Effect of High Influenza Activity on Risk of Ventricular Arrhythmias Requiring Therapy in Patients With Implantable Cardiac Defibrillators and Cardiac Resynchronization Therapy Defibrillators

Mohammad Madjid, MD, MS[a,*], Allison T. Connolly, PhD[b], Yelena Nabutovsky, MS[b], Payam Safavi-Naeini, MD[c], Mehdi Razavi, MD[c], and Charles C. Miller, PhD[d]

Influenza is associated with an increased risk of cardiovascular events. Influenza's association with ventricular arrhythmias (VAs) has not been adequately studied. We investigated the relation of seasonal influenza activity with the incidence of VAs requiring therapy in patients with an implantable cardiac defibrillator or cardiac resynchronization therapy defibrillator. We retrospectively studied 163,831 patients with an implantable cardiac defibrillator or cardiac resynchronization therapy defibrillator who were enrolled in the Abbott Medical Merlin.net remote-monitoring network between January 2009 and December 2015. We used cross-correlation to assess the temporal relationship between influenza activity and the incidence of VAs requiring shock or antitachycardia pacing (ATP). We used a generalized linear model to test the possible effect of seasonal influenza activity on the occurrence of VAs requiring shock or ATP treatment, after adjustment for within-patient effects, age, gender, device type, and calendar year. We found a significant correlation between influenza activity and the incidence of VAs requiring shock or ATP treatment. The multivariate generalized linear model showed that during high influenza activity, patients were more likely to have a VA treated with shock (odds ratio = 1.06, $p < 0.001$) or ATP (odds ratio = 1.06, $p < 0.0001$). The impact of high influenza activity was most prominent during the years 2014 and 2015. We conclude that high influenza activity is associated with increased risk of VAs requiring therapy. **(Am J Cardiol 2019;124:44−50)**

Seasonal influenza poses a major burden on public health. Traditionally, this burden has been assessed in terms of morbidity and mortality due to influenza-associated pneumonia, but emerging data suggest that the burden of influenza is much greater because the disease exacerbates underlying chronic conditions, such as cardiovascular disease (CVD).[1,2] Influenza is an important trigger for cardiac hospitalization, acute coronary syndrome, myocardial infarction, sudden cardiac death, ischemic cardiac death, and cerebrovascular events.[1−3] Influenza can increase cardiovascular risk by inducing a robust inflammatory response.[4] Moreover, influenza vaccination can reduce the incidence of cardiovascular events.[5−7] The effect of influenza on atherosclerosis is well established, but influenza's effect on cardiac arrhythmias has received less attention. In the present study, we examined the effect of influenza on the risk of ventricular arrhythmias (VAs).

Methods

This retrospective observational study included US patients aged 18 to 89 years old who had an implantable cardiac defibrillator (ICD) or cardiac resynchronization therapy defibrillator (CRT-D) (Abbott, Chicago, Illinois) implanted after January 2008. All patients were enrolled in the Merlin.net Patient Care Network, Abbott's remote-monitoring system for implanted cardiac devices[8,9] for at least 6 months between January 2009 and December 2015. Patients were entered into the study when they underwent their first remote evaluation and remained in the study until the day of device deactivation, explantation, or replacement, or until the end of the study period in December 2015. Data from the remote-monitoring system were deidentified before analysis. Remote-monitoring data were linked to Abbott device implantation records containing basic demographic data, including age at implantation, gender, device model, and the first 3 digits of the patient's zip code. This study complies with the Declaration of Helsinki; the University of Texas Health Science Center (UTHealth) at Houston Institutional Review Board reviewed and approved this study. Informed consent was waived because the study was retrospective.

