



Cardiovascular disease related to influenza infection and the protective role of influenza vaccination

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ABSTRACT

Influenza infection is a well-established trigger of severe respiratory and cardiovascular complications, particularly in older adults, frail individuals, and patients with underlying cardiovascular disease. Seasonal peaks are consistently associated with excess hospitalizations and mortality. Epidemiological studies have shown sharp increases in acute cardiac events during and immediately after influenza infection, including a high-rate of acute coronary syndromes and heart failure. The cardiovascular impact of influenza is mediated by multiple mechanisms. Systemic inflammation, plaque destabilization, metabolic imbalance, endothelial dysfunction, and pro-thrombotic activation collectively contribute to acute coronary syndromes, myocarditis, arrhythmias, and acute or worsening heart failure. These complications generate a substantial clinical and socioeconomic burden, particularly in elderly and high-risk individuals.

Despite the availability of effective and inexpensive vaccines, influenza vaccination remains underused in high-risk cardiovascular populations. Randomized trials and meta-analyses consistently support vaccination as a powerful preventive tool, associated with a 25–37% reduction in major adverse cardiovascular events and mortality, with benefits comparable to established cardioprotective therapies. Evidence is strongest in patients with coronary artery disease, ACS, diabetes, and in older adults, although results in heart failure populations remain more heterogeneous. Enhanced vaccines including adjuvanted, high-dose, and cell-based formulations offer superior protection in elderly and immunocompromised individuals and are increasingly recommended by national and international health authorities.

Given the robust evidence linking influenza to cardiovascular events and the proven protective role of vaccination, systematic implementation of tailored influenza immunization strategies in patients with CVD is essential to optimize preventive care.

1. Introduction

Since the early twentieth century and for many decades thereafter it has been well known in the medical community that influenza infection is closely linked to severe respiratory and cardiovascular complications, contributing to increased mortality, particularly during the seasonal influenza peak [1–3].

Cardiovascular complications related to influenza infection are

diverse and occur more frequently in older adults, frail subjects and patients with a history of cardiovascular disease or high cardiovascular risk. Besides acute coronary syndromes (ACS), which are the most frequent cardiovascular complications of influenza, and stroke, other relatively common influenza-associated disorders include heart failure (HF), myocarditis and atrial fibrillation [4].

Despite this evidence and the availability of an effective and non-expensive tool to prevent or mitigate influenza infection and its

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complications, influenza vaccine uptake in patients with cardiovascular diseases remains largely suboptimal [5–6]. Among the reasons contributing to this substantial unmet need in contemporary preventive medicine is the limited awareness and insufficient involvement of cardiologists in promoting vaccination within their practice [7]. Therefore, it is crucial to promote awareness of the relationship between influenza and cardiovascular diseases, as well as the importance of timely and appropriate vaccination among cardiologists and other physicians treating patients with cardiovascular diseases or at high cardiovascular risk.

2. Epidemiology and protective role of influenza vaccination in patients with cardiovascular disease

According to a report of the Global Burden of Disease published in 2017, among 54.5 million cases of influenza infection 145,000 deaths were recorded, with a higher incidence of fatal cases among elderly subjects [8]. In Italy, over 21,000 excess hospital admissions were attributable to the influenza infection. Severe cases are mostly observed in elderly adults aging ≥ 60 years with an estimated rate of 125 hospital admissions per 100,000 citizens. Complications arising during influenza are mostly due to respiratory illness or severe cardiac events [9]. For instance, Kwong and others [10] have reported in 2018 in the *New England Journal of Medicine* a 6-fold increase in the incidence of myocardial infarction during the first week after an influenza diagnosis. Similarly, Chow et al. [11] in 2020 have reported that sudden and severe cardiac events were common in patients hospitalized with influenza (12% of 80,000 individuals in 8 influenza seasons developed an ACS or acute HF).

Supporting the effectiveness of influenza vaccination in preventing cardiovascular complications, Udell et al. [12] have conducted a thorough meta-analysis showing a 36% reduction in major cardiovascular events. Consistently, in a wide systematic review and meta-analysis including observational and interventional studies published in 2021 Yedlapati et al. [13] reported a 13% reduction in major cardiovascular events among patients with cardiovascular diseases or at a higher cardiovascular risk who received influenza vaccination.

