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Optimal timing of influenza vaccination among patients with acute myocardial infarction – Findings from the IAMI trial

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ABSTRACT

Influenza vaccination reduces the risk of adverse cardiovascular events. The IAMI trial randomly assigned 2571 patients with acute myocardial infarction (AMI) to receive influenza vaccine or saline placebo during their index hospital admission. It was conducted at 30 centers in 8 countries from October 1, 2016 to March 1, 2020. In this post-hoc exploratory sub-study, we compare the trial outcomes in patients receiving early season vaccination (n = 1188) and late season vaccination (n = 1344). The primary endpoint was the composite of all-cause death, myocardial infarction (MI), or stent thrombosis at 12 months. The cumulative incidence of the primary and key secondary endpoints by randomized treatment and early or late vaccination was estimated using the Kaplan-

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Meier method. In the early vaccinated group, the primary composite endpoint occurred in 36 participants (6.0%) assigned to influenza vaccine and 49 (8.4%) assigned to placebo (HR 0.69; 95% CI 0.45 to 1.07), compared to 31 participants (4.7%) assigned to influenza vaccine and 42 (6.2%) assigned to placebo (HR 0.74; 95% CI 0.47 to 1.18) in the late vaccinated group (P = 0.848 for interaction on HR scale at 1 year). We observed similar estimates for the key secondary endpoints of all-cause death and CV death. There was no statistically significant difference in vaccine effectiveness against adverse cardiovascular events by timing of vaccination. The effect of vaccination on all-cause death at one year was more pronounced in the group receiving early vaccination (HR 0.50; 95% CI, 0.29 to 0.86) compared late vaccination group (HR 0.75; 35% CI, 0.40 to 1.40) but there was no statistically significant difference between these groups (Interaction P = 0.335). In conclusion, there is insufficient evidence from the trial to establish whether there is a difference in efficacy between early and late vaccination but regardless of vaccination timing we strongly recommend influenza vaccination in all patients with cardiovascular diseases.

1. Introduction

Influenza infection is a risk factor for atherosclerosis progression [1] and may trigger acute myocardial infarction (AMI), stroke and other cardiovascular events [2]. Influenza vaccination prevents influenza infection and is also an effective strategy to prevent adverse cardiovascular events [3]. Four trials randomizing participants to either influenza vaccine or placebo/control have been conducted in patients with recent AMI or stable coronary artery disease. Three were single-centre, single-season trials [4–6], while the most recent (IAMI trial) enrolled 2571 patients over four influenza seasons in 30 centres in eight countries [7]. In a meta-analysis of the four influenza vaccine trials, the pooled estimate of the hazard ratio of cardiovascular death at 12 months was 0.51 (95% CI, 0.36–0.71, P = 0.0001), which equates to 49% vaccine effectiveness against cardiovascular death [7].

Peak influenza circulation in temperate climates normally occurs during winter [8], while in subtropical and tropical climates, the peak is typically during the rainy season [9]. Following influenza vaccination, an antibody response is achieved within two weeks, and peak levels are achieved at four to six weeks [10] which confers protection against influenza. Vaccination is typically performed from September to December in the northern hemisphere and from March to May in the southern hemisphere [11].

A practice of vaccinating before or early in the influenza season has been questioned because of waning of antibodies and possibly reduced vaccine effectiveness in late season primarily among individuals > 65 years of age [12] but also in other age groups [13]. It has been proposed to vaccinate closer to the peak [14] but because of varying patterns of influenza activity beyond seasons [15], optimal timing of vaccination has not been established [16].

In this study we investigated influenza vaccine effectiveness following early or late vaccination as a post-hoc exploratory analysis in the IAMI trial.

2. Methods

We conducted the IAMI trial at 30 centres in eight countries: Australia, Bangladesh, the Czech Republic, Latvia, Denmark, Norway, Sweden, and the UK. It was a randomized, double-blind, placebo-controlled, investigator-initiated trial to evaluate the effectiveness of influenza vaccination following AMI or percutaneous coronary intervention (PCI) among only patients with high risk coronary artery disease from October 1, 2016, to March 1, 2022 [7]. Participants were recruited during the influenza circulation period from September to March in European countries and from May to September in Australia and Bangladesh.

