Influenza Vaccination in Patients with Chronic Heart Failure: The PARADIGM-HF Trial

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ABSTRACT

Background Influenza is associated with an increased risk for cardiovascular events in patients with heart failure.

Objectives To examine the prevalence and predictors of influenza vaccination among participants in the PARADIGM-HF study and to investigate associations between receiving influenza vaccine and cardiovascular death or heart failure hospitalizations, all-cause hospitalizations, and cardiopulmonary or influenza-related hospitalizations.

Methods We utilized data from the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, in which patients with heart failure were randomized to the angiotensin receptor-neprilysin inhibitor LCZ696 (sacubitril/valsartan) or enalapril. We assessed predictors of receiving influenza vaccination, and assessed the relationship between influenza vaccination and outcomes in a propensity-adjusted model.

Results Out of 8099 study participants, 1769 (21%) received influenza vaccination. We observed significant regional variation in vaccination rates, with highest rates in the Netherlands (77.5%), Great Britain (77.2%), and Belgium (67.5%) and lowest rates in Asia (2.6%), with intermediate rates in North America (52.8%). Top predictors of vaccination included enrolling country, white race, implanted defibrillator, older age, lower New York Heart Association functional class, lower heart rate, and a history of diabetes mellitus. Influenza vaccination was associated with a reduced risk for all-cause mortality in propensity adjusted (HR 0.81, 95% CI [0.67, 0.97, p=0.015) models.

Conclusions Influenza vaccination rates varied widely in patients with heart failure with reduced ejection fraction enrolled in the PARADIGM-HF trial, and vaccination was associated with reduced risk for death, although whether this association was causal cannot be determined.

Key words: Chronic heart failure, influenza vaccination, clinical trial

ABBREVIATIONS

NYHA FC = New York Heart Association Functional Class

ARNI = angiotensin receptor neprilysin inhibitor

ACEi = angiotensin converting enzyme inhibitor

ARB = angiotensin receptor blocker

eGFR = estimated glomerular filtration rate

BMI = body mass index

ICD = implantable cardioverter defibrillator

CRT = cardiac resynchronization therapy

INTRODUCTION

Influenza infection can be devastating for patients with cardiovascular disease, and leads to significant morbidity and mortality each year.[1-4] Influenza vaccination is recommended annually for patients with cardiovascular disease by both the Centers for Disease Control and Prevention, the American Heart Association, and the European Center for Disease Prevention and Control.[5,6] A meta-analysis of randomized, controlled studies has shown that receiving influenza vaccination reduced the risk for major adverse cardiovascular events in patients with coronary artery disease compared to no vaccination.[7]

Although widely recognized as beneficial, vaccination rates in patients with heart failure vary widely in the United States and across the world.[8] Heart failure patients are especially susceptible to influenza-related complications including acute heart failure exacerbations and secondary infections such as pneumonia, both of which increase hospitalizations.[4,9]

The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial[10] enrolled patients with symptomatic heart failure with reduced ejection fraction and randomly allocated them to receive the angiotensin receptor neprilysin inhibitor LCZ696 (sacubitril/valsartan) or enalapril. At the time of enrollment, participants were queried about receipt of influenza vaccination in the past 12 months. We utilized data from PARADIGM-HF to assess prevalence of and baseline factors associated with influenza vaccination, as well as outcomes in those who did and did not receive influenza vaccination. We hypothesized that influenza vaccination would be associated with reduced risk for hospitalizations and mortality in patients with heart failure after propensity adjustment.