3. Pathophysiological basis and clinical manifestations of influenza-related cardiovascular disease

The mechanisms underlying the development of cardiovascular disease during influenza are multiple.

First, the systemic inflammatory response triggered by respiratory viruses can precipitate ACS, particularly ST Elevation Myocardial Infarction (STEMI) and Non-ST Elevation Myocardial Infarction (NSTEMI), by promoting the destabilization and rupture of the atherosclerotic plaque [14]. Moreover, the increase in metabolic demand and oxygen consumption in myocytes, along with the activation of the sympatho-adrenergic system with consequent increase in heart rate and smooth muscle cell constriction in larger and smaller vessels of the coronary tree, contribute to myocardial injury and necrosis. These also represent a typical component of type 2 myocardial infarction, which is the clinical manifestation of the unfavourable metabolic discrepancy which leads to severe myocardial injury in the absence of coronary thrombosis [15].

The immunoinflammatory response to influenza virus infection originates at the level of the alveolar epithelium and induces the production of cytokines and other mediators such as tumor necrosis factor α and interferon γ [16]. Together with this systemic and autocrine humoral response, a cellular inflammatory response is also activated, characterized by the proliferation and accumulation of macrophages at the level of the atherosclerotic plaque. These immune cells contribute to fibrous cap erosion through enzymatic pathways, including the activity of metalloproteinases [17]. Finally, the development of a pro-thrombotic state, observed during acute infections caused by

respiratory viruses such as SARS-COV-2 and Respiratory syncytial virus (RSV), may contribute to the development of coronary thrombosis and type 1 myocardial infarction, or ischemic (stroke), by promoting platelets accumulation at the site of vascular lesion [18]. It has been hypothesized, based on animal studies, that influenza infection could also have direct effects on myocardial tissue, potentially leading to myocarditis (and pericarditis), parceled myocardial necrosis, subsequent formation of fibrotic scar and ventricular dysfunction [19]. These pathophysiological processes could be important to explain the cardiovascular consequences of influenza, particularly acute myocarditis, acute or worsening heart failure and cardiac arrhythmias [20–22] (Table 1).

Beside their remarkable clinical impact, cardiovascular consequences of influenza also impose a heavy socio-economic burden. These outcomes are associated with increased medicalization, including larger use of drugs, medical devices, and an upraise in hospitalizations, particularly among elderly and frail subjects. This pattern represents a systematic feature of all influenza seasonal peaks [23].

4. Influenza vaccination and the risk of cardiovascular events

Despite the large body of evidence supporting a tight cause-effect between influenza and cardiovascular disease, the prescription of influenza vaccination is still poorly implemented in clinical practice even among elderly and vulnerable people for whom it is recommended [24].

Randomized clinical trials (RCTs) initially yielded not uniform results, and the effects of vaccination on patients with coronary disease were somewhat uncertain, mostly due to small sample sizes and relatively short follow-up periods.

The “Flu vaccination in acute coronary syndromes and planned percutaneous coronary interventions” (FLUVACS) [25] was the first properly sized RCT ($n = 301$) including patients with myocardial infarction (MI) undergoing percutaneous angioplasty intervention (PCI). Outcomes were compared between patients receiving trivalent influenza vaccination and those who did not. The primary endpoint, death at 6 months, was 2% in the vaccinated group compared to 8% in the control group (RR 0.25; CI 95%: 0.07–0.86; $p < 0.01$); the secondary composite endpoint (death, not fatal MI, or recurrent angina) rates were 11% in the vaccinated group and 23% in the control group (RR: 0.50; CI 95%:

Table 1
Main clinical manifestation of major cardiovascular complications that may occur during influenza.

Acute coronary syndromes	STEMI NSTEMI Unstable Angina Tako-Tsubo syndromes Myocardial Infarction with Non-Obstructive Coronary Arteries (MINOCA) Ischemia with Non-Obstructive Coronary Arteries (INOCA) Type 2 Myocardial Infarction
Heart failure	Acute heart failure Worsening heart failure Left ventricular dysfunction
Arrhythmias	Atrial fibrillation Ventricular ectopic arrhythmias Sudden death
Ischemic stroke Pulmonary embolism Cardiomyopathies	Dilated cardiomyopathy with reduced Ejection fraction
Valvular disease secondary to endocarditis Myocarditis and pericarditis Sudden cardiac death	

STEMI: ST Elevation Myocardial Infarction; NSTEMI: Non-ST Elevation Myocardial Infarction.