The study methods have previously been published in detail elsewhere [7,17]. The trial was approved by the respective participating sites' ethical review board and national regulatory authority, and at the European Union Drug Regulating Authorities Clinical Trials Database as 2014–001354-42.

Participants meeting the following inclusion criteria: age > 18 years, STEMI (symptoms for at least 30 min before hospital admission, time from onset of symptoms of less than 24 h) or NSTEMI, or stable coronary artery disease in patients > 75 years of age who had at least one additional risk criterion and a completed coronary angiography or PCI were asked to participate in the study. For Bangladesh, the inclusion criterion of completed coronary angiography or PCI was waived because medical treatment alone without PCI is routine in that country [18]. Exclusion criteria included vaccination or the intention to receive vaccination during the current influenza season [7].

Patients who consented to participate in the trial were assigned to receive either vaccine or placebo within 72 hours of coronary angiography/PCI or, hospital admission (in Bangladesh) during the influenza season relevant to each participating country by unblinded study nurses who were not otherwise involved in the trial. The participants and trial staff were blinded. The randomization list in a 1:1 ratio was generated with a permuted block design stratified by trial site with a block size of six. This list was prepared by a data scientist unaffiliated with the trial, ensuring an unbiased approach to participant allocation. For the IAMI trial, the minimum sample size was set at 4,400 participants, with 2,200 allocated to each of the two groups: influenza vaccine and placebo. This size was determined to achieve sufficient statistical power for the study's endpoints [7].

We used 0.5 ml of trivalent inactivated vaccine (Vaxigrip) in the 2016 northern hemisphere season and quadrivalent inactivated vaccines (Vaxigrip Tetra or FluQuadri) in the subsequent seasons. We used 0.5 ml sterile 0.9% normal saline solution for the placebo. Influenza vaccines were provided by Sanofi Pasteur who had no role in the design, conduct of the trial, analyses, or review of this manuscript.

The primary endpoint was the composite of all-cause death, AMI, or stent thrombosis at 12 months post-randomization. All endpoints were adjudicated by an independent event committee of experienced cardiologists who remained blinded to the trial group assignments. In this study we report effectiveness of early or late vaccination for the primary endpoint, all cause death, and cardiovascular (CV) death at 12 months post randomization.

We used descriptive statistics to summarize baseline characteristics according to randomized group. We considered early randomization (subsequently stated as vaccination) when vaccine/placebo was administered during September-November in the Northern Hemisphere or during May-July in the Southern Hemisphere. Similarly, if study participants were randomized during December-February in the Northern Hemisphere or August-September in the Southern Hemisphere, it was considered late vaccination in this study.

We estimated Hazard ratios (HR) and 95% confidence intervals (CIs) using a Cox proportional hazards model (checked visually), including early vs. late vaccination interaction term. The Kaplan–Meier method was applied to estimate cumulative incidences of endpoints at 12 months of randomization and early vs. late vaccinations. The lost to follow-up cases were censored on the day of randomization. Absolute differences and 95% CIs at 12 months were calculated using the Kaplan–Meier method and Greenwood standard errors. This was repeated for each of the three endpoints: primary endpoint, all-cause

Table 1
Baseline Characteristics of the Patients According to Early and Late vaccination.