The follow-up data in the Merlin.net remote-monitoring database included programming and therapy information on every device-detected arrhythmia episode. The bedside unit, Merlin@Home, communicated wirelessly with the patient's implanted device at regular intervals and did not

[a]Department of Medicine, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, Texas; [b]Abbott, Sunnyvale, California; [c]Electrophysiology Clinical Research and Innovations, Texas Heart Institute, Houston, Texas; and [d]Department of Cardiothoracic and Vascular Surgery, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, Texas. Manuscript received January 10, 2019; revised manuscript received and accepted April 1, 2019.

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*Corresponding author: Tel: (713) 500-6590; fax: (713) 500-6556.
E-mail address: mmadjid@gmail.com (M. Madjid).

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require patient engagement. Episodes were included in the analysis if the device identified the episode as ventricular tachycardia (VT) or ventricular fibrillation (VF) and treated it with antitachycardia pacing (ATP) or shock. Episodes were excluded if they were categorized as supraventricular tachycardia or as VT or VF episodes that did not result in device therapy. The episodes were not adjudicated, so the appropriateness of therapy could not be determined. The date of therapy delivery was determined from the episode logs. Episode data were converted into a binary variable indicating the presence or absence of a treated VA during each week for each patient. This analysis was done separately for VA episodes treated with ATP only and for VA episodes treated with at least 1 shock.

For this study, "influenza activity" was defined as the percentage of respiratory specimens that tested positive for influenza virus during each influenza season. We obtained US influenza activity data for January 2009 through December 2015 from open-source databases provided by the Centers for Disease Control and Prevention.[10] These data were reported on a weekly basis for both the entire country and the 10 Health and Human Services regions. We then assessed the influenza activity level for each week of the study period and compared the weekly-reported influenza activity to the annual mean-reported influenza activity for the respective year. The thresholds used for different influenza activity levels were based on the annual mean and SD of the national influenza activity data. The activity levels were defined as follows: low activity (percentage less than the mean for the season), moderate activity (percentage exceeding the mean but less than the mean + 1 SD for the season), and high activity (percentage exceeding the mean + 1 SD for the season).

For plotting purposes, the percentage of enrolled patients who had a VA treated with therapy was smoothed by applying a moving average filter. The odds of having a VA treated with shock or a VA treated with ATP were calculated by using a generalized linear model with a binomial distribution, logit link function, autoregressive error structure, and random subject effect. A generalized estimating equation was used to account for within-patient correlations. The model covariates included influenza activity level, age, gender, device type, and calendar year. In a subgroup analysis, data were partitioned according to gender, device type, age group (<65, 65−74, ≥75 years), and calendar year.

A cross-correlation analysis with a lag from −26 weeks to +26 weeks was used to study the relation between the Health and Human Services region-specific percentage of influenza-positive specimens and the percentage of enrolled patients each week who had a VA requiring therapy. Cross-correlation analysis was performed for the years of study data when an effect of year trended toward significance in the subgroup analysis. The 95% significance threshold for the correlation was calculated as $\pm 1.96/\sqrt{N-3}$, where N was the number of samples used for the calculation at a given lag. For all tests, a significance level of 0.05 was used. All computations were performed with RStudio version 1.0.136 (RStudio, Boston, Massachusetts) with R version 3.2.2 or SAS Software version 9.4 (SAS Institute, Inc., Cary, North Carolina).

The study was suggested and designed by the principal investigator. Abbott Inc. reviewed the proposal and agreed to provide the dataset analysis. The analysis plan and statistical approach were designed and planned by UTHealth investigators and were implemented by Abbott staff. Abbott Inc. kept exclusive possession of the data throughout the study. The manuscript was written with contributions from all of the authors. No funds were provided for this study from any side.

Results

We reviewed the records from 193,455 patients who had an ICD or CRT-D device and were enrolled in the Merlin.net remote-monitoring network; of these patients, 163,831 (Table 1) met the inclusion criteria for our study (Figure 1). During the study period (January 2009 to December 2015), 3,653,822 device-detected episodes occurred; of these episodes, 1,356,645 were VAs. The number of VA episodes requiring therapy was 583,600 (ATP only = 504,695; shock = 78,905).

