

**VENERDI' 1 MARZO**

# **NESSO DI CAUSALITÀ TRA INFLUENZA ED INFARTO. IPOTESI FISIOPATOLOGICHE E RIPERCUSSIONI CLINICHE**

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- Co-author ESC Guidelines on Atrial Fibrillation 2010-2012
  - Steering Committee member, National Coordinator for Italy, and Co-author of APPRAISE-2, ARISTOTLE, AVERROES, ENGAGE AF-TIMI 38, Re-DUAL PCI
  - Fees, honoraria and research funding from Sanofi-Aventis, Boehringer Ingelheim, Bayer, BMS/Pfizer, Daiichi-Sankyo, Novartis, Merck, Portola, Roche
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# Influenza e Infarto

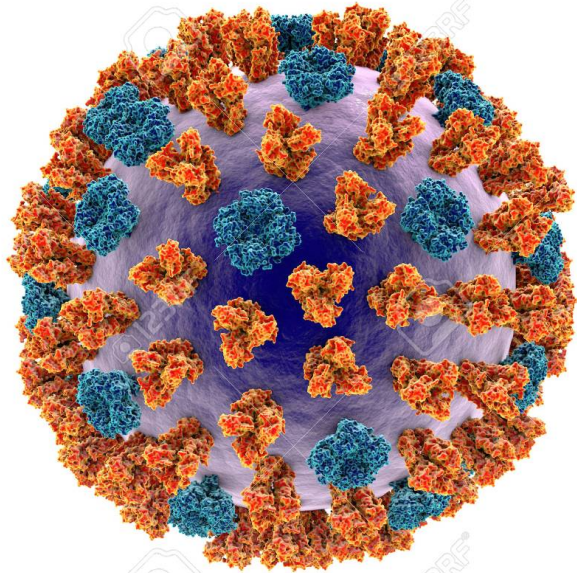
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- ▶ Fino all'inizio del secolo scorso l'aspettativa di vita era di meno di 50 anni e le infezioni spesso fatali
- ▶ Solo nel secolo scorso l'uomo ha cominciato a vivere abbastanza perché si manifestassero le attuali malattie cardiovascolari in tutta la loro rilevanza epidemiologica
- ▶ E solo da poco più di 60 anni si sono rese disponibili terapie antimicrobiche che hanno reso comune la sopravvivenza da infezioni
- ▶ Nessuna sorpresa dunque se l'associazione tra infezioni e infarto è stata apprezzata solo di recente!



# Influenza: the beautiful face of a killer

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Influenza virus isolated on white background showing surface glycoprotein spikes  
----- hemagglutinin red and neuraminidase blue

- ▶ Influenza spreads around the world in yearly outbreaks,
- ▶ resulting in about three to five million cases of severe illness and about 250,000 to 500,000 deaths.<sup>[1]</sup>
- ▶ About 20% of unvaccinated children and 10% of unvaccinated adults are infected each year.<sup>[2]</sup>

1. Influenza Fact sheet N°211". who.int. March 2014.
2. Somes MP et al. *Vaccine*. 2018 **36** (23): 3199–3207.

# Influenza e Infarto

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- ▶ Ma questa relazione è solida?
- ▶ E se sì, è una relazione causale?
- ▶ E se c'è una relazione causale, che cosa possiamo fare, vista l'amplissima diffusione della patologia influenzale nella popolazione?

# Influenza e infarto

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- ▶ Evidenze epidemiologiche
- ▶ Presupposti razionali fisiopatologici
- ▶ Il nesso causale
- ▶ La vaccinazione influenzale per la prevenzione secondaria della malattia coronarica



# Influenza e infarto

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- ▶ Evidenze epidemiologiche
  - ▶ Rischio a breve termine
  - ▶ Rischio oltre la fase acuta