Patient Characteristic	Statistic	Overall (n = 2532)	Early (n = 1188)	Late (n = 1344)	P-value
Randomised allocation					
Placebo	n (%)	1260 (49.8)	584 (49.2)	676 (50.3)	
Vaxigrip	n (%)	1272 (50.2)	604 (50.8)	668 (49.7)	0.567
Sex					
Male	n (%)	2070 (81.8)	941 (79.2)	1129 (84.0)	
Female	n (%)	462 (18.2)	247 (20.8)	215 (16.0)	0.0018
Age at randomization	N	2532	1188	1344	
	Mean (SD)	59.9 (11.2)	60.2 (11.3)	59.6 (11.1)	0.181
	Median (IQR)	60 (52, 67)	60 (53, 68)	60 (52, 67)	
	[min, max]	[21, 95]	[24, 95]	[21, 95]	
Body mass index	N	2408	1131	1277	
	Mean (SD)	27.5 (5.0)	27.7 (5.3)	27.3 (4.8)	0.041
	Median (IQR)	27 (24, 30)	27 (24, 30)	27 (24, 30)	
	[min, max]	[16, 65]	[17, 65]	[16, 53]	
Smoking					
Never smoked	n/N (%)	924/2454 (37.7)	448/1149 (39.0)	476/1305 (36.5)	
Former smoker	n/N (%)	660/2454 (26.9)	330/1149 (28.7)	330/1305 (25.3)	
Current smoker	n/N (%)	870/2454 (35.5)	371/1149 (32.3)	499/1305 (38.2)	0.0074
Medical History/Comorbidities					
Diabetes	n/N (%)	528/2507 (21.1)	275/1175 (23.4)	253/1332 (19.0)	0.0069
Hyperlipidemia	n/N (%)	836/2506 (33.4)	412/1174 (35.1)	424/1332 (31.8)	0.084
Hypertension	n/N (%)	1245/2502 (49.8)	590/1179 (50.0)	655/1323 (49.5)	0.790
Previous MI	n/N (%)	363/2502 (14.5)	165/1177 (14.0)	198/1325 (14.9)	0.512
Previous PCI	n/N (%)	267/2514 (10.6)	122/1181 (10.3)	145/1333 (10.9)	0.657
Previous CABG	n/N (%)	65/2515 (2.6)	37/1182 (3.1)	28/1333 (2.1)	0.104
Killip class $\geq$ 2	n/N (%)	95/2312 (4.1)	54/1086 (5.0)	41/1226 (3.3)	0.049
Left main coronary artery disease	n/N (%)	124/2495 (5.0)	52/1172 (4.4)	72/1323 (5.4)	0.249

Table 2
Study sites, Hemisphere, enrolment year, influenza season according to Early and Late vaccinated participants.

Patient Characteristic	Statistic	Overall (n = 2532)	Early (n = 1188)	Late (n = 1344)	P-value
Country					
Australia	n (%)	47 (1.9)	29 (2.4)	18 (1.3)	
Bangladesh	n (%)	620 (24.5)	296 (24.9)	324 (24.1)	
Czech Republic	n (%)	110 (4.3)	44 (3.7)	66 (4.9)	
Denmark	n (%)	572 (22.6)	250 (21.0)	322 (24.0)	
Latvia	n (%)	38 (1.5)	23 (1.9)	15 (1.1)	
Norway	n (%)	21 (0.8)	7 (0.6)	14 (1.0)	
Sweden	n (%)	965 (38.1)	483 (40.7)	482 (35.9)	
United Kingdom	n (%)	159 (6.3)	56 (4.7)	103 (7.7)	0.0006
Hemisphere					
Northern	n (%)	1865 (73.7)	863 (72.6)	1002 (74.6)	
Southern	n (%)	667 (26.3)	325 (27.4)	342 (25.4)	0.276
Enrolment year					
2016	n (%)	130 (5.1)	86 (7.2)	44 (3.3)	
2017	n (%)	517 (20.4)	259 (21.8)	258 (19.2)	
2018	n (%)	647 (25.6)	320 (26.9)	327 (24.3)	
2019	n (%)	1104 (43.6)	523 (44.0)	581 (43.2)	
2020	n (%)	134 (5.3)	0 (0.0)	134 (10.0)	<0.0001
Influenza season					
2016–17	n (%)	292 (11.5)	86 (7.2)	206 (15.3)	
2017–18	n (%)	598 (23.6)	259 (21.8)	339 (25.2)	
2018–19	n (%)	593 (23.4)	325 (27.4)	268 (19.9)	
2019–20	n (%)	1049 (41.4)	518 (43.6)	531 (39.5)	<0.0001

death and CV death. We also used the Kaplan–Meier method to obtain estimates and standard errors at one year and then used these to test homogeneity. A sensitivity analysis was conducted adjusting for age, sex, BMI, smoking status, diabetes comorbidity and country but did not alter the conclusions. All analyses were performed using Stata version 16.1 (StataCorp LLC, College Station, Texas, USA).