National and region-specific influenza data showed seasonal variations; years 2011 to 2015 had peaks between December and February, but years 2009 to 2010 had multiple peaks, and the influenza activity was spread over a longer period of time (Figure 2). Over the study period (2009 to 2015), the national incidence of VAs treated with shock or with ATP declined, with some annual modulations (Figure 2). The effect of influenza activity on the incidence of VAs requiring therapy became more prominent over the last 3 years of the study (2013 to 2015) (Figure 2).

The multivariate model (Table 2) showed that the incidence of VAs requiring shock therapy was slightly elevated during periods of moderate influenza activity; the risk was further elevated during periods of high influenza activity. Similarly, the incidence of VAs treated with ATP was significantly higher during periods of both moderate and high influenza activity. This analysis also showed that age, gender, device type, and calendar year had statistically significant effects on the odds of a VA occurring that required therapy, independent of influenza activity.

The effect of high influenza activity on various patient subgroups is illustrated in Figure 3. The observed effect was similar in male and female patients. During periods of high influenza activity, the incidence of shocks and the incidence of ATP were significantly higher in patients

Table 1
Baseline characteristics of the study cohort

Variable	All patients (n = 163,831)
Age (years)	67.4 ± 12.2 (18−89)
Men	119,118 (72.7%)
Follow-up (years)	3.03 ± 1.77
Device type	
Cardiac resynchronization therapy defibrillator	75,603 (46.1%)
Implantable cardioverter defibrillator (dual-chamber)	55,578 (33.9%)
Implantable cardioverter defibrillator (single-chamber)	32,680 (19.9%)

