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## Trends in Cardiovascular Medicine

journal homepage: [www.elsevier.com/locate/tcm](http://www.elsevier.com/locate/tcm)

## The impact of influenza vaccination in patients with cardiovascular disease: An overview of systematic reviews

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### ARTICLE INFO

#### Keywords:

Systematic review  
Coronary heart disease  
Heart failure  
Cardiomyopathy  
Cardiovascular diseases  
Secondary prevention  
Stroke  
Cerebrovascular disorders

### ABSTRACT

Whether influenza vaccination can play a prognostic role in patients with cardiovascular (CV) disease (coronary artery disease (CAD), heart failure, stroke, peripheral artery disease (PAD)) is still not completely well-established. We conducted this overview of systematic reviews (SR) evaluating the effects of influenza vaccination in secondary prevention of CV disease.

An electronic search was performed in the MEDLINE (to November 2019). Eligibility criteria included SR evaluating the effect of influenza vaccination in patients with CV disease. The risk of bias of the included systematic reviews was evaluated using the ROBIS tool. All-cause mortality, CV mortality, major adverse cardiovascular events (MACE) and hospitalizations were evaluated. Whenever required, data were recalculated through a random-effects meta-analysis to obtain pooled data for the patients at secondary CV prevention.

The search process yielded four SR: two in CAD, one in heart failure and one in stroke. There were no SR evaluating the vaccine in PAD. The risk of bias was unclear (2 SR) and high (2 SR). Influenza vaccination in patients with CAD showed a risk reduction in all-cause mortality (data recalculated), cardiovascular mortality and MACE, particularly in patients with recent acute coronary syndrome. In patients with heart failure, vaccination was associated with a decreased risk of all-cause mortality. There was a non-significant trend in recurrent stroke risk reduction in patients with previous stroke.

The available evidence suggests that influenza vaccination was associated with a protective effect in CAD and HF patients. However, these results need to be clarified with higher quality evidence studies.

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### Background

Cardiovascular (CV) diseases are the leading cause of mortality in the world, being responsible for 17.9 million deaths globally (31% of all deaths) [1]. In addition to the most conventional risk factors for CV disease (smoking, physical inactivity, unhealthy diet, obesity, hypertension, diabetes and dyslipidemia) [1], there

are some non-traditional risk factors, such as infection with the influenza virus.

Several studies have shown a temporal association between the peak of seasonal influenza infection and a peak in CV mortality in the winter [2,3]. Influenza infection is hypothesized to act as an acute inflammatory trigger of CV events leading to impaired coronary blood supply and/or myocardial demand due to hypoxemia and/or systemic inflammatory response syndrome. Furthermore, it can lead to the rupture of vulnerable atherosclerotic plaques and consequently coronary artery occlusion [4,5]. Epidemiological studies also show an association between influenza infection and other CV diseases, such as stroke [6] and heart failure (HF) [7,8].

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<https://doi.org/10.1016/j.tcm.2020.06.003>

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Therefore, influenza vaccination was considered to have a preventive role regarding CV events [9]. Taking this into account, we aimed to conduct an overview of systematic reviews evaluating the effects of influenza vaccination in the subset of patients at the highest stratum of CV risk, which are the patients with established of CV disease, i.e. in secondary prevention of cardiovascular events.

## Methods

This overview of systematic review was conducted using as a reference the recommendations from the Cochrane Collaboration [10] and, when applicable, the PRISMA guidelines [11].

### Eligibility criteria

#### Study design

We considered all systematic reviews (with or without meta-analysis) evaluating the effect of influenza vaccination in patients with CV disease (heart disease, cerebrovascular disease or peripheral arterial disease). RCTs (randomized controlled trials), other clinical trials, observational studies, case-reports and opinion reviews were excluded.

#### Participants of interest

We considered patients with CV disease if they had a diagnosis of heart disease (myocardial ischemic disease, heart failure, cardiomyopathies, pericardial diseases, rhythm disorders, others), cerebrovascular disease (stroke or transient ischemic accident) or peripheral artery disease.

#### Intervention

Influenza vaccination, regardless of type and dose of the vaccine used.

#### Comparators

No influenza vaccination.

#### Outcomes

We considered all-cause mortality, CV mortality, all-cause hospitalizations, CV hospitalizations, outcomes related to quality of life or quantification of symptoms.

When more than one systematic review was available for the same topic, we selected according to the following criteria: included studies with participants more concordant with the population of interest, pooled results from the greatest amount of studies for that specific outcome, inclusion of RCTs. Those cases were scrutinized by two authors (BR and DC).