ORIGINAL ARTICLE

# Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection

----- Kwong JC et al. N Engl J Med 2018;378:345-53. -----



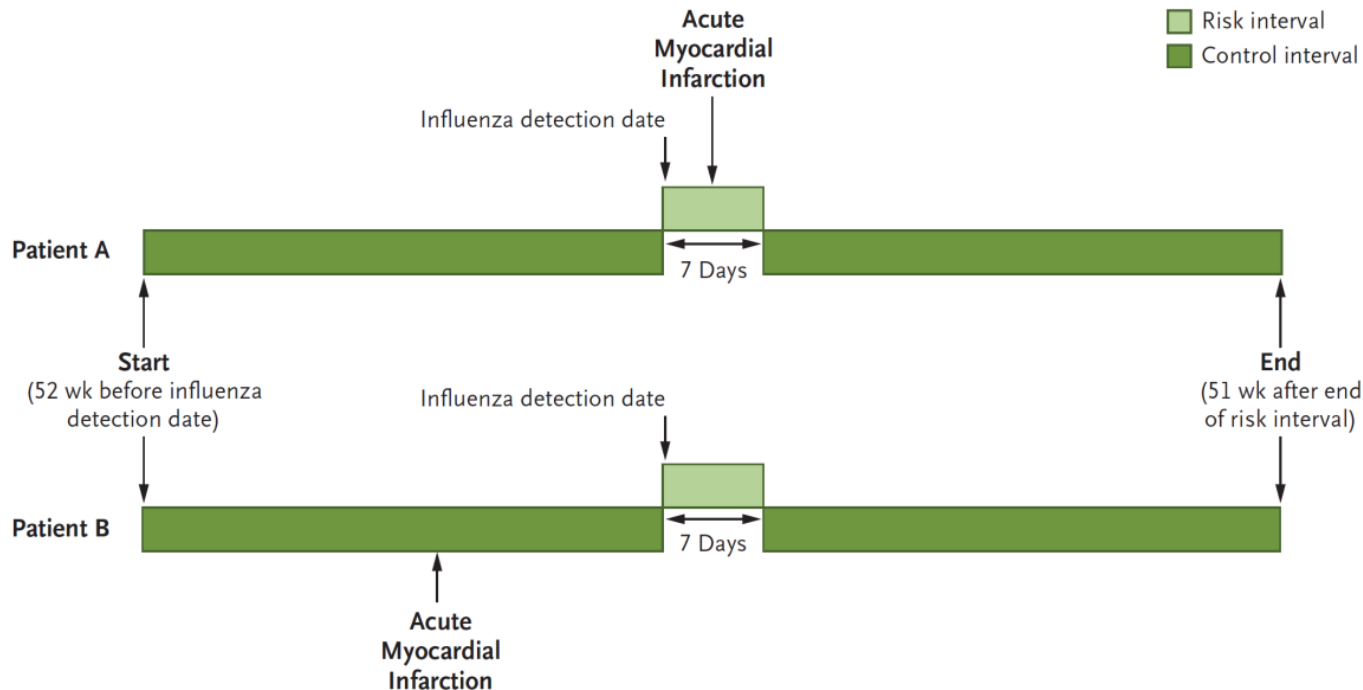
Acute Myocardial Infarction after  
Laboratory-Confirmed Influenza Infection

- ▶ Inclusion of all Ontario residents registered for provincial publicly funded health insurance
- ▶ who underwent testing for one or more respiratory viruses between May 1, 2009, and May 31, 2014
- ▶ who were 35 years of age or older at the time of testing
- ▶ and who were hospitalized for an acute myocardial infarction between May 1, 2008, and May 31, 2015

Acute Myocardial Infarction after  
Laboratory-Confirmed Influenza Infection

- ▶ Patients tested for influenza A (with subtype information available for 56% of the positive specimens) and influenza B
- ▶ 88% of the specimens also tested for  $\geq 1$  of the following: respiratory syncytial virus (RSV), adenovirus, coronavirus, enterovirus (including rhinovirus), parainfluenza virus, and human metapneumovirus

# Study Design: Comparing the relative incidence of acute myocardial infarction during the risk interval with the control interval



Additional analyses with narrower risk intervals (days 1 through 3 and days 4 through 7) and alternative risk intervals (days 8 through 14 and days 15 through 28)

# Incidence ratios for acute MI after laboratory-confirmed influenza infection

Variable	Incidence Ratio (95% CI)
<b>Primary analysis: risk interval, days 1–7</b>	<b>6.05 (3.86–9.50)</b>
Days 1–3	6.30 (3.25–12.22)
Days 4–7	5.78 (3.17–10.53)
Days 8–14	0.60 (0.15–2.41)
Days 15–28	0.75 (0.31–1.81)

- ▶ There were 20.0 admissions per week during the risk interval and 3.3 admissions per week during the control interval (incidence ratio, 6.05; 95% confidence interval [CI], 3.86 to 9.50).

