[3] These findings are consistent with those of an earlier 2005 study that reported that vaccination rates among persons with heart disease averaged 34% (unpublished data from CDC's Behavioral Risk Factor Surveillance System).[3] Moreover, the study showed that vaccination rates varied with patient age: 71% among older adults (≥65 years) compared to 41% among middle-aged (50 to 64 years) and 23% among younger (18 to 49 years) adults.

The low rates of influenza vaccination provide ample opportunities for pharmacists to make

a significant impact. Pharmacists can play an important role by educating patients with known CVD about the importance of getting the influenza vaccine and when possible serving as immunization providers. Although the optimal window for vaccination is generally September through November before influenza arrives, vaccination should be encouraged through January and possibly into March to protect against late season peaks.

The CDC provides a comprehensive Web site for information on current recommendations for influenza vaccination and available vaccines.[25] Two types of vaccine are available: inactivated and live attenuated. For individuals with known CVD, only the inactivated vaccines are recommended. No studies have been done to evaluate the efficacy or safety of using the live attenuated vaccine to reduce cardiovascular risk. It should also be noted that an inactivated intradermal vaccine is also now available. This lower strength vaccine is sometimes used in younger individuals, but it is not known whether high-risk individuals would derive cardioprotective benefit. The vast majority of inactivated vaccines are trivalent. Prior to each season, the influenza vaccine is reformulated to contain 3 antigens for viruses expected during the season. For the 2013-2014 season, the trivalent vaccines contain an A/California/7/2009 (H1N1)–like virus, an H3N2 virus that is a cell-propagated prototype virus A/Victoria/361/2011, and a B/Massachusetts/2/2012–like virus. Although less commonly used in the United States, quadrivalent vaccines are also available that include the above virus particles plus a B/Brisbane/60/2008–like virus. The only vaccines that contain a mercury-based preservative are the multidose vials. A list of available inactivated vaccines is shown in **Table 1**.

Table 1. Inactivated influenza vaccines available in the United States

Vaccine type	Trade name	Manufacturer	Package type
Inactived influenza vaccine trivalent (IIV3)	*Afluria*	CSL Limited	Prefilled syringe or Multidose vial
	Fluarix	GlaxoSmithKline	Prefilled syringe
	Flucelvax	Novartis	Prefilled syringe
	FluLaval	ID Biomedical Corp	Multidose vial
	Fluvirin	Novartis	Prefilled syringe or Multidose vial
	Fluzone	Sanofi Pasteur	Prefilled syringe or Multidose vial
	Fluzone intradermal[a]	Sanofi Pasteur	Prefilled injection system
Inactivated influenza vaccine trivalent (IIV3) high dose	*Fluzone* high dose	Sanofi Pasteur	Prefilled syringe
Inactivated influenza vaccine quadrivalent (IIV4)	*Fluarix* quadrivalent	GlaxoSmithKline	Prefilled syringe
	Fluzone quadrivalent	Sanofi Pasteur	Prefilled syringe or Single-dose vial
Recombinant influenza vaccine trivalent (RIV3)	*FluBlok*	Protein Sciences	Single-dose vial

[a]Intradermal vaccine is only indicated for individuals who are 18 to 64 years of age. No studies have evaluated efficacy for reducing cardiovascular risk.
Adapted from Centers for Disease Control and Prevention (CDC). *Summary recommendations: Prevention and control of influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices—(ACIP)—United States, 2013-14*. http://www.cdc.gov/flu/professionals/acip/2013-summary-recommendations.htm. Accessed August 25, 2013.

Potential contraindications to the vaccine include a history of severe allergic reactions to prior vaccination, known egg allergy, and history of Guillain–Barre syndrome. These individuals should be told to discuss the relative benefits and risks of vaccination with their doctor. Individuals with acute febrile illnesses should wait until their symptoms resolve before vaccination. In the absence of contraindications, adverse effects from the influenza vaccine are generally mild and self-resolving.

CONCLUSIONS

Although the evidence continues to evolve, current studies suggest an association between influenza and cardiovascular-related morbidity and mortality. For persons with a history of CVD, influenza vaccine may reduce this risk. As a result, vaccination is now being recommended as a strategy for secondary cardiovascular prevention by major cardiovascular organizations. Current vaccination rates, however, remain well below the national goals. Pharmacists are in the ideal position to assume a leadership role in identifying high-risk individuals and promoting and providing influenza vaccines as part of the effort to reduce cardiovascular risk.

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