#### Information sources and search strategy

BR and DC retrieved potential eligible reviews using an electronic search in MEDLINE, from inception to November 2019. Search terms are detailed in supplementary data 1. Authors hand-searched the reference list of included reviews in order to identify additional eligible reviews. There was no restriction by language of publication.

#### Data extraction, selection, collection and management

Two reviewers (DC and BR) screened all articles resulting from the search. Initially, titles and abstracts were screened independently according with the eligibility criteria and any doubts or disagreements were discussed and solved by consensus. The selected studies were thoroughly evaluated for their fulfillment of the eligibility criteria.

Study characteristics and results were independently extracted into a standardized form, including the following categories: first

author, year of publication, type of studies included in the systematic review and eligibility criteria, risk of bias tools and results, GRADE assessments (if performed), if the study includes a meta-analysis or not, effect estimates from meta-analysis (if performed), results from subgroup analysis (if performed), authors' conclusions. Other included categories were: characteristics of the sample (total number of patients included, mean age, proportion of women, CV risk factors), the time of year in which the influenza vaccination was administered, mean follow-up time (if applicable).

If the reviews did not provide analyses of data for the populations of interest but provided detailed data about the individual studies that fulfilled our criteria, we sought such data to perform additional analyses.

#### Data quality assessment

The risk of bias of the included systematic reviews was evaluated using the ROBIS tool [12], which uses a three phase process to evaluate the risk of bias in systematic reviews: assessment of relevance, risk of bias in the review process (in four domains) and the final judging of the risk of bias. The risk of bias assessment was performed independently by two authors (BR, MA, GD). Inconsistencies were solved through an additional author (GD or DC).

#### Data synthesis

The included systematic reviews were separated according to the baseline CV disease (coronary disease; heart failure; stroke; peripheral artery disease). The most representative estimates for each outcome were summarized in a plot generated by Review Manager version 5.3. Overall there was only one estimate for each outcome in each disease.

When systematic reviews did not analyze the data for the populations of interest (for example analyzed a broader population) but provided detailed data regarding that population, we proceeded to perform a meta-analysis. We used the Mantel-Haenszel method and a random effects model. The outcome reporting metric was the risk ratio with the 95% confidence (interval). Statistical heterogeneity was assessed using I<sup>2</sup> metric, considering studies with I<sup>2</sup>>50% to have substantial heterogeneity.

## Results

### Study selection

Four reviews were included after the full-text eligibility (Fig 1). For more details regarding the selection of these four reviews view supplementary data 2.

### Study characteristics

Table 1 details the main characteristics of the four selected reviews. For CAD patients two systematic reviews of RCTs were included; for HF patients and stroke patients only systematic reviews of observational studies were available. There were no systematic reviews evaluating the impact of influenza vaccination in patients with peripheral artery disease.

The most important outcomes reported for each group are referred in Table 1.

For a detailed explanation of the relationship between outcomes and selected reviews view supplementary data.

### Risk of bias and confidence in the results

According to the ROBIS-tool for systematic reviews, two reviews had an unclear risk of bias and the other two had a high risk of bias – Supplementary data 3.