METHODS

Study Design and Patient Selection

PARADIGM-HF was a double blind, randomized, active controlled trial designed to assess the impact of the angiotensin receptor neprilysin inhibitor LCZ696 (sacubitril/valsartan) compared with enalapril on cardiovascular mortality and heart failure hospitalizations in patients with LVEF ≤ 40% and New York Heart Association (NYHA) Functional Class II-IV HF. Eligible subjects had elevated natriuretic peptide levels and were treated with stable doses of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) and beta adrenergic receptor blockers for at least 4 weeks prior to trial enrollment. Patients with symptomatic hypotension, estimated glomerular filtration rate (eGFR) less than 30 ml/min/1.73m^2, potassium concentration > 5.2 mmol/L at screening, or history of angioedema were excluded. The study design and detailed inclusion and exclusion criteria have been previously reported.[11]

Participants underwent two back-to-back single blind run-in phases with enalapril at a dose of at least 10mg twice daily for 2 weeks, followed by LCZ696 (sacubitril/valsartan), first dosed at 100mg twice daily, then 200mg twice daily for 4-6 weeks. Participants were then randomized to receive enalapril 10mg twice daily or LCZ696 (sacubitril/valsartan) 200mg twice daily. Participants were followed for a median duration of 27 months. Participants were asked if they received the seasonal influenza vaccine during the previous 12 months, and this information was recorded in the case report form. Cardiopulmonary and influenza-related hospitalizations were captured through investigator reporting of cause of hospitalization on the case report form. The protocol was approved at each participating site by an ethics committee or institutional review board. All participants provided written informed consent in accordance with established guidelines for the protection of human subjects.

Statistical Analyses

In order to identify potential differences, baseline characteristics were compared between participants who received influenza vaccination and those who did not. Between-group assessments were performed using t-tests for continuous variables, and chi-square or Fisher's exact tests, as appropriate, for categorical variables. Logistic regression models were used to examine associations between baseline characteristics and receipt of influenza vaccination, adjusting for treatment assignment and the following covariates: age, sex, race, country, body mass index, ejection fraction, eGFR, New York Heart Association functional class, history of diabetes mellitus, myocardial infarction, respiratory disease, and use of ACE inhibitors or ARBs, beta adrenergic blockers, mineralocorticoid receptor antagonists, and diuretics at screening. A propensity score was created for receipt of influenza vaccination based on the logistic regression model. For the analysis of multivariable predictors of vaccination, country was included as a continuous covariate, represented by the observed overall vaccination rate of each participant's home country, rather than country on its own. As an exploratory analysis, we utilized each country's per-capita gross domestic product (GDP) as a continuous variable in the multivariable model. Cox proportional hazards models were constructed to investigate associations of influenza vaccination with the risk for all-cause mortality, cardiovascular death or heart failure hospitalization, all-cause hospitalizations, and cardiopulmonary or influenza-related hospitalizations, unadjusted as well as in propensity-matched models. The propensity models were implemented by creating 100 equally sized groups of patients based on their estimated propensity for having received influenza vaccination, as described above. These groups were subsequently used as a stratification factor in the Cox model, so that the reported hazard refers to the comparison of vaccinated and unvaccinated patients within the same propensity stratum. We

performed a sensitivity analysis examining the association of influenza vaccine receipt and clinical outcomes, censoring events at 12 months since we did not have data on vaccination after randomization. A p-value of <0.05 was considered statistically significant. All analyses were completed using Stata, version 13 (StataCorp LP, College Station, TX).

RESULTS

Out of 8399 participants in the PARADIGM-HF trial, 1769 (21%) received influenza vaccination within a 12 month period while enrolled in the study. Baseline characteristics by influenza vaccination status are shown in Table 1. Influenza vaccine recipients were significantly older, had higher BMI, lower NYHA functional class and eGFR, and were more likely to be male and Caucasian. More vaccine recipients had a history of diabetes, myocardial infarction, were taking beta-blockers, and had received cardiac resynchronization therapy, and less were taking mineralocorticoid receptor antagonists. There was significant variation in vaccination rates by country (Table 2), with vaccination rates highest in the Netherlands (77.5%) the United Kingdom (77.2%), and Belgium (67.5%), and lowest in Asia (2.6%)(Table 2).

In a multivariable regression model, significant predictors of receiving influenza vaccine included, in descending order of association: country, older age, history of diabetes mellitus, lower NYHA functional class, lower heart rate, use of digoxin, use of an ICD or CRT, lower eGFR, higher ejection fraction, white race, and history of hospitalization for heart failure (Table 3). In an exploratory analysis, we observed a correlation between vaccination rates and country-specific GDP data (supplementary figure 1).