## Is this strong association specific for influenza?

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- ▶ Alternative exposures studied (i.e., RSV, other respiratory viruses, and illness with no respiratory virus identified) were also associated with a significantly higher incidence of acute myocardial infarction
- ▶ but the incidence ratio point estimates were lower than the incidence ratio point estimate for influenza
- ▶ No significant association was observed between influenza infection and hospitalizations for diabetes and associated complications

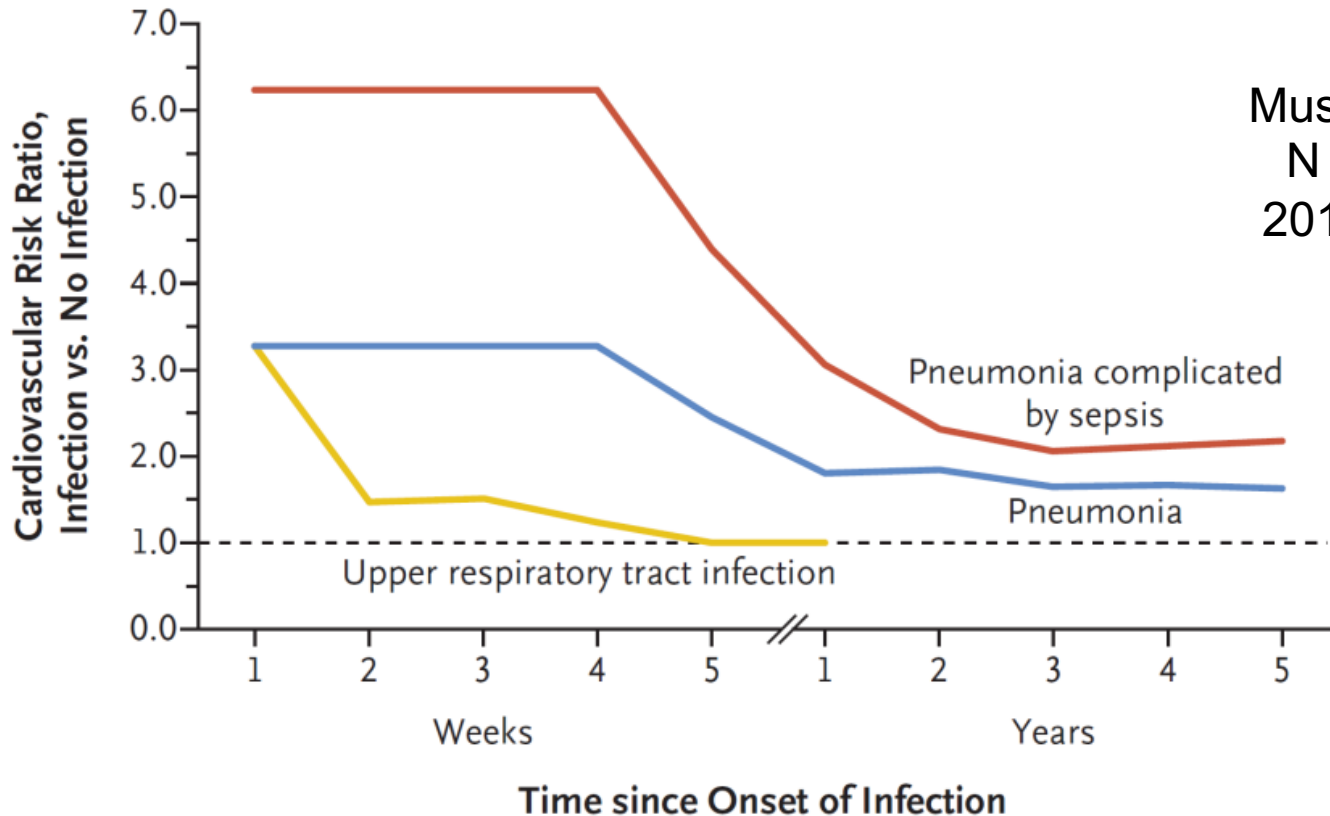
# Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection

## CONCLUSIONS

We found a significant association between respiratory infections, especially influenza, and acute myocardial infarction. (Funded by the Canadian Institutes of Health Research and others.)



# Temporal Pattern of Cardiovascular Risk after the Onset of Acute Infection



Musher, DM et al.  
N Engl J Med  
2019;380:171-6.