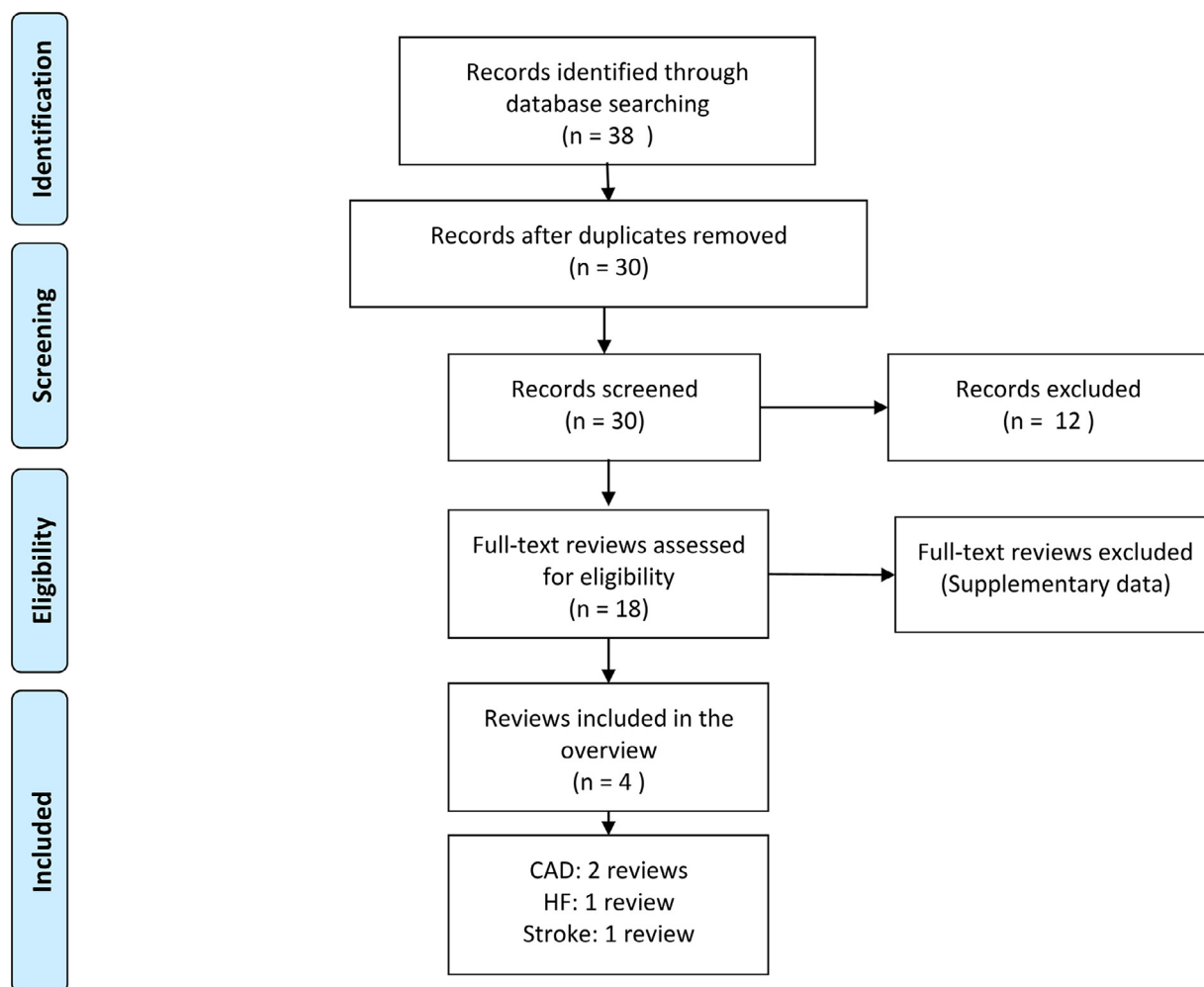


Fig. 1. Flowchart of studies selection.

The number of databases searched ranged between 2 and 8, with a median of 4. MEDLINE, EMBASE and CENTRAL were the most used databases.

All reviews evaluated the risk of bias of the included studies: the two reviews [13,14] that included RCTs for our outcomes of interest used the Cochrane risk of bias tool; one of the reviews [16] that included observational studies used NewCastle Ottawa scale (NOS) to assess study quality and the other used the more recent ROBINS-I tool [15].

### Synthesis of the results

#### CAD patients

In patients with CAD, influenza vaccination was associated with a statistically significant reduction in all-cause mortality (RR 0.39 95%CI 0.30, 0.81; 4 RCT; recalculated from [14], Fig 2), CV mortality (RR 0.44 95%CI 0.26, 0.76; 4 RCT, Fig 2) [13] and major adverse cardiovascular events (MACE) (RR 0.50 95%CI 0.27, 0.95; 4 RCT, Fig 2) [14].

The referred results were not considered robust due to methodological weaknesses of included studies, particularly in the allocation concealment, blinding of outcome assessment and risk of reporting bias.

The vaccine was not significantly associated with a decreased risk of MI, myocardial revascularization, heart failure or stroke, the latter two based on the data from one trial.

#### HF patients

Influenza vaccination in patients with HF was associated with a significant effect in all-cause mortality (HR 0.83 95%CI 0.76, 0.91; 6 observational studies, Fig 2) [15]. The evidence was graded as very low.

The vaccine was not associated with a statistically significant effect in all-cause hospitalizations and in CV mortality, according to the pooled analysis of two observational studies (Fig 2) [15].

Regarding HF hospitalization, the influenza vaccine was associated with a risk reduction of these events in one cohort study [15]. This study was considered to have a moderate risk of bias according to the ROBINS-I tool and a low GRADE of certainty.