3. Results

Because of the COVID-19 pandemic, the data safety and monitoring board recommended that it would not be feasible for the trial to continue and recruitment in the trial was stopped in 2020 before reaching the prespecified sample size of 4400 participants. A total of 2571 patients consented to participate in the study and underwent randomization. Of them, 2532 (98.5%) received either vaccine (n = 1272) or placebo (n = 1260) and are included in the analysis for this study. Baseline characteristics with respect to early and late vaccination are listed in Table 1. Randomization during early and late seasons by study sites, hemispheres, enrollment years, and influenza seasons are also listed in Table 2.

In the early vaccinated group the primary composite endpoint occurred in 36 participants (6.0%) assigned to influenza vaccine and 49 (8.4%) assigned to placebo (HR 0.69; 95% CI 0.45 to 1.07) (Table 3, Fig. 1), compared to 31 participants (4.7%) assigned to influenza vaccine and 42 (6.2%) assigned to placebo (HR 0.74; 95% CI 0.47 to 1.18) in the late vaccinated group (P = 0.848 for interaction on HR scale at 1

Table 3
Primary and key secondary endpoints.

Endpoint	N	Number (%)[a] with event			Hazard Ratio[b] (95 % CI)		P_{int}	KM Risk Difference[c] (95 % CI)	P_{int}
		All	Vaccine	Placebo					
Primary Composite Endpoint									
Early	1,188	85 (7.2)	36 (6.0)	49 (8.4)	0.69	(0.45–1.07)		−2.4% (−5.4%, 0.5%)	
Late	1,344	73 (5.5)	31 (4.7)	42 (6.2)	0.74	(0.47–1.18)	0.848	−1.6% (−4.0%, 0.9%)	0.666
All Cause Death									
Early	1,188	58 (4.9)	20 (3.3)	38 (6.5)	0.50	(0.29–0.86)		−3.2% (−5.7%, −0.7%)	
Late	1,344	40 (3.0)	17 (2.6)	23 (3.4)	0.75	(0.40–1.40)	0.335	−0.9% (−2.7%, 1.0%)	0.136
CV Death									
Early	1,188	54 (4.6)	19 (3.2)	35 (6.0)	0.51	(0.29–0.90)		−2.8% (−5.2%, −0.5%)	
Late	1,344	36 (2.7)	15 (2.3)	21 (3.1)	0.72	(0.37–1.40)	0.440	−0.9% (−2.6%, 0.9%)	0.188

[a] percentages are cumulative Kaplan-Meier at 1 year; [b] hazard ratio (vaccine v placebo); [c] KM = Kaplan-Meier risk difference at 1 year (vaccine v placebo); N = total number of patients; P_{int} = interaction p-value;

Notes: Early = Sep-Nov N.Hemisphere/May-July S.Hemisphere; Late = Dec-Feb N.Hemisphere/Aug-Sept S.Hemisphere.

