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**Influenza Vaccination as Secondary Prevention for Cardiovascular Disease: A Science Advisory From the American Heart Association/American College of Cardiology: Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Association of Critical Care Nurses, the American Association of Heart Failure Nurses, the American Diabetes Association, the Association of Black Cardiologists, Inc., the Heart Failure Society of America, and the Preventive Cardiovascular Nurses Association. : The American Academy of Nurse Practitioners supports the recommendations of this scientific advisory.: This science advisory is consistent with the recommendations of the Centers for Disease Control and Prevention and the Advisory Committee on Immunization Practices.**

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## Influenza Vaccination as Secondary Prevention for Cardiovascular Disease

A Science Advisory From the American Heart Association/  
American College of Cardiology

*Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Association of Critical Care Nurses, the American Association of Heart Failure Nurses, the American Diabetes Association, the Association of Black Cardiologists, Inc., the Heart Failure Society of America, and the Preventive Cardiovascular Nurses Association.*

*The American Academy of Nurse Practitioners supports the recommendations of this scientific advisory.*

*This science advisory is consistent with the recommendations of the Centers for Disease Control and Prevention and the Advisory Committee on Immunization Practices.*

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**Abstract**—Evidence from cohort studies and a randomized clinical trial indicates that annual vaccination against seasonal influenza prevents cardiovascular morbidity and all-cause mortality in patients with cardiovascular conditions. The American Heart Association and American College of Cardiology recommend influenza immunization with inactivated vaccine (administered intramuscularly) as part of comprehensive secondary prevention in persons with coronary and other atherosclerotic vascular disease (Class I, Level B). Immunization with live, attenuated vaccine (administered intranasally) is contraindicated for persons with cardiovascular conditions. It is important to note that influenza vaccination coverage levels overall and in this population remain well below national goals and are marked by disparities across different age and ethnic groups. One of the barriers to vaccination for patients with cardiovascular disease is that cardiology practices frequently do not stock and administer influenza vaccine. Healthcare providers who treat individuals with cardiovascular disease can help improve influenza vaccination coverage rates by providing and strongly recommending vaccination to their patients before and throughout the influenza season. (*Circulation*. 2006;114:1549-1553.)

**Key Words:** AHA Scientific Statements ■ cardiovascular diseases ■ influenza, human ■ influenza vaccines

Influenza is estimated to cause >36 000 deaths and 225 000 excess hospitalizations in the United States every year. Children and adults with chronic conditions, including cardiovascular disease (CVD) and diabetes, are particularly vulnerable to complications of influenza infection.<sup>1-3</sup>

Immunization against seasonal influenza has a critical but perhaps underappreciated role in the prevention of morbidity and mortality in patients with CVD. Recognizing the importance of vaccination, the American Heart Association (AHA) and American College of Cardiology (ACC) recommend

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influenza vaccination as part of comprehensive secondary prevention in children and adults with coronary and other atherosclerotic vascular disease.<sup>4</sup> Influenza vaccination is now recommended with the same enthusiasm as control of cholesterol, blood pressure, and other modifiable risk factors. Nevertheless, influenza vaccination coverage levels among persons with CVD (34% nationally in 2005) remain well below national goals and are marked by disparities across age categories and ethnic groups.

The challenge to the profession is to translate the recommendation for influenza vaccination into action. This translation is challenging to the cardiovascular community because immunization falls out of what is commonly perceived as the realm of typical cardiology practice. Currently, about one half of cardiology practices nationwide do not stock influenza vaccine.<sup>5</sup> A recent study indicated that the most effective ways to increase influenza vaccination coverage among persons with CVD are to make influenza vaccine available at all cardiology practices and to have physicians strongly recommend the vaccine to their patients.<sup>6</sup>

This Science Advisory summarizes information for cardiovascular care providers on influenza and vaccination against influenza. It focuses on the increased risk and complications of influenza for persons with CVD, the effectiveness of influenza vaccine for secondary prevention of cardiovascular events, and opportunities for healthcare providers to improve rates of vaccination against influenza among persons with cardiovascular conditions. The purpose of this advisory is to equip practitioners with the information they need to adopt these recommendations into practice and ensure that cardiovascular patients have routine, annual influenza vaccination.