Influenza vaccination was associated with a lower risk for all-cause mortality compared to no vaccination in unadjusted models (Figure 1) and after adjusting for the propensity to receive influenza vaccine (HR 0.81, 95% CI [0.67, 0.97], p=0.015). In contrast, vaccination was

associated with increased rates of cardiopulmonary, influenza-related, and all-cause hospitalization in unadjusted models, but not in propensity-adjusted models (Table 4). Sensitivity analyses censoring events at 12 months post randomization revealed similar results (data not shown). The overall benefit of LCZ696 (sacubitril/valsartan) over enalapril on the trial's primary outcome was maintained regardless of influenza vaccination (p-interaction = 0.31).

DISCUSSION

In patients with heart failure and reduced ejection fraction enrolled in the PARADIGM-HF study, we found substantial world-wide regional variation in influenza vaccination rates, with rates substantially higher in Western Europe, the United States, and Canada compared to Asia. However, even in the United States, despite strong recommendations from the CDC and a science advisory statement published by the American Heart Association advocating for annual vaccination, vaccination rates were only 53% in this high-risk population.[5,12] Aside from country, the most significant predictors of vaccination included older age, history of diabetes mellitus, lower NYHA functional class, lower heart rate, use of digoxin, and use of either an ICD or CRT therapy. Influenza vaccination was associated with lower all-cause mortality even when adjusted for the propensity to receive influenza vaccine. Vaccination did not affect the efficacy of LCZ696 (sacubitril/valsartan).

There are limited data on influenza vaccination rates in patients with heart failure worldwide. Even in the United States, influenza vaccination rates in patients with heart failure have ranged from 25% to approximately 76%, depending on the population studied.[13-15] In one study of patients with heart failure who were mostly indigent or had Medicare or Medicaid, baseline rates were 28.3% prior to a vaccination campaign program, and improved to 50.3% after the program.[14] In an analysis of the impact of American Heart Association's Get With The

Guidelines–Heart Failure (GWTG-HF) "Plus" program, which recognized hospitals for additional quality measures such as influenza vaccination, the increase in influenza vaccination rates slowed following program implementation compared to years leading up to the program, although baseline vaccination rates were greater than 50%.[13] The reasons for poor influenza vaccine uptake in the heart failure population remain unclear, but include factors such as reduced accessibility to vaccination clinics in rural areas, cost of vaccination if uninsured or if vaccination programs are not offered through employers, limited knowledge regarding the benefits of vaccination, mistrust of ingredients contained in the vaccine, or the misconception that influenza vaccination will cause influenza infection.[14,16]

We found that the most important factor influencing vaccination was country. We observed low vaccination rates among Asians as previously reported, which may be due to factors such as competing health care priorities and inadequate resources, particularly in developing countries, incomplete region-specific data regarding influenza vaccine effectiveness, or differing practice patterns between regions.[17-19] Older age, white race and concomitant diabetes mellitus were also significant predictors of vaccination, potentially due to increased health care utilization or improved access to health care.[20] Country specific GDP appeared to be associated with per-country vaccination rates, suggesting that socioeconomic status may play a role in vaccination, although these findings should be interpreted with caution, as we did not have participant-specific socioeconomic data and these factors can vary widely within countries.

We found that patients who received influenza vaccination had lower all-cause mortality, even when adjusting for the propensity to receive vaccination. This finding is consistent with other observational studies that have similarly reported lower rates of death in individuals receiving influenza vaccination, including a retrospective analysis of over 100,000 patients with

heart failure from the Veterans Health Administration,[15] and a prospective cohort analysis of patients hospitalized for heart failure.[21] Despite the adjustment for the propensity to receive influenza vaccine, the observed association between influenza vaccination and lower mortality may simply be indicative of better access to health care, improved surveillance, or ambulatory independence of vaccine recipients, and does not prove that influenza vaccination reduces mortality in this population. As we observed substantial differences between those who did and did not receive vaccine, we cannot rule out the possibility that unmeasured confounding for which we are not able to adjust may contribute to the observed findings among influenza vaccine recipients.