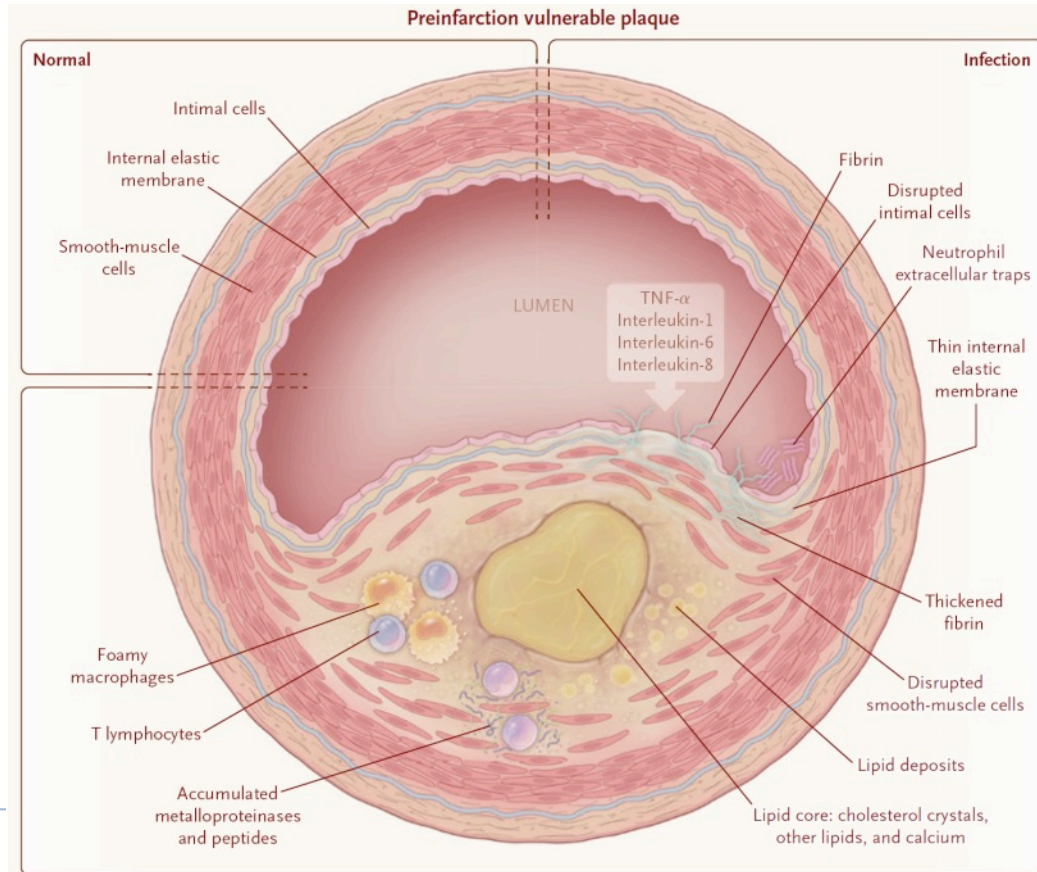
# Influenza e infarto

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- ▶ Evidenze epidemiologiche
- ▶ Presupposti razionali fisiopatologici



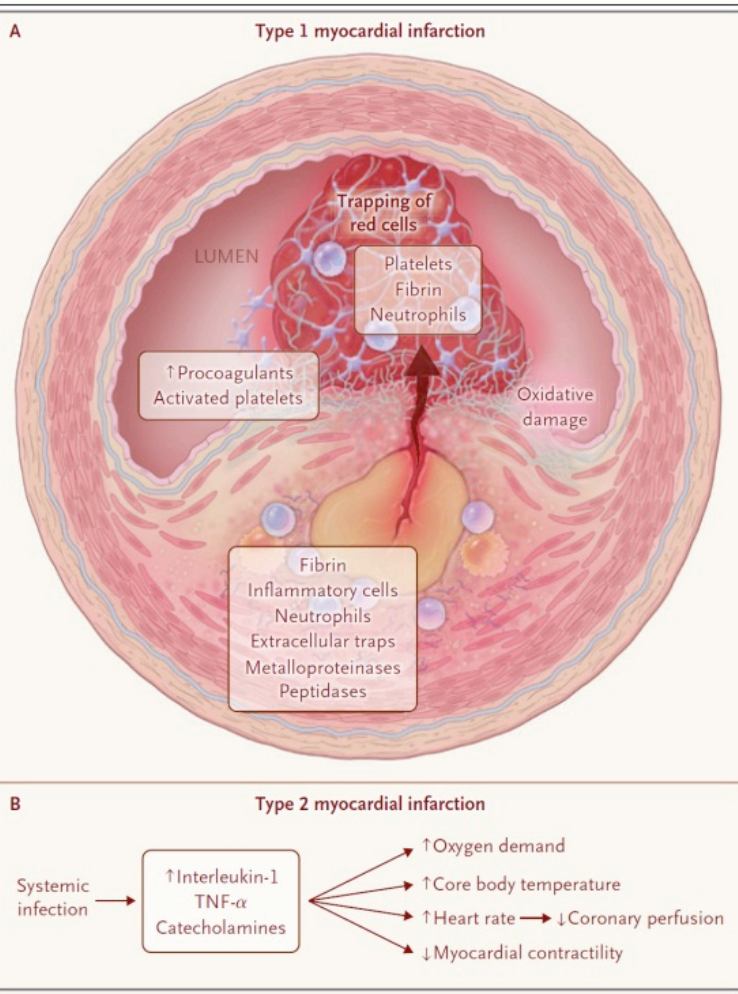
# Features Present at the Time of Cardiac Involvement in Acute Infection