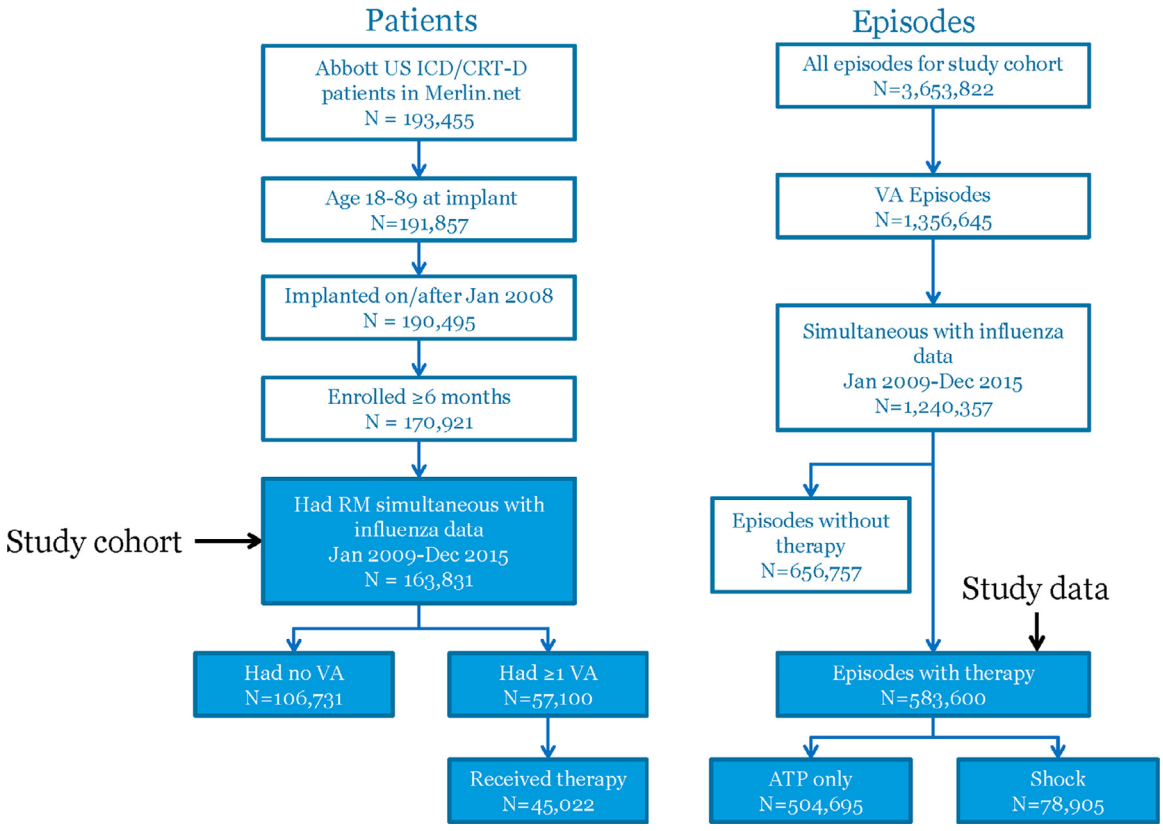

Figure 1. Schematic showing the data selection process for the patients (*left*) and arrhythmia episodes (*right*).
ATP = antitachycardia pacing; CRT-D = cardiac resynchronization therapy defibrillator; ICD = implantable cardioverter defibrillator; RM = remote monitoring; VA = ventricular arrhythmia.

with an ICD, whereas this effect was limited to the incidence of ATP in patients with a CRT-D. Across all age groups, the odds of either shock or ATP therapy were higher during high influenza activity. When the data were analyzed by individual calendar year, the effect of influenza activity on the incidence of VAs requiring therapy was found to be significant only during the later years (2014 and 2015) of the study period. In 2013, this effect trended toward but did not reach significance for VAs requiring ATP ($p = 0.099$).

The possibility of a time lag between influenza activity and the occurrence of VAs requiring therapy was investigated by introducing a variable lag in the data. Over the last 3 years of the study (2013 to 2015), the maximum correlation between regional influenza activity and the incidence of shock was found to occur at a 3-week lag, indicating that influenza activity preceded the shock therapy (max correlation coefficient $r = 0.106$ at lag -3 weeks, $p < 0.001$) (Figure 4). However, the maximum correlation between regional influenza activity and the incidence of ATP was found to occur at a lag of 0, indicating that influenza activity coincided in time with the highest incidence of ATP (max $r = 0.117$ at lag 0 weeks, $p < 0.001$).

Discussion

In this large cohort of patients with an ICD or CRT-D, we found that periods of high influenza activity were associated with an elevated risk of device-detected VAs requiring shock or ATP therapy. This elevated risk was seen in all patients, although the effect size was larger in the years 2014 and 2015. The odds of having a VA requiring treatment were higher during periods of high influenza activity than during periods of moderate influenza activity. This effect of influenza activity is clinically important because ICD shocks can have adverse consequences that negatively affect quality of life, and they are associated with higher mortality.[11,12]

Our findings are in line with those of our previous studies, which showed that cardiovascular events increase during peak seasonal influenza activity.[1] Influenza can affect the cardiovascular system and trigger arrhythmias through multiple mechanisms. We have shown that influenza infection can lead to a severe systemic, arterial, and myocardial inflammatory reaction.

Moreover, influenza is known to exacerbate congestive heart failure (CHF) and increase CHF-related hospital admissions.[13] Severe CHF is the underlying indication for ICD or CRT-D implantation in a large proportion of patients who receive one, and CHF exacerbation can further destabilize these patients, potentially leading to shock or ATP therapy. In patients with underlying ischemic cardiomyopathy, the worsening of ischemia, increased oxygen demand, and triggering of potential acute coronary syndrome by influenza can lead to more frequent arrhythmia events.