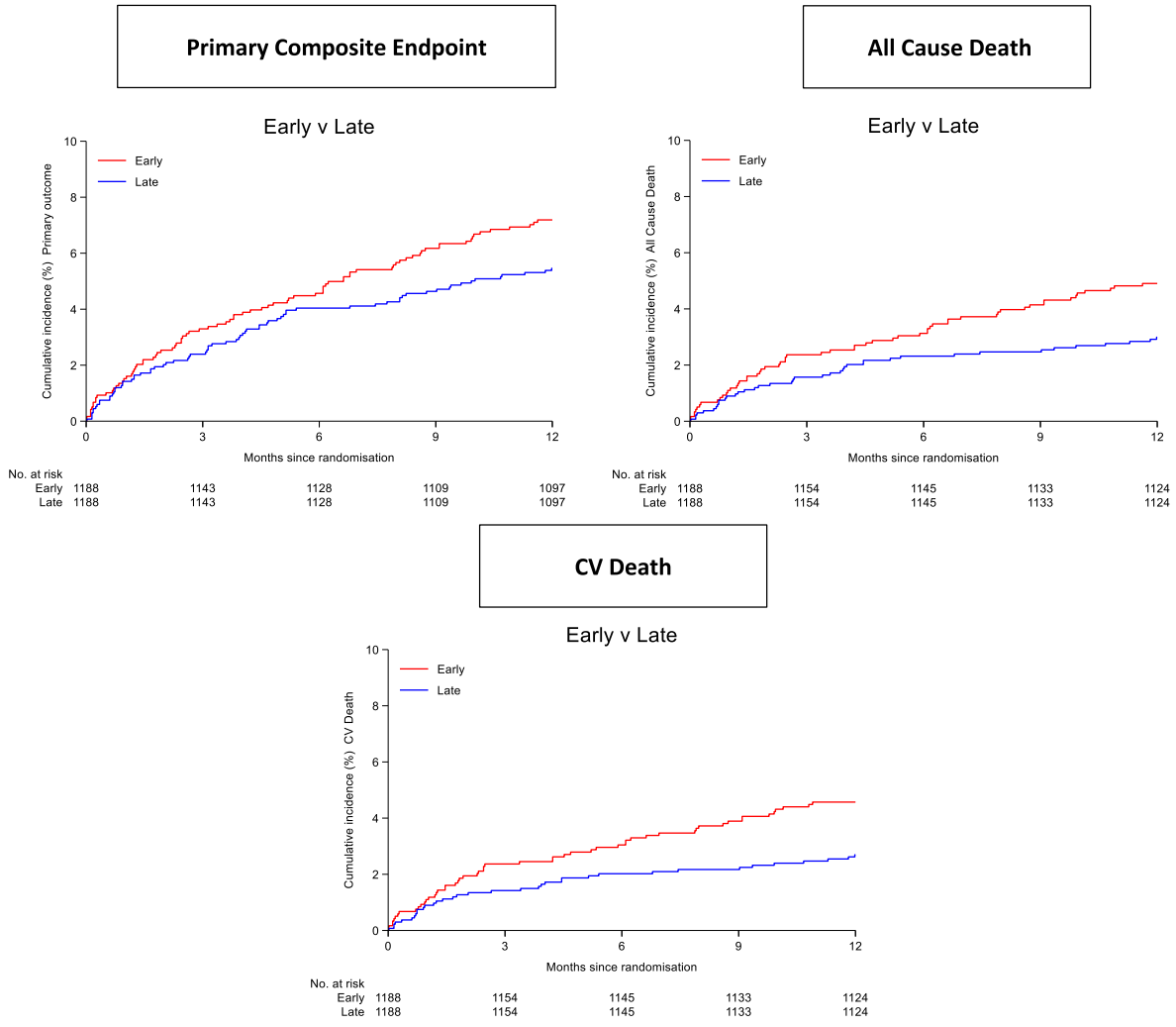

Fig. 1. Kaplan-Meier plots of early v late season vaccination for each of the 3 endpoints: primary endpoint, all-cause death, CV death. (Note that this is not adjusted for any confounding variables).

year). We observed similar estimates for the key secondary endpoints of all-cause death and CV death. There was no statistically significant difference in vaccine effectiveness against adverse cardiovascular events by timing of vaccination. The effect of vaccination on all-cause death at one year was more pronounced in the group receiving early vaccination (HR 0.50; 95% CI, 0.29 to 0.86) compared to late vaccination (HR 0.75; 95% CI 0.40 to 1.40), but there was no statistically significant difference between these groups (P = 0.335 for interaction on HR scale at 1 year).