Studies in animals and autopsy studies in humans have shown that inflammatory activity in atheromatous plaques increases after an infectious stimulus.

Activated intraplaque inflammatory cells up-regulate host response proteins, including metalloproteinases and peptidases, and promote an oxidative burst, all of which contribute to destabilization of the plaques

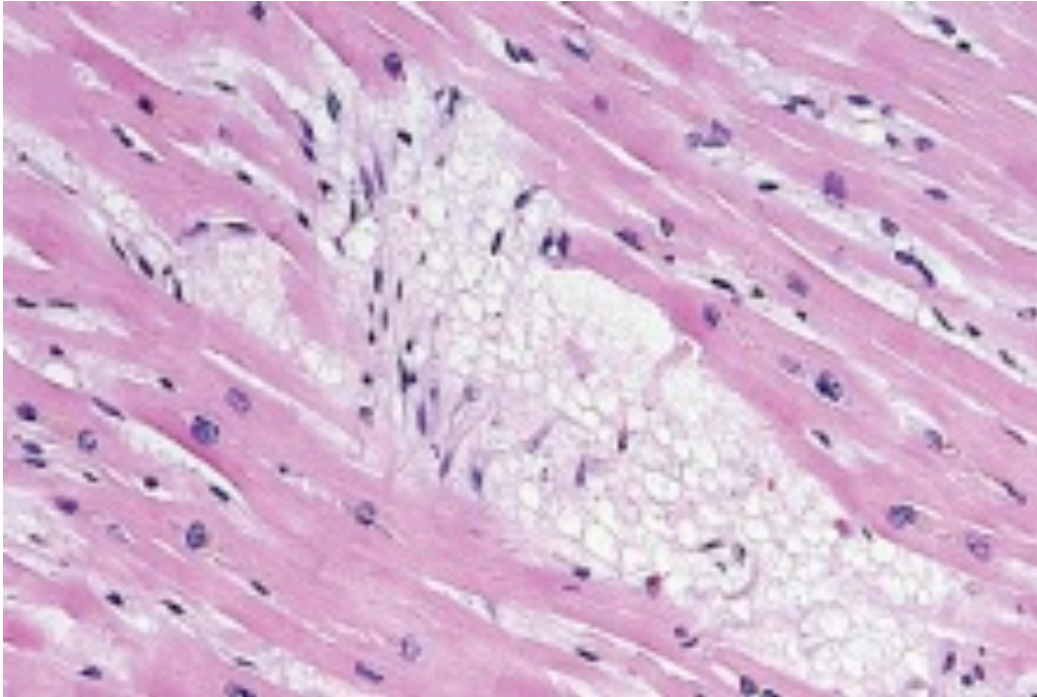
Musher, DM et al.  
N Engl J Med  
2019;380:171-6.



# Type 1 and Type 2 Myocardial Infarction in Acute Infections

Musher, DM et al.  
N Engl J Med  
2019;380:171-6.

# Features Present in the Myocardium after Cardiac Involvement in Acute Infection



A third possible mechanism by which infection might adversely affect cardiac function: cardiac lesions with loss of myocytes without accumulation of inflammatory cells; associated with elevated troponin levels, arrhythmias, and the presence of ECG abnormalities

Musher, DM et al.  
N Engl J Med  
2019;380:171-6.

Disrupted myocytes and there is a relative absence of neutrophil infiltration in a patient died of pneumococcal pneumonia

# Influenza e infarto

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- ▶ Evidenze epidemiologiche
- ▶ Presupposti razionali fisiopatologici
- ▶ Il nesso causale
- ▶ La vaccinazione influenzale per la prevenzione secondaria della malattia coronarica





# Influenza vaccination and cardiovascular events

[Cochrane Database Syst Rev.](#) 2008 Jul 16;(3):CD005050. doi:  
10.1002/14651858.CD005050.pub2.