0.29–0.85; $p < 0.009$). The benefits were observed mostly in the higher risk group [age > 65 years, diabetics, Thrombolysis in Myocardial Infarction (TIMI) score ≥ 6] and were confirmed by a pre-specified 1-year follow-up analysis [26].

The “Influenza vaccination in secondary prevention from coronary ischemic events in coronary artery disease” (FLUCAD) [27] was a prospective, randomized, placebo-controlled double-blind study comparing trivalent influenza vaccine delivered during hospitalization to placebo in 658 outpatients with angiography-confirmed chronic ischemic heart disease receiving standard medical therapy. The trial failed to show a significant benefit in terms of CV death reduction or the composite endpoint, although there was a favorable trend for hospitalizations due to myocardial ischemia.

In contrast, a study conducted by Phrommintikul [28] in 439 patients admitted with ACS, reported a benefit in the composite endpoint of CV death, hospitalizations for ACS, HF or stroke, with a reduction of 30% in the vaccinated (with split inactivated vaccine) group compared to placebo. Moreover, a meta-analysis by Udell et al. on 6 studies including 36% of patients with cardiovascular diseases reported that influenza vaccination was associated with a reduced risk of major adverse cardiovascular events (MACE), especially in patients with ACS compared to those with stable coronary disease. These results support the role of inflammation as a key pathogenic mechanism linking influenza infection to CV events [12].

More recently, the “Influenza vaccination after myocardial infarction”, (IAMI) a double-blind, placebo-controlled RCT, involved 2532 patients with MI or high-risk chronic coronary disease (age ≥ 75 years and at least one additional criteria of risk, like previous MI, smoking diabetes, eGFR < 40 ml/min or a previous coronary bypass or PCI). Patients received influenza vaccination (trivalent inactivated vaccine in the 2016 Northern Hemisphere season and quadrivalent inactivated vaccine in the following seasons) within 72 h from MI, and a 28% reduction in the primary composite outcome (all-cause mortality, MI or stent thrombosis within 12 months) was observed in the vaccinated group compared to placebo (5.30 vs 7.2%, HR 0.72, CI 0.52–0.99, $p = 0.040$). These results, mostly driven by the 41% reduction in all-cause mortality, were consistent among subgroups. The limitations of the IAMI study were its premature interruption due to the COVID pandemic, resulting in enrolment of only half of the planned target population, and the underrepresentation of women [29]. A subsequent meta-analysis including 4211 patients revealed that influenza vaccination is associated with a 37% risk reduction of MACE (RR: 0.63; 95% CI: 0.51–0.77), all-cause mortality and cardiovascular mortality [30]. A recent and comprehensive systematic review and meta-analysis including 237,058 patients from 16 studies (4 RCTs and 12 observational studies) with at least 50% of patients with established coronary disease or heart failure, revealed that influenza vaccination was associated with a 25% reduction of all-cause mortality and 18% reduction of CV mortality compared to control, despite large heterogeneity among studies [13]. Also, MACE was reduced by 13%. Taken together, these results provide strong support for the preventive value of influenza vaccination, with benefits approaching those obtained with established therapies in coronary disease such as beta-blockers, statins, aspirin or ACE inhibitors, or smoke cessation [31].

A recent RCT, “Vaccination against influenza to prevent cardiovascular events after acute coronary syndromes” (VIP-ACS) [32] compared a strategy based on a double-dose of quadrivalent inactivated influenza vaccine at hospital discharge with a standard dose of quadrivalent inactivated influenza given in an outpatient setting 30 days after hospital discharge in 1800 patients admitted for ACS. No differences were observed between the two groups in terms of fatal and non-fatal cardiovascular endpoints, which suggests the non-inferiority of early post-ACS vaccination and suggests that this could represent an effective strategy for secondary prevention after an ACS.