The effect of the vaccine in ventricular arrhythmias was only evaluated by one observational study and was not different among patients vaccinated. One additional small study evaluated a surrogate outcome (all-ICD therapies) and no difference was found. All these analyses were associated with a serious risk of bias and very low GRADE of certainty [15].

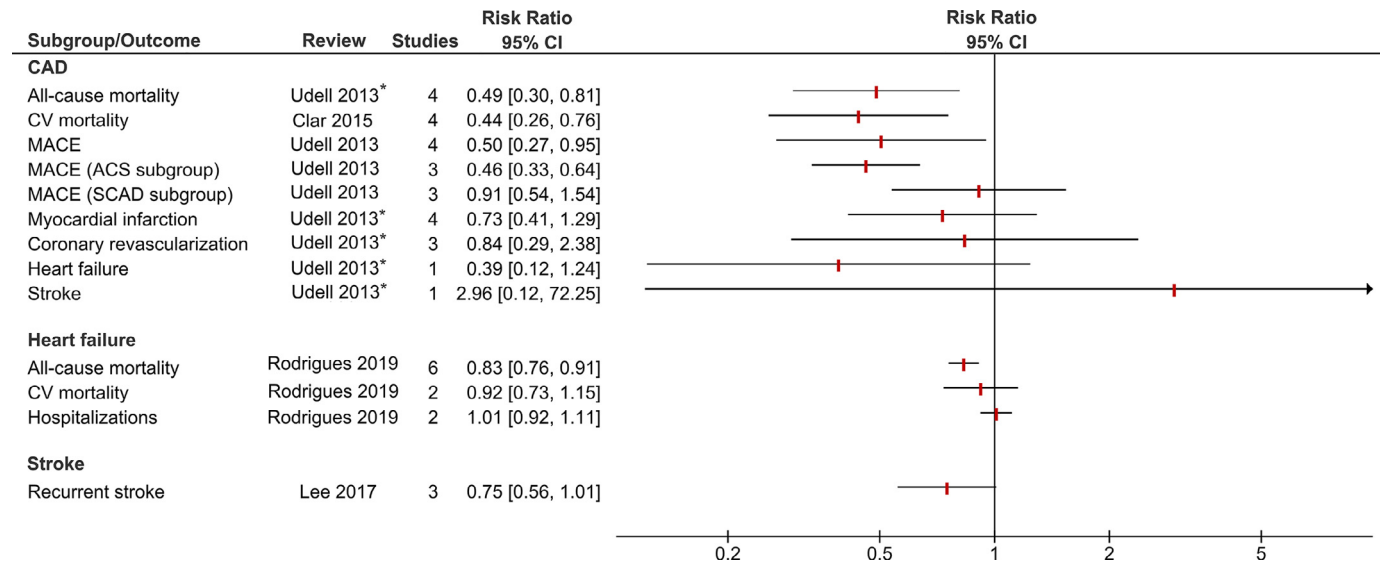
#### Stroke patients

Lee et al. performed a systematic review evaluating the risk of stroke associated with influenza vaccination. For this overview we only considered the occurrence of recurrent stroke, as it reflects the incidence of stroke in a secondary prevention setting. Influenza vaccine was not associated with a significant reduction in the risk of stroke (RR 0.75 95%CI 0.70–1.01; 3 studies, Fig 2) [16].

**Table 1**  
Main characteristic of the included reviews.

First author + year	Study designs MA or no MA	Characteristics of the participants of the included studies	Important outcomes evaluated (number of the included studies) Subgroup analysis	ROBIS – risk of bias in systematic reviews
<b>CAD patients</b>				
Clar 2015[13]	RCTs MA	- FLUVACS, FLUCAD, IVCAD and Phrommintikul had 100% of the sample with CAD. + Govaert and De Villiers had a sample with 13.5% and 16.2% of the patients with cardiac disease. Data were recalculated excluding these studies.*	CV mortality (4 studies)* Risk of MACE (2 studies, not pooled) Risk of MI (2 studies, not pooled) Risk of stroke (1 study) Risk of HF hospitalization (1 study) Risk of PCI or CABG (2 studies)	Unclear
Udell 2013[14]			All-cause mortality (4 studies)* CV mortality (4 studies) – stratified by recent ACS vs. stable CAD Risk of MI (4 studies)* Risk of stroke (1 study) Risk of HF (1 study) Risk of coronary revascularization (3 studies)*	High
<b>HF patients</b>				
Rodrigues 2019[15]	Observational studies MA	All included studies had a sample of only patients with HF.	All-cause mortality (6 studies) CV mortality (2 studies) All-cause hospitalization (2 studies) HF-hospitalizations (1 study) Risk of ventricular arrhythmias (1 study, 1 surrogate)	Unclear
<b>Stroke patients</b>				
Lee 2017[16]	Observational studies MA	Patients with stroke	Risk of recurrent stroke (3 studies)	High

ACS acute coronary syndrome CAD coronary artery disease MA meta-analysis MACE major adverse coronary events MI myocardial infarction RCT randomized-controlled trials.  
\* Data recalculated using only studies enrolling 100% patients with CAD.



