Influenza Vaccination or Treatment for Influenza-Associated Myocardial Infarction

To the Editor—Warren-Gash and colleagues provide further evidence that an association exists between influenza, hospitalization, and death from acute myocardial infarction (AMI) [1]. Their earlier review [2] and an editorial commentary by Finelli and Chaves accompanying their article [3] document many studies of different design that support their findings. Yet acute respiratory infections due to other pathogens, including *Streptococcus pneumoniae* and *Staphylococcus aureus*, can also be followed within a few days by AMI [4,5]. Inflammatory changes induced by infection can disrupt the surface of coronary plaques, exposing underlying thrombogenic material. An increase in procoagulant factors and platelet activation, together with vasoconstriction and endothelial dysfunction, create conditions that precipitate thrombosis. The severity of these changes determines the levels of increased metabolic demand, hypoxemia, and disturbed coronary and systemic circulation that eventually lead to myocardial infarction [5].

According to Finelli and Chaves, “interventions targeted against influenza could avert some proportion of influenza-related AMI [5].” Influenza vaccination has been reported to reduce the occurrence of AMI in some, but not all, studies [3, 5]. Nonetheless, if influenza-associated AMIs account for only a small proportion of all AMIs each year [1], influenza vaccination will not have a major impact on the total number of AMI-related hospitalizations and deaths. Reducing the occurrence and severity of AMIs in patients at risk can be achieved by treating them with several medications, statins (hydroxymethyl glutaryl coenzyme A reductase inhibitors) being the most important. In addition to their use in primary and secondary prevention, statins can be used in patients with AMI [6–8]. When statins are given shortly after hospitalization, observational studies have shown that they reduce hospital mortality by approximately 40% [7]. This effect can be demonstrated within the first few days after hospital admission [6–8]. Moreover, high-dose statins benefit patients undergoing percutaneous coronary intervention for stable angina or acute coronary syndrome [9]. In a collaborative patient-level meta-analysis of 13 randomized, controlled trials involving 3341 patients, short-term statin treatment significantly
reduced the occurrence of periprocedural myocardial infarction (odds ratio, 0.56; 95% confidence interval, 44–71). The benefits shown in these studies have not been due to changes in levels of low-density cholesterol. Instead, they have been ascribed to the anti-inflammatory and immunomodulatory (pleiotropic) effects of statin treatment.

The association between influenza and AMI can be scrutinized in another way. Several years ago, it was suggested that treatment and prophylaxis with statins might alter the clinical course and outcome of interpandemic and pandemic influenza [10, 11]. As with AMI, the dysregulated host response to influenza includes molecular targets that are affected by anti-inflammatory and immunomodulatory agents, including not only statins but also peroxisome proliferator-activated receptor (PPARα) and PPARγ agonists (fibrates and glitazones, respectively) and AMP-activated protein kinase (AMPK) agonists (eg, metformin) [12]. In limited studies of influenza virus-infected mice, fibrates, glitazones, and AMPK agonists were observed to reduce mortality by 40%–50% without increasing viral replication. It is controversial, however, whether statins would benefit patients hospitalized with influenza, with or without concomitant AMI. Findings of several observational studies, but not all, suggest that outpatient statin treatment reduces rates for pneumonia hospitalization [13, 14]. During the recent influenza A(H1N1) pandemic, elevated levels of proinflammatory cytokines were documented in hospitalized patients [15], and preadmission statin treatment was associated with a modest but not statistically significant decrease in the severity of hospital illness [16, 17]. A recently published observational study showed that among 3043 patients hospitalized with laboratory-confirmed influenza during the 2007–2008 influenza season, statin treatment led to a 41% decrease in mortality in the hospital or within 30 days of discharge [18]. The mortality reduction was in addition to that conferred by previous influenza vaccination or antiviral treatment. Unfortunately, randomized controlled clinical trials could not be organized in time to evaluate the efficacy of statin treatment during the recent H1N1 influenza pandemic.

These observations are important for developing countries. During the recent H1N1 pandemic, very few people living in these countries had timely access to affordable vaccines and antiviral agents. In contrast, statins and the other agents mentioned above are currently produced as generic pharmaceuticals in these countries, and the cost of treating an individual patient would be less than $1.00 [12]. This alone constitutes a strong argument for undertaking the laboratory and clinical research needed to determine whether these agents could reduce severe influenza-related morbidity and mortality [19].

**Note**

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**References**


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