### **Influenza Illness and Influenza Vaccine**

Two types of influenza viruses, influenza A and B, cause epidemic human disease in a seasonal pattern.<sup>7</sup> Influenza A viruses are further classified into subtypes based on 2 surface antigens (hemagglutinin and neuraminidase), and influenza A and B viruses are both further separated into groups (identified geographically) on the basis of other antigenic characteristics.<sup>2</sup> Immunity to surface antigens protects individuals against infection and, should they be infected, against severe disease,<sup>8</sup> but antibodies against one influenza virus type or subtype confer little or no immunity against other types and subtypes. Frequent antigenic changes ("antigenic drift") generate new influenza virus variants that cause seasonal epidemics. Pandemic influenza may occur when antigenic shifts are more pronounced than usual.<sup>2</sup>

Vaccination is the primary mode of prophylaxis against influenza. The US Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention recommends annual influenza vaccination for all persons  $\geq 50$  years of age, for children 6 months to 59 months of age, for women who will be pregnant during influenza season, and for adults and children with chronic conditions, including CVD and diabetes.<sup>2</sup> These groups are also prioritized during influenza seasons when supplies of influenza vaccine are expected to be lower than the demand. Although antiviral medications may be used for short-term prophylaxis of high-risk persons with known exposure to a case of

influenza, as well as for treatment of influenza cases, these medications are not recommended as a general preventive strategy at the population level.<sup>2</sup>

Two forms of the vaccine exist: one inactivated (administered intramuscularly) and the other in a live, attenuated form (administered intranasally). Each year, influenza vaccine is reformulated to include 3 antigens that are representative of viruses that are expected to circulate during the forthcoming influenza season. In inactivated vaccines, only subvirion and purified surface antigens are used, which makes the vaccines noninfectious. It is important to note that individuals with CVD should not receive the live, attenuated influenza vaccine because it can cause influenza illness in this high-risk population.<sup>2</sup>

The optimal time for influenza vaccination is usually September through November for high-risk persons, including persons with CVD. This timing maximizes the benefit of vaccination before the typical onset of influenza activity in the United States. However, as long as vaccine is available, influenza vaccination should continue into January or later because influenza activity most commonly peaks in January, February, or March in the United States.<sup>2</sup> Vaccination efforts late in the season are especially important when vaccine supply is delayed in the fall.

Persons with known anaphylactic hypersensitivity to eggs or a history of Guillain-Barre syndrome should not receive the inactivated influenza vaccine without first consulting a physician. If a person eligible for vaccination has moderate-to-severe acute febrile illness, vaccination should be delayed until symptoms have resolved.<sup>2</sup>

### **Influenza Among Patients With CVD**

Influenza-related death is more common among individuals with CVD than among patients with any other chronic condition.<sup>9</sup> Influenza can exacerbate underlying medical conditions, including CVD and diabetes, and can also lead to viral pneumonia, secondary bacterial pneumonia, or a coinfection with other viruses or bacteria.<sup>10</sup> Epidemiological data indicate that risks for complications, hospitalizations, and death from influenza are higher for individuals at the extremes of age ( $< 5$  years old,  $\geq 65$  years old) and for persons with chronic medical conditions than for healthy older children and younger adults.<sup>1,11-16</sup>

The mechanism through which influenza may cause cardiovascular events is not well understood. One current hypothesis is that the inflammatory response of the body to viral infection leads to production of autoantibodies to modified low-density lipoprotein, which causes the development and progression of atherosclerotic vascular injury. Another current hypothesis is that direct colonization of the vessel wall initiates local cell autoimmune reactions by activation of antigen-presenting cells.<sup>17</sup>

### **Evidence for Protective Effect of Influenza Vaccination Against Cardiovascular Events**

The AHA/ACC recommends annual influenza vaccination as secondary prevention for individuals with coronary and other atherosclerotic vascular disease (Class I, Level B).<sup>4</sup> (Definitions of the ACC/AHA classes of recommendations and levels of evidence are listed in the Appendix.) This recom-

mentation, issued in 2006, reflects the growing body of evidence that influenza vaccination is protective against cardiovascular events for individuals with known CVD.<sup>18–24</sup> In addition, no evidence suggests that influenza vaccination is harmful for individuals with cardiovascular conditions.<sup>25</sup>