According to available evidence, the European Society of Cardiology highly recommends delivering influenza vaccination during

hospitalization for acute cardiovascular disease (for ACS with class IA evidence [33]; for HF with class II [34]).

4.1. The effect of influenza vaccination in specific populations

4.1.1. Influenza vaccination in patients affected by heart failure

In the clinical setting of HF, available evidence has generated conflicting results, and the benefits of influenza vaccination remain somewhat uncertain. In a large meta-analysis of 6 observational studies, influenza vaccination was associated with a 17% statistically significant reduction of all-cause mortality (HR: 0.83; 95% CI: 0.76–0.91). However, in the same study the effects on CV mortality and all-cause hospitalizations did not achieve statistical significance [31].

A retrospective Danish study involving 134,048 patients with HF demonstrated a 18% reduction of mortality among vaccinated subjects. These benefits were more pronounced when vaccination was administered early in the influenza season [35].

In 2022, Loeb et al. [36] reported the results of a pragmatic, double-blind, randomized controlled trial involving 5129 patients with HF (NYHA class II–III) recruited in 10 countries over three influenza seasons and evaluating the impact of influenza vaccination (with inactivated trivalent vaccine) in preventing adverse events. Although there was a reduction in the primary composite endpoint (cardiovascular death, non-fatal MI, non-fatal stroke) in the vaccinated group compared to placebo, results did not achieve statistical significance (14.8% vs 16%, respectively, HR 0.93, 95% CI 0.81–1.07). However, it is important to note that the study was performed mostly during COVID pandemic and was prematurely interrupted in seven countries. Furthermore, patients with an ischemic aetiology of HF were relatively few, possibly accounting for a higher benefit of influenza vaccination in patients with a history of ischemic heart disease.

4.1.2. Influenza vaccination in elderly

Several studies have supported the benefits of influenza vaccination in patients aged ≥ 65 years [37]. The risk of hospitalization due to a CV disease is dramatically reduced by vaccination (RR: 0.50, 95% CI 0.27–0.91) [36]. These results have been supported by the study of Nichol et al. [38], that analyzed hospital admission rates in vaccinated versus non-vaccinated elderly patients, and by the study of Liu et al. [39], that reported that vaccination was associated with reductions in all-cause mortality and hospitalizations due to cardiovascular causes or ischemic heart disease (HR 0.84; 95% CI: 0.76–0.93). Although the benefits of influenza vaccination in elderly patients is well established, it is likely that outcomes could be further improved through the selection of appropriate vaccines.

4.1.3. Influenza vaccination in patients affected by diabetes

Despite the recognized high-risk of fatal and non-fatal complications, including hospitalizations associated with influenza infection in subjects with diabetes, recent reports confirm an under-utilization of influenza vaccination in this population, with more than one third of diabetic patients not receiving the vaccine [40].

The Danish registry has monitored nine consecutive influenza seasons from 2007 to 2016 tracking more than 240,000 patients with diabetes. In this report, influenza vaccination was associated with a significant reduction in both all-cause and CV mortality [40]. These results are corroborated by consistent findings reported by Hung et al. [41] in the U.S., as well as from the diabetic subgroup analysis of the IAMI trial [29].

Moreover, a very recent report has shown that the quadrivalent high-dose influenza vaccine provides higher protection compared to quadrivalent standard-dose vaccine in the diabetic population, leading to lower rates of mortality and hospitalizations [42,43].

4.1.4. Influenza vaccination in high-cardiovascular risk patients without previous CAD

Patients with a high estimated cardiovascular risk (SCORE2 > 10%) may also benefit from influenza vaccination, similarly to other high-risk groups such as those with coronary artery disease, asymptomatic HF, diabetes, and older age. These individuals should be considered for effective vaccination with appropriate vaccines, although further studies are warranted to confirm the benefit in this specific population [42].