## **Influenza vaccines for preventing coronary heart disease**

[Keller T<sup>1</sup>](#), [Weeda VB](#), [van Dongen CJ](#), [Levi M](#)

### **AUTHORS' CONCLUSIONS:**

Despite the significant effect noted in the studies, we concluded that there are not enough data to evaluate the effect of vaccination on coronary heart disease.

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# Influenza vaccination and cardiovascular events

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[Cochrane Database Syst Rev.](#) 2015 May 5;(5):CD005050. doi:  
10.1002/14651858.CD005050.pub3.

## **Influenza vaccines for preventing cardiovascular disease**

[Clar C<sup>1</sup>](#), [Oseni Z](#), [Flowers N](#), [Keshtkar-Jahromi M](#), [Rees K](#)

### AUTHORS' CONCLUSIONS:

In patients with cardiovascular disease, influenza vaccination may reduce cardiovascular mortality and combined cardiovascular events. However, studies had some risk of bias, and results were not always consistent, so additional higher-quality evidence is necessary to confirm these findings. Not enough evidence available for influenza vaccination in the primary prevention of cardiovascular disease.

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See also Udell JA et al. JAMA 2013; 310:1711-20.

# Influenza vaccination and cardiovascular events

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Curr Atheroscler Rep. 2003 Mar;5(2):146-9

Myocardial infarction, stroke, and sudden cardiac death may be prevented by influenza vaccination

Meyers DG

**Influenza vaccine is extremely safe and has a 50% efficacy.**

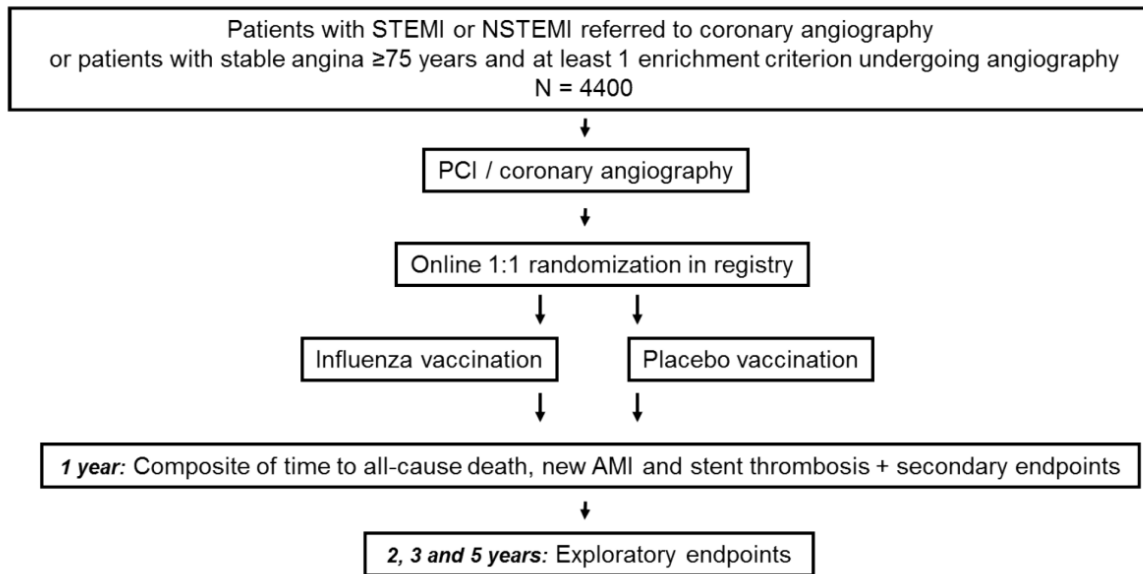
**Theoretically, up to 104,500 AMIs and 192,000 nonembolic ischemic strokes could be prevented each year by influenza vaccination**

# Ole Fröbert, MD, PhD (Sponsor, PI)

## Influenza vaccination After Myocardial Infarction (**IAMI** trial)

A multicenter, prospective, randomized controlled clinical trial based on national angiography and angioplasty registries

**IAMI** trial flow chart



Therefore, considering the benefits and the risk, please think twice before not strongly recommending the influenza vaccination to a cardiac patient....



Grasse, France,  
XVII century  
scale







Grazie!