The strongest evidence for a protective effect comes from a randomized, controlled trial of influenza vaccination (FLU Vaccination in Acute Coronary Syndromes [FLUVACS]) in which 301 patients hospitalized for either myocardial infarction (MI) or planned angioplasty/stenting were randomly assigned to receive influenza vaccination or remain unvaccinated.<sup>18,19</sup> At 1 year, the relative risk of cardiovascular mortality in the vaccinated group was 0.25 (95% confidence interval [CI] 0.07 to 0.86) compared with the unvaccinated group (overall rates 2% versus 8%), and the relative risk of a composite end point (cardiovascular death, nonfatal MI, or severe ischemia) was 0.59 (95% CI 0.30 to 0.86; 11% versus 23%).<sup>18</sup> At 2 years, although risk reductions of similar magnitude were measured, the remaining sample size after loss to follow-up was too small to find statistical significance.<sup>19</sup> Of note, the FLUVACS trial was conducted without financial support from the influenza vaccine industry.

Other evidence supporting a protective effect of influenza vaccination stems from cohorts of elders identified through health plans as well as from clinically derived case-control analyses.<sup>22–24</sup> Two studies indicate vaccine-associated significant reductions in the risk of hospitalization, specifically for individuals with congestive heart failure.<sup>20,21</sup> A third study reports a significant reduction in the risk of cerebrovascular accidents (CVAs) associated with influenza vaccination.<sup>23</sup> The principal limitation of these or any cohort and case-control analyses is that lower event risks may be confounded by sociodemographic and health factors also associated with influenza vaccination.<sup>20–24</sup>

No study has indicated higher rates of cardiovascular events for individuals who receive influenza vaccination. A recent multiyear cohort study of >39 000 patients with CVD (either MI or CVA) in the United Kingdom found no increased risk of MI or CVA in the 90-day period immediately after influenza vaccination.<sup>25</sup> In fact, incidence rates of MI and CVA were significantly lower in the 28 days after vaccination than in the period immediately preceding vaccination, though these differences disappeared with adjustment for age. Another multiyear study of a cohort of private health plan enrollees who were identified on the basis of a hospitalization for nonfatal first MI reported no protective effect associated with influenza vaccination.<sup>26</sup> The primary contrast between this negative study and others that support a protective effect for influenza vaccination is that this study population was generally younger.<sup>26</sup>

Overall, the majority of published evidence indicates that influenza vaccination is associated with a significantly reduced risk of cardiovascular events for individuals with known coronary and other atherosclerotic conditions, including prior CVA. The sole randomized trial of influenza vaccination among persons with CVD (FLUVACS) demonstrated significant reductions in cardiovascular mortality and in a composite end point including death, nonfatal MI, and ischemia at 1 year.<sup>18,19</sup> Future trials should elucidate further

the relative benefits of influenza vaccination for younger versus older persons with CVD. Currently, data from FLUVACS (which included patients younger than 65 years but did not distinguish them from older patients in analyses)<sup>27</sup> and other studies support the recommendation of influenza vaccination for persons of all ages with CVD.

### Low Vaccination Coverage Rates Among Persons With CVD

The AHA and ACC recommend that the >12 million persons in the United States with cardiovascular conditions get annual influenza vaccination.<sup>2,28</sup> Current influenza vaccination coverage among persons with heart disease is far below national coverage goals set in *Healthy People 2010* (>60% for persons <65 years of age; >90% for persons ≥65 years of age): Only 1 in every 3 adults with heart disease (34%) received influenza vaccination in 2005 (Behavioral Risk Factor Surveillance System; CDC, unpublished data), a level of coverage that is essentially unchanged from other below-target rates achieved in 2002.<sup>29</sup> In 2005, vaccination coverage among older adults (≥65 years old) with heart disease was much higher (71%) than among middle-aged (50 to 64 years old) and younger (18 to 49 years old) adults with heart disease (41% and 23%, respectively). Non-Hispanic white adults had similar influenza vaccination rates (38%) to black adults (36%), but rates in both groups were higher than among Hispanic adults (30%).