We found that the relation between influenza activity and device-detected VAs requiring therapy was strongest

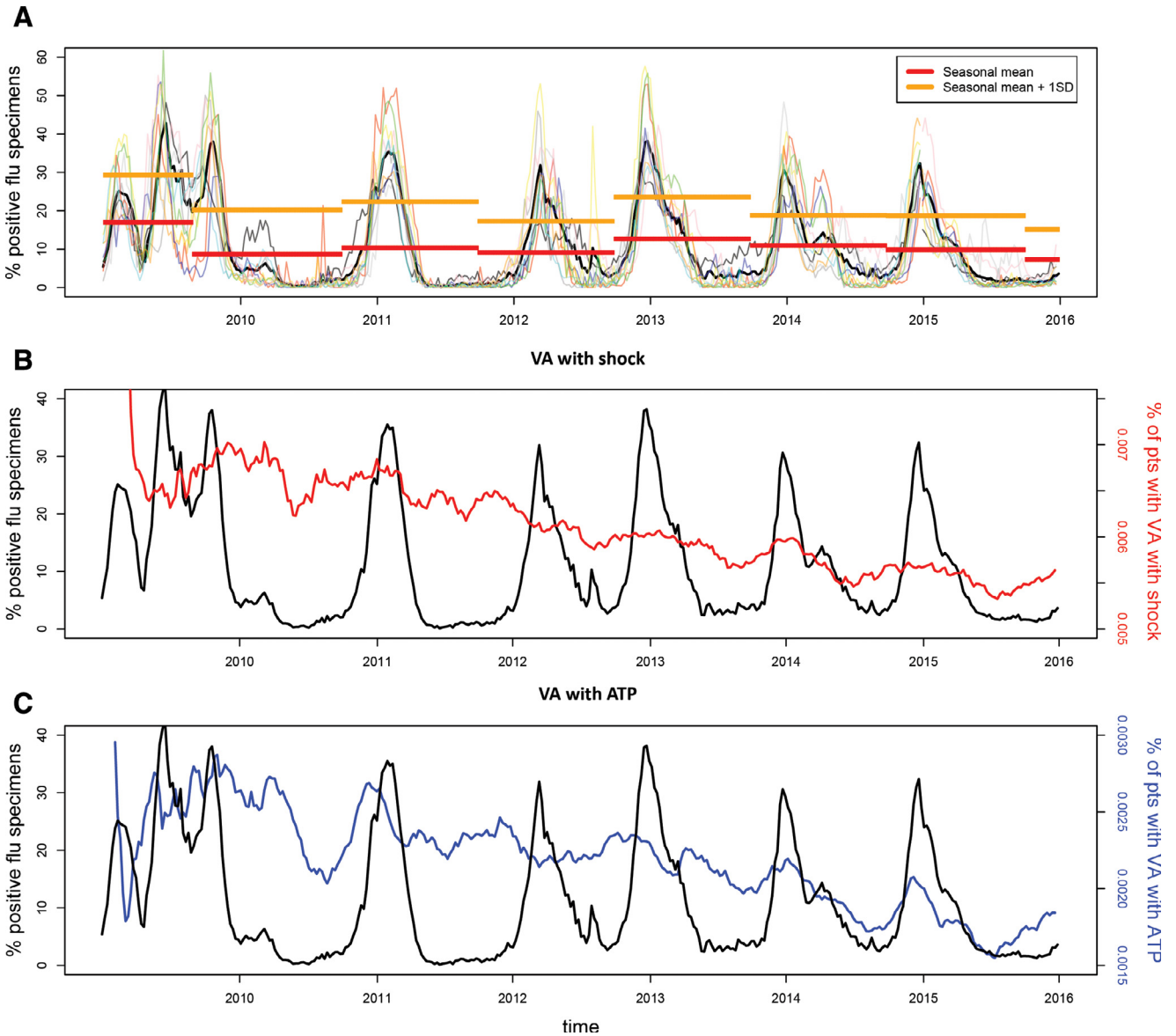

Figure 2. Annual variations in the incidence of ventricular arrhythmia (VA) with shock, VA with antitachycardia pacing (ATP), and influenza activity. (*A*) National percentage of influenza-positive specimens (*black line*) over the study period. The Health and Human Services region-specific percentages of influenza-positive specimens are shown as thin colored lines, and the influenza activity thresholds are shown as thick horizontal red and orange lines. (*B*) Percentage of enrolled patients having a VA with shock (*red line*) overlaid on the national influenza activity data (black line). (*C*) Percentage of enrolled patients having a VA with ATP (*blue line*) overlaid on the national influenza activity data (*black line*). VA with ATP and VA with shock traces were smoothed with a moving average filter.
SD = standard deviation.