**Fig. 2.** Risk ratio for outcome in patients with cardiovascular disease. \*data based only on studies with 100% of the sample with CAD, as referenced in table 1.

**Discussion**

In this overview of systematic reviews evaluating the CV impact of influenza vaccination, 4 systematic reviews were included to describe the effect of the vaccine on clinically significant outcomes among patients with CV disease (Fig. 3). Evidence was only available for CAD patients, HF patients, and stroke patients. There were no data for patients with peripheral (lower limb) arterial disease. The quality of these systematic reviews was globally low or unclear, according to the ROBIS tool.

In patients with CAD, vaccinating against influenza is associated with a decrease in all-cause mortality, CV mortality and major adverse coronary events. The decrease of all-cause mortality in patients with CAD is a novel result, derived from the recalculating of data from previous reviews. This is not surprising because CV deaths are expected to be the major share of the global mortality in patients with CAD. These findings may have a biological basis: if influenza infection can destabilize atherosclerotic plaques [4], preventing influenza infection leads to less coronary events and concurrently to a lower CV mortality. Interestingly, the benefit in

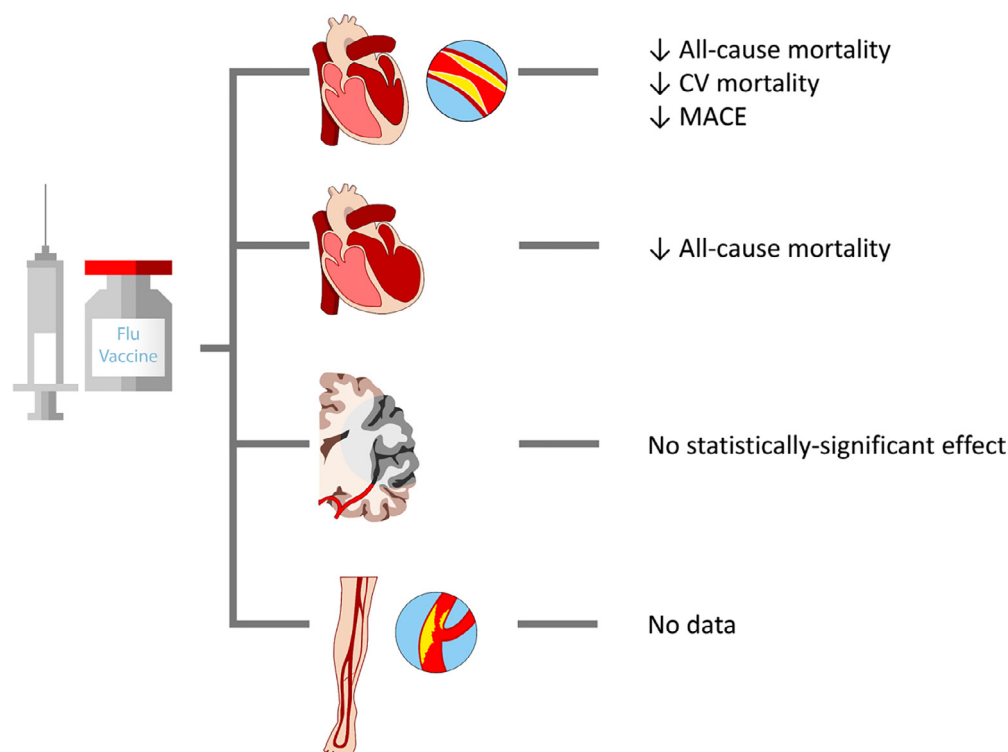


Fig. 3. The main findings of the overview of systematic reviews.

terms of coronary events was greater in patients with a recent ACS – which may relate to a greater instability of atherosclerotic plaques immediately after a coronary event, and therefore with a greater potential for the protective effect of the vaccine when comparing with patients with stable plaques.

In HF patients, only observational studies were available, which increases the risk of bias since patients that received the vaccine may have been the most compliant patients and more likely to be performing the most prognostically impactful therapies. However, most observational studies included in the review used outcome adjustment strategies to minimize the risk of bias.