Failure to vaccinate persons with cardiovascular conditions and disparities in vaccination coverage across age categories and ethnic groups represent major opportunities for healthcare providers to improve the care of this patient population. A central barrier to vaccination against influenza is that only about one half of cardiology practices nationwide stock influenza vaccine, as opposed to >70% of endocrinology practices and of generalist primary care practices and >90% of pulmonology practices.<sup>5,30</sup>

Outpatient visits to cardiology practices present a superb but frequently missed opportunity to administer influenza vaccine to millions of adults with CVD,<sup>31</sup> as do outpatient visits in primary care settings and hospitalizations for cardiovascular causes. A recent study suggests that the most effective ways to improve influenza vaccination rates among nonelderly adults with heart disease are for cardiology practices to have influenza vaccine available in their offices for patient visits, for cardiovascular care providers to strongly recommend vaccination to their patients during vaccination season, and for practices to implement standing-orders protocols that permit staff to administer influenza vaccine to patients with cardiovascular indications without waiting in each case for a physician's order.<sup>6</sup>

It is important to emphasize that strong recommendations from health professionals about vaccination against influenza can be very influential, especially for urban, predominantly black patients.<sup>32</sup> Patient-level barriers to influenza vaccination, specifically for persons with CVD, have not been well characterized and should be examined in future research.

Providers and practices that provide care for patients with CVD should stock influenza vaccine annually. There is a choice of manufacturers, and the vaccines are considered equally effective. Ordering information for all manufacturers licensed to provide influenza vaccine in the United States for the 2006/2007

**TABLE. How Providers Can Place an Order for Influenza Vaccine in the United States**

| Influenza Vaccine Manufacturers*<br>(Alphabetical Order) | How to Order for the 2006/2007 Influenza Season†‡   |
|--|---|
| GlaxoSmithKline  | Call Flurix Service Center at 1-866-475-8222 (choose option 1).   |
| Novartis (formerly Chiron)                               | Call 1-800-244-7668 (choose option 2) to receive a list of vaccine distributors in your area.                               |
| Sanofi Pasteur   | Set up a provider account and then place order at <a href="http://www.vaccineshoppe.com">http://www.vaccineshoppe.com</a> . |

\*These are manufacturers of inactivated trivalent influenza vaccine. Live, attenuated intranasal influenza vaccine (FluMist; MedImmune) is not recommended for individuals with cardiovascular conditions.

†Providers are encouraged to order vaccine in the spring and summer for delivery in the fall before each influenza season.

‡Providers who wish to have more information about influenza vaccine should contact their local or state public health departments.

season is provided on the American Heart Association Web site ([www.americanheart.org](http://www.americanheart.org)) and in the Table.

## Conclusions

Seasonal influenza represents a major preventable threat to the health of persons with CVD. Clinical trials and observational studies have demonstrated that vaccination against influenza is associated with significantly reduced risk of cardiovascular death and nonfatal events. Vaccination is currently recommended for persons with diabetes, a condition common to patients with CVD.<sup>33</sup> On the basis of this evidence, the AHA and ACC recommend inactivated influenza vaccination as a component of secondary prevention for persons with coronary disease and other atherosclerotic vascular

conditions (Class I, Level B). This level of recommendation is based on the judgment that influenza vaccination should be administered to all persons with CVD (unless they have a contraindication to receiving the vaccine) and on evidence from a single randomized clinical trial and several nonrandomized population cohort studies.

Currently, below-target vaccination rates and disparities in vaccination coverage across different ethnic groups represent missed opportunities to maximize the preventive benefits of influenza vaccination. Providers who care for patients with CVD can increase influenza vaccination coverage among their patients by stocking the vaccine and promoting annual vaccination immunization with strong recommendations and standing orders.

## Appendix

### ACC/AHA Classes of Recommendation and Levels of Evidence

#### Class of Recommendation

|           |   |
|-----------|---|
| Class I   | Conditions for which there is evidence and/or general agreement that a given procedure/therapy is beneficial, useful, and effective.                  |
| Class II  | Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of performing the procedure/therapy.  |
| Class IIa | Weight of evidence/opinion is in favor of usefulness/efficacy.  |
| Class IIb | Usefulness/efficacy is less well established by evidence/opinion.   |
| Class III | Conditions for which there is evidence and/or general agreement that a procedure/therapy is not useful or effective and in some cases may be harmful. |

#### Level of Evidence

|                     |   |
|---------------------|---|
| Level of Evidence A | Data derived from multiple randomized clinical trials or meta-analyses. |
| Level of Evidence B | Data derived from a single randomized trial or nonrandomized studies.   |
| Level of Evidence C | Only consensus opinion of experts, case studies, or standard-of-care.   |

## Disclosures

### Writing Group Disclosures

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