during the last few years of the study period. There are 2 possible confluent reasons for this finding. First, we observed that the absolute number of VAs requiring therapy declined over the 6-year study period. This trend is probably related to the development of better algorithms for discriminating between supraventricular arrhythmias and VAs, new programming strategies that detect arrhythmias at higher cutoff rates and delay intervention, and the use of ATP to reduce the number of inappropriate and unnecessary shocks.[14] If so, the device therapies in the later years of the study would be more likely associated with true VT or VF. The second factor is the effect of the H1N1 influenza epidemic of 2009 to 2010 and subsequent years. The H1N1 influenza epidemic not only primarily affected younger individuals (a population with a lower prevalence of having an ICD or CRT-D), but it also happened in an off-cycle pattern that differed from the typical influenza season.

Our study has potential limitations. This was a retrospective study and subject to the inherent shortcomings typical of such studies. The Merlin.net database is primarily designed for managing patients with an ICD or CRT-D. Although it provides a unique and unrivalled opportunity for research, it is not designed to contain data on all of a patient's baseline characteristics (such as the indication for ICD or CRT-D implantation and the associated co-morbidities, risk factors, and medical therapies). In our heterogenous group of

Table 2
Generalized linear model of the factors affecting the incidence of ventricular arrhythmias requiring shock or antitachycardia pacing in patients with an ICD or CRT-D

Parameter	Shock			Antitachycardia pacing		
	OR	95% CI	p Value	OR	95% CI	p Value
Moderate influenza activity*	1.04	1.01−1.07	0.0039	1.05	1.03−1.07	<0.0001
High influenza activity*	1.06	1.03−1.09	<0.0001	1.06	1.04−1.08	<0.0001
Age (decades)	0.99	0.99−0.99	<0.0001	0.99	0.99−0.99	<0.0001
Female (vs Male)	1.47	1.41−1.54	<0.0001	1.50	1.44−1.56	<0.0001
ICD (vs CRT-D)						
Single-chamber	0.89	0.84−0.93	<0.0001	0.96	0.92−1.00	0.0765
Dual-chamber	1.25	1.20−1.30	<0.0001	1.38	1.34−1.43	<0.0001
Calendar year	0.96	0.95−0.96	<0.0001	0.98	0.97−0.98	<0.0001

CI = confidence interval; CRT-D = cardiac resynchronization therapy defibrillator; ICD = implantable cardiac defibrillator; OR = odds ratio.
* Reference = low influenza activity.

patients, there could have been specific subsets of patients with different basic and clinical characteristics and varying degrees of disease severity that responded differently to influenza. Combining all different subgroups in a single study probably dilutes the observed effect size.

Device-detected arrhythmia episodes were labeled as supraventricular or ventricular in origin by the device, but it was not possible to adjudicate the episodes to individual patients because of the study's large sample size. Because this was a retrospective analysis, the multiplicity of