The Kaplan-Meier risk differences of early vs. late vaccination at 1-year (Table 3) for the primary endpoint (−2.4%, 95% CI −5.4% to 0.5% vs. −1.6%, 95% CI −4.0% to 0.9%; interaction P = 0.666), all cause death (−3.2%, 95% CI −5.7% to −0.7% vs. −1.6%, 95% CI −2.7%

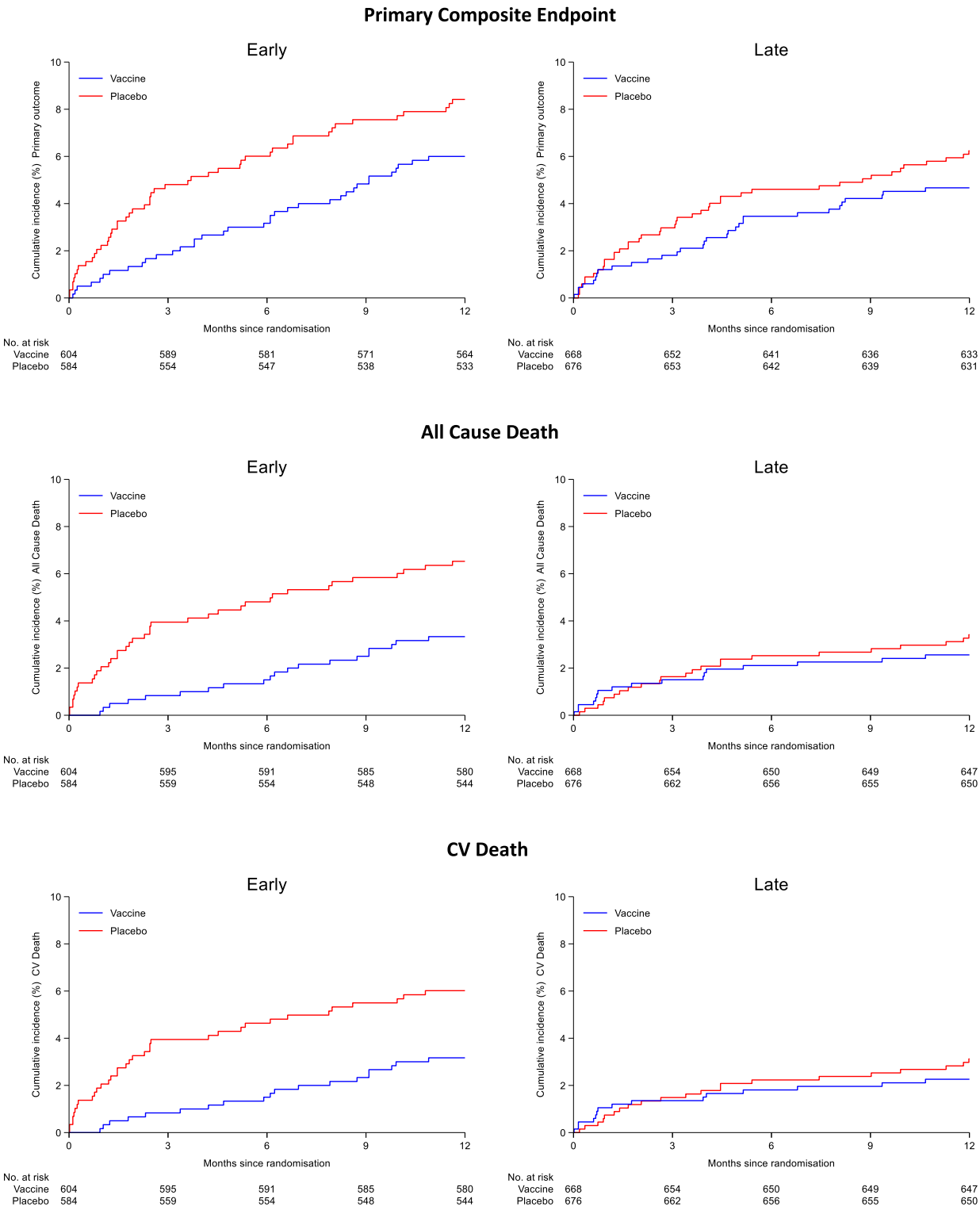

Fig. 2. Kaplan-Meier event curves of the influenza vaccine and placebo groups in patients vaccinated early (left panels) and late (right panels) for the primary composite endpoint of all-cause death, myocardial infarction, or stent thrombosis in a time-to-event analysis (A); for all-cause death (B); and for cardiovascular death (C).

to 1.0%; interaction P = 0.136) and CV death (−2.8%, 95% CI −5.2% to −0.5% vs. −0.9%, 95% CI −2.6% to 0.9%; interaction P = 0.188) are also illustrated in Fig. 2.