In HF patients, the influenza vaccine is associated with a significant decrease in all-cause mortality. The rationale for this protective effect is probably associated with a higher risk of acute HF exacerbations and MI related with influenza infections. [17,18] In addition to that, the protective effect in CV mortality and MACE observed in CAD patients may translate to a significant proportion of HF patients, since ischemic heart disease is an important etiology of HF – and therefore a protection against MACE events in patients with HF of ischemic etiology can contribute to a lower mortality.

The vaccine was not associated with a statistically significant effect in CV mortality. However, this estimate was only based on two heterogeneous cohort studies with heterogeneous results. The results that seems to have a lower risk of bias is a large Danish cohort study with more than 100,000 patients. In this cohort, a nested case-control analysis showed an association between influenza vaccination and lower CV mortality risk (HR 0.82, 95%CI 0.81, 0.84). This effect seemed more significant in the patients that received the vaccine in September and October when comparing with November and December [19].

These findings regarding CV mortality may also be explained by a paradox related to the protective effect in all-cause mortality: if HF patients have less acute exacerbations and respiratory complications of influenza infection, they may survive longer past the acute phase and therefore remain more time in a position of

vulnerability to CV causes of death. This does not mean a greater number of CV events. Other possible explanation is related to the hospitalization of HF patients with respiratory infections and possible complications – if these patients die, the cause of death is considered non-CV.

The sparse data on CV and HF hospitalizations, ventricular arrhythmias (since sudden death is one major cause of death in HF patients) and importantly HF mortality (since this outcome was not evaluated by any study in any of the included reviews), highlight the need for RCTs and more studies to clarify this association.

In an overall analysis, vaccinating against influenza was associated with a decreased risk of stroke. Influenza vaccination has showed a tendency to decrease the risk of recurrent stroke. [16] The biological basis for this protective effect of the vaccine in stroke risk may be related to the already mentioned effect of the inflammation associated with the infection in atherosclerotic plaques. Other proposed mechanism relates to the infectious burden concept – the risk of atherosclerosis and ischemic diseases increases with the aggregate burden of chronically persistent pathogens and/or past infections to which an individual has been exposed [20]. Therefore an aggregate burden of viral infections (including but not limited to influenza infections) may be the explanation for the decreased risk with the influenza vaccination [16]. It would be an interesting idea to evaluate if patients vaccinated in a higher number of years had an extra protective effect. Other possible explanation for the protective effect of the vaccine is the protection observed in heart disease, which can decrease the risk of cardiac embolism. However, no systematic review evaluated the effect of the vaccine in patients with atrial fibrillation.

#### Clinical importance of the results

The links between influenza infection and cardiovascular diseases are nowadays more solid than before [21]. Nevertheless, the whole spectrum of potential benefits of the vaccine is still not completely understood in terms of mechanisms in certain out-

comes and groups of population, and the rates of vaccination in patients with CV diseases is still strikingly low, particularly in HF patients.

It is vital to seek more data, with higher quality and detail, to allow us to understand more fully the mechanisms and impact of this intervention. But until a more complete knowledge is attained, we have enough evidence to encourage vaccination in secondary CV prevention, on an individual basis and on a population basis. It is important to start considering influenza vaccination as an add-on treatment in CV patients, and not only as a preventive measure in patients with chronic conditions (as a group of the population with a higher risk of having complications of the infection).

### Limitations

First, the reviews included have their own primary studies which have their risk of bias and the risk of bias of this overview is directly related to these studies and their limitations. Two of the included systematic reviews were considered to have a high risk of bias and the other two an unclear risk of bias. In view of our risk of bias assessment, the results must be interpreted with caution regarding the quality of the available evidence on this matter.

Second, the data here presented were derived from studies with a relevant clinical heterogeneity regarding the patients' characteristics but also with methodological heterogeneity. The reviews evaluating CAD included RCT and the remainder only included observational studies due to the lack of RCTs.

These limitations have implications in the results and their interpretations. Currently, and until evidence of higher quality is available, this is the best pool of data available to support clinical decisions.

### Conclusions

The present overview allows us to conclude that influenza vaccination may have a protective effect in CAD and HF patients. Further studies are needed, particularly RCT, to better clarify and quantify the putative benefit of influenza vaccination in secondary CV prevention.

### Declaration of Competing Interest

None.

### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.tcm.2020.06.003](https://doi.org/10.1016/j.tcm.2020.06.003).

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