That influenza vaccination was associated with a higher unadjusted rate of hospitalization of any type, but not an increased risk of death, suggests that in PARADIGM-HF, influenza vaccination was a potential surrogate for higher level of and improved access to health care, evidenced by more hospitalizations, for any given severity of illness, among individuals who received influenza vaccine. The fact that the risk for hospitalization was substantially altered following propensity adjustment implies that factors that influence the likelihood of vaccination might also influence rates of hospitalization. Nevertheless, other large, but more geographically homogenous, observational studies have shown associations between influenza vaccination and reduced risk for hospitalizations.[22,23]

Several additional limitations of this analysis should be noted. First, we only had vaccination information during a 12 month period in the trial, and as such could not examine associations between multiple year receipt of influenza vaccination and clinical outcomes, as these data were not collected. Influenza vaccination history was collected by site personnel via a case report form, and may be subject to recall bias. Additionally, we did not collect information

about the type of vaccine participants received (high dose, quadrivalent, adjuvant), therefore we were not able to explore whether certain vaccine formulations were more strongly associated with better outcomes. Patients with heart failure exhibited blunted immune responses to standard dose trivalent influenza vaccination in previous studies,[24,25] and use of a higher dose of influenza vaccine resulted in enhanced antibody titers compared to a standard dose formulation.[26] However, the vaccine formulation that portends the greatest protection against influenza-related complications remains unclear.

In conclusion, in a cohort of patients with heart failure and reduced ejection fraction who were well managed on guideline directed medical therapy, we observed significant regional variation in rates of influenza vaccination, despite well publicized recommendations from public health organizations advocating for annual immunization in this high risk population. Recipients of influenza vaccination tended to be older, of Caucasian heritage, and more commonly had other co-morbidities that may necessitate closer medical follow up. Influenza vaccination did not affect the efficacy of LCZ696, but was associated with lower all-cause mortality, even after adjustment for the propensity to receive influenza vaccination, although whether this association was causal cannot be determined from these observational data.

CLINICAL COMPETENCIES

Medical Knowledge: influenza vaccination is recommended on an annual basis in patients with heart failure and may be associated with reduced mortality.

Patient Care: Health care providers should educate patients on the benefits of annual influenza vaccination and provide opportunities for vaccination in clinic settings.

Translational outlook 1: Future studies should examine associations between multiple year influenza vaccination and cardiovascular outcomes in patients with heart failure.

Translational outlook 2: Although annual influenza vaccination is recommended by clinical guidelines, it is not known which specific influenza vaccine (trivalent, high dose, quadrivalent) may be most beneficial in this high-risk population.

Translational outlook 3: The exact mechanisms by which influenza vaccination may lead to improved outcomes in patients with heart failure requires further study

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FIGURE LEGEND

Figure 1. Crude and propensity adjusted hazard ratio for all-cause death, cardiovascular death or heart failure hospitalization (primary endpoint), all-cause hospitalization, and cardiopulmonary/influenza-related hospitalization or death.

Table 1. Baseline characteristics by influenza vaccine use

Characteristic	No influenza vaccination N=6630 (79%)	Influenza vaccination N=1769 (21%)	p-value
Age	62.7 ± 11.5	67.9 ± 10.1	p < 0.0001
Female sex (%)	1481 (22.3%)	351 (19.8%)	p = 0.024
Caucasian Race	4008 (60.5%)	1536 (86.8%)	p<0.0001
Body mass index	27.93 ± 5.50	29.06 ± 5.51	p<0.0001
Ischemic etiology	3949 (59.6%)	1087 (61.4%)	p=0.15
NYHA FC I II III IV	 306 (4.6%) 4569 (69.0%) 1694 (25.6%) 52 (0.8%)	 83 (4.7%) 1350 (76.5%) 324 (18.4%) 8 (0.5%)	p<0.0001
Left ventricular ejection fraction	29.53 ± 6.17	29.32 ± 6.41	p=0.1968
History of heart failure hospitalization	4267 (64.4%)	1007 (56.9%)	P<0.0001
History of hypertension	4722 (71.2%)	1218 (68.9%)	p=0.052
History of diabetes	2184 (32.9%)	723 (40.9%)	p<0.0001
History of myocardial infarction	2761 (41.6%)	873 (49.3%)	p<0.0001
Use of ICD	667 (10.1%)	576 (32.6%)	p<0.0001
Use of CRT	305 (4.6%)	269 (15.2%)	p<0.0001