4. Discussion

In this substudy from the IAMI trial we found no significant differences in vaccine effectiveness with early influenza season vaccination compared to late vaccination in prevention of cardiovascular events.

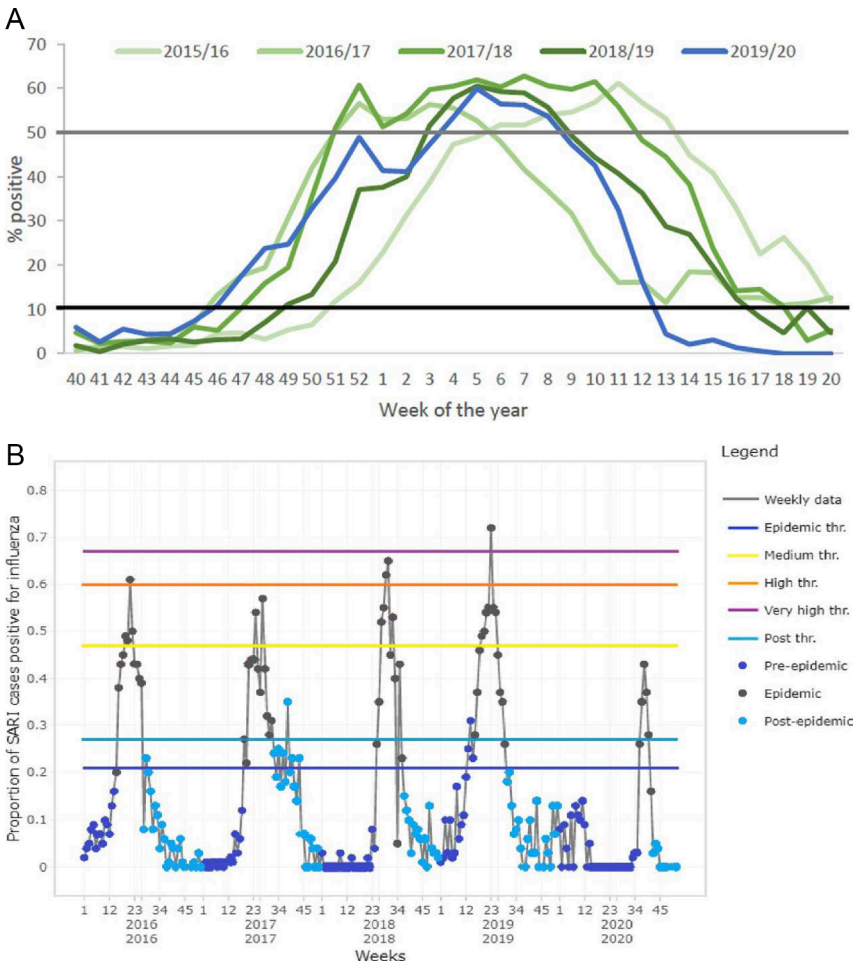

Fig. 3. A. Weekly proportion of sentinel specimens positive for influenza virus by season and week of reporting, EU/EEA [19] 2015/16–2019/2020 B. Time series of influenza epidemic, the epidemic periods modelled for season 2016–2020 in Bangladesh [20].

Despite the non-significant findings we found an inclination towards more events and better vaccine effectiveness in early season.