5. Influenza vaccination strategies in Italy: current objectives, selection of vaccines and appropriateness

Besides its fundamental role in protecting individual subjects from infection and mitigating pathogen transmission in the population, influenza vaccination can be viewed today as a pillar of preventive care in high-risk populations, particularly among patients with cardiovascular diseases. Indeed, this represents one of the main objectives of the National Vaccinal Prevention Plan (PNPV) 2023–2025 in Italy [44] (Table 2). For season 2024–2025, among the categories eligible for actively offered and free influenza vaccination, there is a specific indication for people at high-risk of complications or hospitalizations due to influenza. This includes patients with cardiovascular diseases aged between 7 and 59 years, as well as all subjects aged ≥60 years regardless of the presence of any underlying diseases [44].

In these subjects, it is crucial to provide a vaccine with demonstrated “efficacy” and/or “effectiveness”. This concept stems from the need to ensure adequate protection in patients who could have a progressively reduced immune response and/or clinical conditions associated to an increased risk to develop influenza complications. Accordingly, the selection of the most appropriate vaccine for these high-risk categories (which also include patients with HF, previous stroke, chronic kidney disease, diabetes) should be guided by the available evidence [5].

The effectiveness of influenza vaccines is not the same for all patients and some of them have been specifically designed and registered for elderly population due to immunosenescence, or for people with reduced immune system capacities [45,46].

Adjuvanted, high-dose and recombinant vaccines have shown to be more effective than standard vaccines in the elderly population [47–52]. The level of protection obtained with these vaccines may vary across different influenza seasons. Nevertheless, when considering the rates of death and influenza-related hospitalizations among vaccinated versus unvaccinated elderly subjects in Italy, a preventive effect spanning between 30 and 40% can be viewed as a remarkable result [53,54].

Adjuvanted trivalent vaccines have demonstrated a superior effectiveness against severe laboratory-confirmed influenza compared to standard quadrivalent vaccines in a test-negative case-control study conducted in a hospital setting in Italy. Relative effectiveness was 59.2% (95% CI: 14.6%, 80.5%), 54.7% (95% CI: –28.7%, 84.0%) and 56.9% (95% CI: –7.8%, 82.8%) against any influenza, A(H1N1)pdm09 and A(H3N2), respectively [49]. The high-dose influenza vaccine has shown superior effectiveness compared to the standard-dose vaccine in a

randomized clinical trial (24.2%, 95% CI: 9.7, 36.5) [53] and in a systematic review performed by Lee and collaborators [11.2% on hospitalizations due to influenza (95% CI, 7.4, 14.8), 8.2% on all cause hospitalizations (95% CI, 5.5, 10.8), 16.7% on hospitalizations due to cardiorespiratory causes (95% CI, 13.8, 19.5)] [55]. A retrospective test-negative design, published in 2024, has explored the relative vaccine effectiveness of the adjuvanted vaccine compared to the high-dose vaccine in preventing test-confirmed influenza during 2017–2020 influenza seasons in US adults aged ≥65 years. Results (–2.5%, 95% CI: –19.6, 12.2) indicated that the two vaccines were comparable in preventing laboratory-confirmed influenza [48]. The reasons underlying the greater benefits of the enhanced vaccines (high-dosage and adjuvanted) are likely linked to the enhanced multi-functional response of CD4+ and CD8+ T-cells, as it has been shown in a randomized clinical study [56]. Cell-based vaccines have been developed to overcome the issue of egg-adaption, a phenomenon resulting from receptors differences between avian and human cells. These differences can promote the selection of viral variants better adapted for propagation in eggs, potentially compromising vaccine effectiveness.

Several studies have demonstrated the capability of cell-based influenza vaccine to provide broader protection in comparison to standard-dose egg vaccine. Recently, a study carried out in three consecutive seasons (2017/18 to 2019/20) in subjects from 4 to 64 years of age, has demonstrated the superior effectiveness of cell-based vaccines in comparison to standard egg-based vaccines in preventing test-confirmed influenza with consistent results across seasons [14.8% (95% CI, 7.0–22.0) in 2017–2018; 12.5% (95% CI, 4.7–19.6) in 2018–2019; 10.0% (95% CI, 2.7–16.7) in 2019–2020] [57]. In this view, subjects with cardiovascular disorders, due to the increased risk to develop infection-related complications, are ideal candidates to receive an appropriate influenza vaccination. Recommendations for the appropriate use of enhanced vaccines are increasingly being adopted worldwide [58]. Countries including United Kingdom [59], Australia [60], US [61], and more recently also Germany [62], and France [63], recommend the preferential use of adjuvanted or high-dose influenza vaccines in the elderly population (≥ 65 years or 60 years). Similarly, the Italian Ministry of Health recommends the use of enhanced vaccines in subjects ≥65 years and actively offers free influenza vaccination in patients aged 60–64 years [64–68]. In line with these considerations and the available evidence reported here, vaccines recommended in patients with underlying cardiovascular disorders are listed below in Table 3 [68].