Baseline medications			
ACE inhibitors	5120 (77.2%)	1412 (79.8%)	p=0.02
ARBs	1519 (22.9%)	373 (21.1%)	p=0.10
Beta blockers	6139 (92.6%)	1672 (94.5%)	p=0.005
MRAs	3817 (57.6%)	854 (48.3%)	p<0.0001
Diuretic	5307 (80.0%)	1431 (80.9%)	p=0.43
Digoxin	2100 (31.7%)	439 (24.8%)	p<0.0001
eGFR	69.5 ± 19.5	63.1 ± 17.9	p<0.0001
NT-proBNP	2967.5 ± 4121.7	2641.7 ± 3420.0	p=0.002

Table 2. Vaccination rate by country

Country	Percent
Argentina	30.2
Belgium	67.6
Bulgaria	1.4
Brazil	29.7
Canada	47.0
Chile	44.1
China	0.6
Columbia	7.3
Czechoslovakia	10.0
Germany	37.1
Denmark	54.7
Dominican Republic	0
Ecuador	7.8
Spain	52.8
Estonia	3.4
Finland	60.0
France	39.1
Great Britain	77.2
Guatemala	2.9
Hong Kong	8.7
Hungary	22.7

India	0.2
Iceland	55.6
Israel	36.6
Italy	41.0
Korea	20.7
Lithuania	0
Latvia	0
Mexico	17.5
Malaysia	0
Netherlands	77.5
Panama	13.3
Peru	0
Philippines	4.0
Poland	4.6
Portugal	53.1
Romania	4.4
Russia	0.2
Singapore	9.3
Slovakia	14.3
Sweden	55.2
Thailand	0
Turkey	1.6
Taiwan	5.8