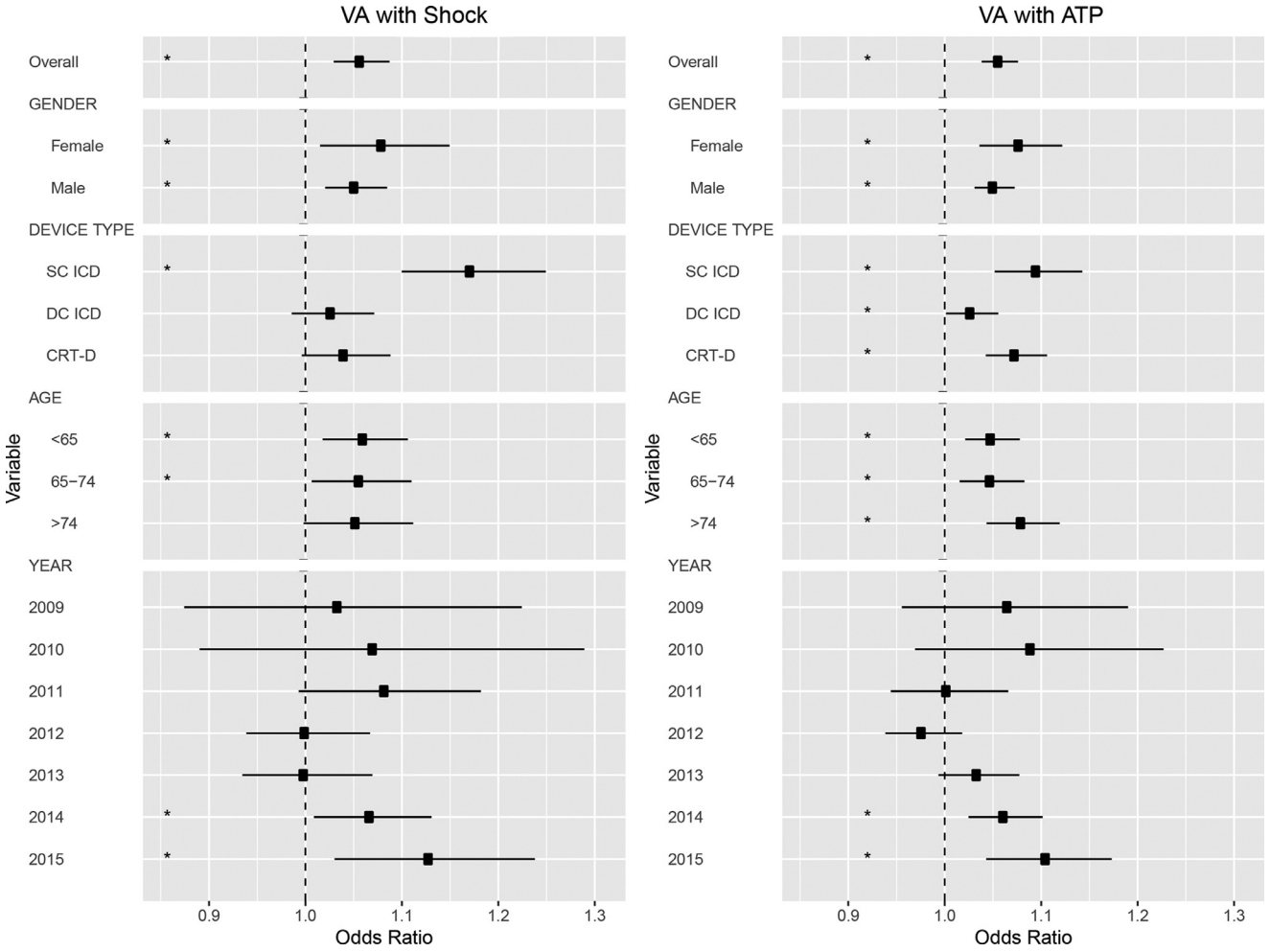

Figure 3. Effect of high influenza activity on the incidence of ventricular arrhythmia (VA) requiring therapy in different subgroups. Plots show the odds ratios (*circles*) and 95% confidence intervals (*horizontal bars*) for the incidence of VA requiring shock (*left*) or antitachycardia pacing (ATP; *right*) treatment during periods of high influenza activity for various patient subgroups. Asterisks (*) denote statistical significance, $\alpha < 0.05$.
CRT-D = cardiac resynchronization therapy; DC = dual-chamber; ICD = implantable cardioverter defibrillator; SC = single-chamber.