Among the various initiatives implemented in Italy to improve influenza vaccination uptake, the Ospivax project is a national hospital-based program aimed at promoting influenza vaccination among hospitalized patients, healthcare workers, and caregivers, with a particular focus on individuals at high cardiovascular risk. By integrating

Table 2
Influenza vaccines available in Italy.

Influenza vaccine	Age indication
Standard-dose inactivated influenza vaccine (IIV-SD)	≥ 6 months
Live attenuated influenza vaccine (LAIV) (nasal spray)	2–17 years
Cell-based inactivated influenza vaccine (IIVc)	≥ 2 years
Adjuvanted inactivated influenza vaccine (IIVa, adjuvanted with MF-59)	≥ 50 years
High-dose influenza inactivated vaccine (IIV-HD, containing 60 µg of antigen)	≥ 60 years
DNA recombinant influenza vaccine (approved but not yet marketed in Italy)	≥ 18 years

Table 3
Current recommendations for the use of the different influenza vaccines according to age according to SIPREC-SITI joint document [68].

	<60 years	60–64 years	≥65 years
Cell-based inactivated influenza vaccine (IIVc)	P	S	S
Standard-dose inactivated influenza vaccine (IIV-SD)	S	S	S
Adjuvanted inactivated influenza vaccine (IIVa)	S (50–60 years old) (potentially preferred based on clinical evaluation)	S (potentially preferred)	R
High-dose influenza inactivated vaccine (IIV-HD)		S (potentially preferred)	R

P: preferential; R: recommended; S: available for administration.

vaccination strategies into routine hospital care, Ospivax seeks to improve vaccination coverage and reduce preventable influenza-related complications [69].

6. Conclusions

Influenza infection represents a significant and preventable trigger of acute cardiovascular events across a broad range of high-risk populations. Robust evidence from epidemiological studies, randomized trials, and meta-analyses consistently demonstrates that influenza vaccination reduces major adverse cardiovascular events and mortality, with benefits comparable to other cornerstone therapies in cardiovascular prevention. Despite this, vaccination rates in patients with cardiovascular disease remain suboptimal [70]. There are different types of vaccines available, and choosing the most appropriate according to the patient's age or clinical characteristics is essential to ensure optimal protection. In subjects aged 65 years or older, administration of inactivated adjuvanted or high-dose influenza vaccines is strongly recommended, in line with the recommendations released by the Italian Ministry of Health and other relevant authorities worldwide. Pending further data, it seems preferable to extend this recommendation to the population aged over 60 years. Adjuvanted vaccines have recently been authorized for use in the population aged ≥ 50 years. Based on the clinician's judgment, it could be the preferred option for subjects with frailty or immunocompromise. Moreover, recent data have demonstrated greater relative effectiveness (approximately 10%) for cell-based vaccines compared to standard egg-based vaccines, making them the preferable choice in subjects < 60 years.

In conclusion, it is highly recommended to extensively suggest influenza vaccination to subjects with cardiovascular disorders, both during cardiology practice and at hospital discharge, selecting the most appropriate vaccine for each patient's age and/or clinical conditions. In line with emerging evidence, including recent studies on behavioral interventions, targeted communication strategies may further enhance influenza vaccination uptake among patients with cardiovascular disease, thereby reinforcing its role as a simple and effective preventive measure in this high-risk population [71].

CRediT authorship contribution statement

Massimo Volpe: Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Allegra Battistoni:** Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Giovanni Gabutti:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Paolo Bonanni:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Giulio Nati:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Roberta Siliquini:** Writing – review & editing, Supervision, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

MV has been part of advisory boards of Seqirus, Sanofi Pasteur, Pfizer and GSK.

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The other authors declare nothing to disclose in relation to this paper.

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