USA	55.1
Venezuela	0
South Africa	6.2

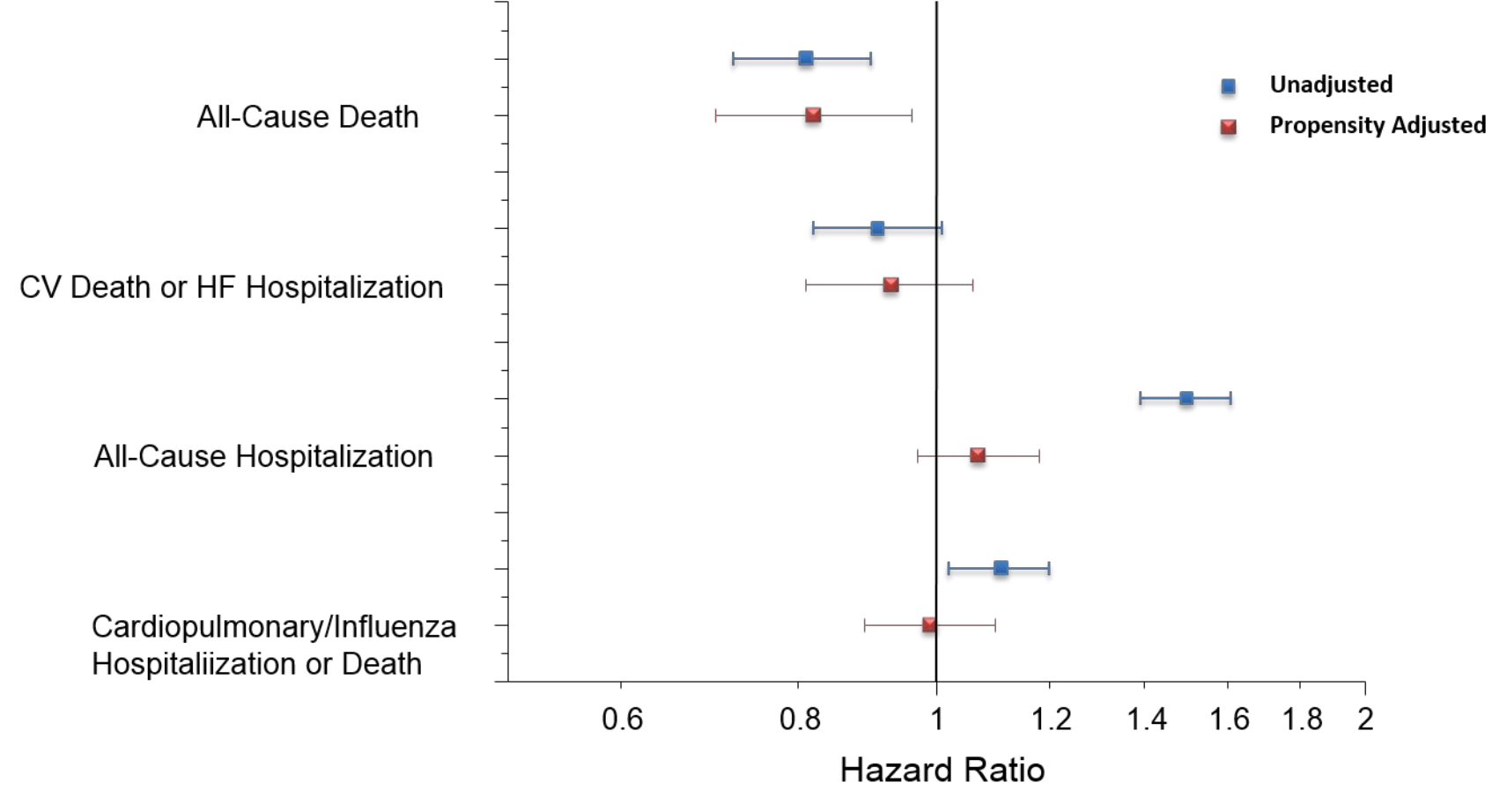
Table 3. Predictors of Receipt of Influenza Vaccine