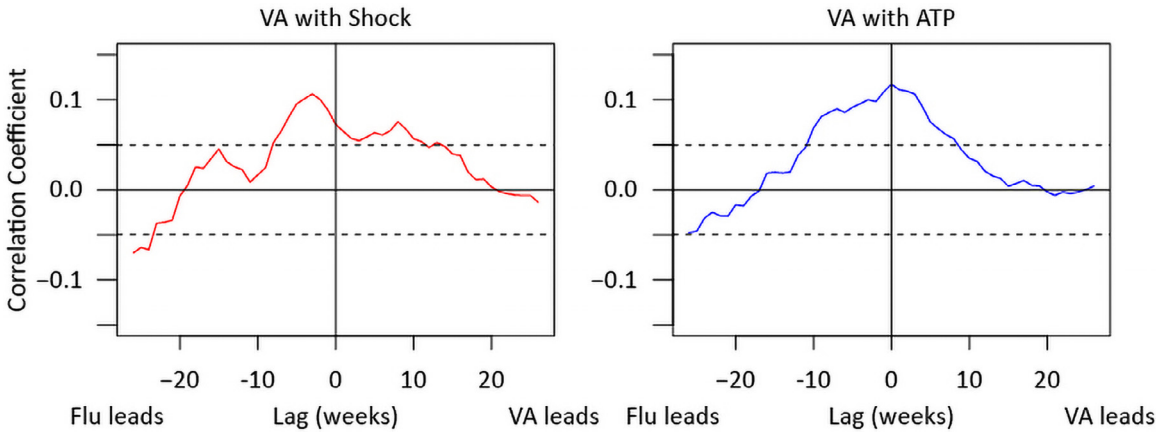

Figure 4. Cross-correlation between regional influenza activity and incidence of ventricular arrhythmia (VA) requiring therapy. Cross-correlation between regional influenza and VA with shock (*left*) and VA with antitachycardia pacing (ATP; *right*) for January 2013 through December 2015 with lags of −26 to 26 weeks. Dashed lines: 95% confidence limits.

programming parameters could not be controlled for. Therefore, we cannot claim with 100% certainty that the database contains accurately detected rhythms, that the therapy for each case was appropriate, or that using different programming strategies would not have affected the results. In addition, the database was not designed to contain information about the patients' medical therapies or the adequacy of their treatment.

Furthermore, in our study, we used influenza activity levels in general population; we could not feasibly adjudicate the 163,831 individual patients' status. Therefore, the influenza activity levels used in the study represent the intensity of environmental exposure, rather than a direct measurement of infection rates in study participants. Moreover, we would expect about half of the patients to be vaccinated against influenza, which would have diluted influenza's effect and led to further underestimation of it in this study.

This single retrospective study shows an association between influenza and VAs, but it should be noted that no single study can prove a cause-and-effect relation. Previously, we have discussed in detail the various aspects of the relation between influenza and CVD and the epidemiological criteria that need to be met to prove such a relation.[15]

Our studies and data from the Centers for Disease Control and Prevention suggest that overall, only approximately 55% of patients with CVD receive the influenza vaccine in most years.[16] A small study by Singh et al[17] showed a trend toward more ICD therapies during influenza season in patients who did not receive an influenza vaccine than in those who did. Therefore, every effort should be made to optimize the vaccination rate in high-risk cardiac patients per national guidelines.

In conclusion, high influenza activity may contribute to an increased risk of VAs requiring shock or ATP therapy in patients with an ICD or CRT-D. These findings parallel those of previous studies showing that influenza can trigger acute coronary syndrome. This proof-of-concept study suggests a need for further studies to investigate the possible role of influenza in increasing the incidence of cardiac arrhythmia.

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