The study started earlier in northern hemisphere sites, which were all European, and roughly 75% of patients were enrolled here. Patients in the southern hemisphere were primarily enrolled in the last study season (2019) and predominately in Bangladesh. In Europe, influenza seasons peaked early in all but the last season (Fig. 3A) [19] and in Bangladesh the 2019 season also peaked early (Fig. 3B) [20]. Thus, our findings indicate some co-variation between peak influenza season and vaccine effectiveness but, importantly, influenza vaccination had an overall statistically significant effect on clinical outcomes in the IAMI trial and seasonality was unlikely to be critical. Furthermore, inclusion of periods when influenza circulation was not circulating may have attenuated the apparent benefits of vaccination.

Another possible explanation for observed non-significant differences may be attributed to influenza vaccine effectiveness against circulating strains. In Europe, vaccine effectiveness was 23–47% in 2016/17, 25–52% in 2017/18, 32–43% in 2018/19 and 29–61% in the 2019/20 season[21–24]. The corresponding vaccine effectiveness numbers concerning the primary endpoint in IAMI was 28% (HR 0.72 [95% CI, 0.52–0.99]; P = 0.040) [7]. Australia had few enrollments and in Bangladesh routine influenza vaccination is not implemented, so vaccine effectiveness estimates were not done [25,26].

Intra-seasonal waning of influenza vaccination is another variable which may have affected our findings. Findings in the USA from 2010/11 to 2015/16 documented that delaying vaccination into the season derived beneficial effects in population primarily among individuals ≥ 65 years of age [27]. In another study, reporting the 2012/13 season, the authors suggested not to change current vaccine recommendations because of corollaries of delayed vaccination depending heavily on influenza season timing and rate of waning [28]. A more recent study from Australia discusses the fact that primary care practitioners vaccinate at the same time each year, and delaying vaccination outside of routine vaccination times may result in forgotten or missed, which would offset any gains of delayed vaccination [14].

Because of the significant differences between groups in the IAMI trial showing beneficial effects of influenza vaccination on cardiovascular outcomes it is possible that influenza vaccination early after AMI induces a pleiotropic effect by antibodies interfering with the pathophysiology of atherosclerosis and resulting in an atheroprotective effect [29]. However, blood samples were not collected in IAMI and such possible effects remain hypothetical although the Fig. 2 (b) & (c) plots are are supportive of the hypothesis that there might be a true difference in efficacy, but this requires a larger body of evidence to be confirmed.

This study has a number of limitations. This sub-group analysis of the IAMI Trial was not included in the statistical analysis plan but was an exploratory post-hoc analysis. As such, the study was not powered to determine the benefits of early or late influenza vaccination in lowering the risk of adverse cardiovascular events at one year. Although study was underpowered and our findings are not statistically significant, they suggest further research with a well powered sample size is warranted to study the efficacy between early vaccination and late vaccination into the season. Vaccine effectiveness concerning influenza illness likely varied not only on regional but also on a national level and this could not

be addressed in a relatively small study as IAMI. Also, enrollment was not distributed equally across study sites and influenza seasons.

In conclusion, we did not find significant differences in vaccine effectiveness between early or late season vaccination in IAMI. Since placebo-controlled trials in this area are unlikely to be conducted in the future, any possible inclination towards more events and better vaccine effectiveness in early season will need to be explored using observational data. Following the publication of IAMI's primary outcomes, and in part due to these results, guidelines for post-AMI influenza vaccination have been revised. The European Society of Cardiology (ESC) now assigns it a Level of Evidence 1A [30]. Consequently, influenza vaccination during the influenza season is strongly recommended for patients with cardiovascular disease, without consideration of timing.

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These information regarding the trial has been published elsewhere and not relevant to this study findings.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr Fröbert reports grants from Sanofi Pasteur, during the conduct of the study. Dr Engstrøm reports personal fees from Abbott, Bayer, and Novo Nordisk, outside the submitted work. Dr Götberg reports personal fees from Boston Scientific, Medtronic, and Abbott, outside the submitted work. Dr MacIntyre reports grants from Sanofi, outside the submitted work. Dr Persson reports personal fees from Abbot, grants from Abbott, outside the submitted work. All other authors declare no competing interests.

Data availability

Requests for data collected for the study can be made to the principal investigator of the IAMI trial and will be considered by the steering group on an individual basis. A contract should be signed.

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