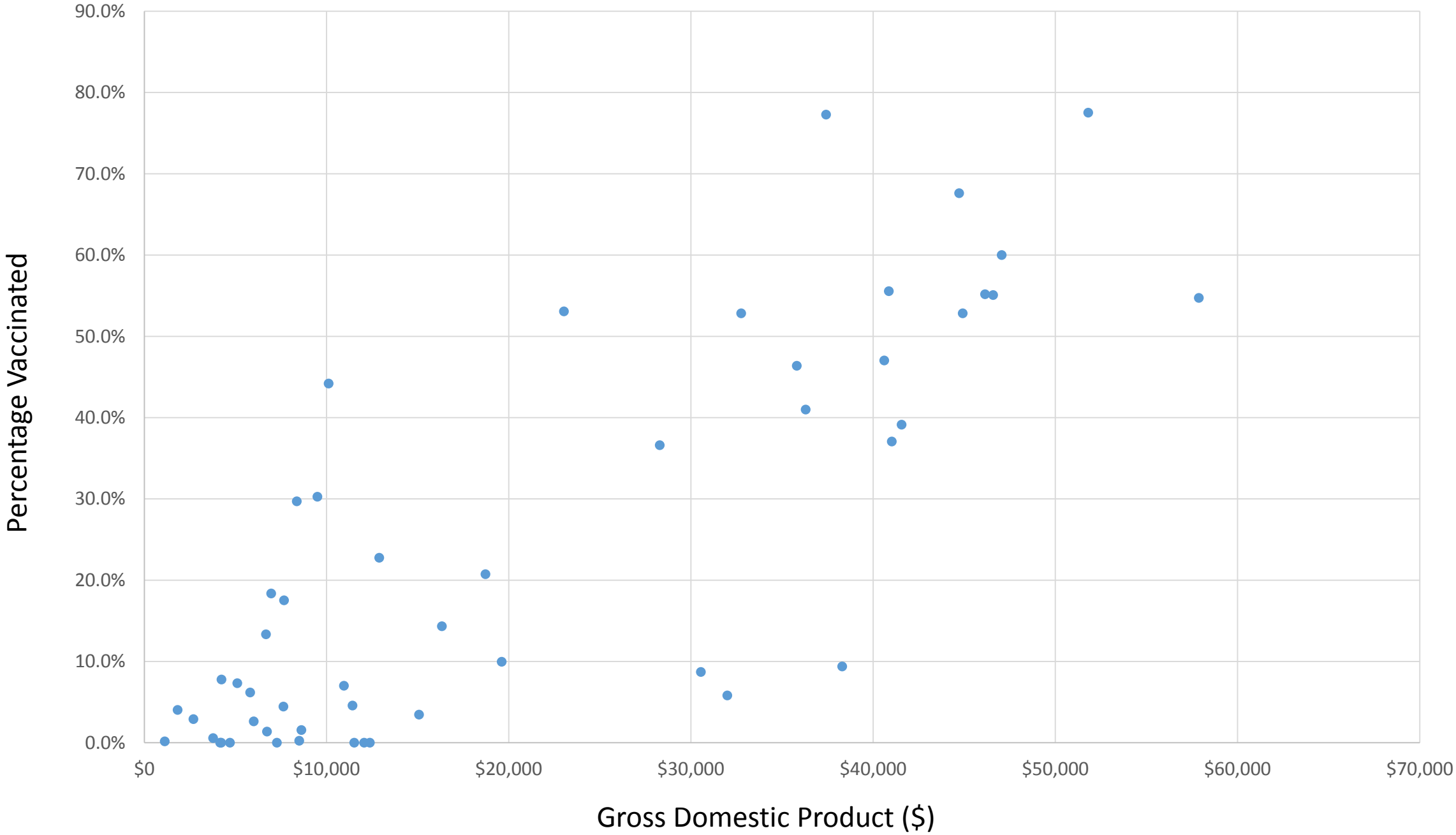
Predictor	Z score	Odds Ratio (95% CI)
Country	31.8	1.79 (1.72, 1.85)
Age	7.32	1.02 (1.02, 1.04)
History of diabetes mellitus	4.16	1.35 (1.17, 1.55)
NYHA functional class	3.38	0.79 (0.68, 0.90)
Heart rate	2.51	0.99 (0.986, 0.998)
Use of digoxin	2.51	1.22 (1.04, 1.43)
Use of an ICD	2.37	1.33 (1.02, 1.47)
Use of CRT	2.18	1.22 (1.05, 1.69)
eGFR	2.18	0.995 (0.992, 1.0)
Ejection fraction	2.06	1.01 (1.0, 1.02)
White race	2.01	1.21 (1.0, 1.45)
History of hospitalization for heart failure	1.98	0.87 (0.76, 1.0)

*Other model covariates which were not significant included: history of myocardial infarction, left ventricular ejection fraction, blood pressure, sex, body mass index, use of ACE inhibitor, ARB, beta blocker, MRA, or diuretic, NT-proBNP, and BNP.

Table 4. Association between influenza vaccination and outcomes

	Unadjusted		Propensity Adjusted	
Outcome	HR	95% CI	HR	95% CI
Death	0.81	0.71, 0.92	0.82	0.70, 0.96
Cardiovascular death or heart failure hospitalization	0.91	0.81, 1.01	0.93	0.81, 1.06
Cardiopulmonary or influenza-related hospitalization or death	1.11	1.02, 1.20	0.99	0.89, 1.10
All-cause hospitalization	1.50	1.39, 1.61	1.07	0.97, 1.18


All-Cause Death
CV Death or HF Hospitalization
All-Cause Hospitalization
Cardiopulmonary/Influenza Hospitaliization or Death
Unadjusted
Propensity Adjusted
0.6
0.8
1
1.2
1.4
1.6
1.8
2
Hazard Ratio


90.0%
80.0%
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Percentage Vaccinated
$0
$10,000
$20,000
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$40,000
$50,000
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$70,000
Gross Domestic Product ($)