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Interaction of cardiac implantable electronic device and patent foramen ovale in ischemic stroke: a case-only study

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Abstract

Background—Cardiovascular implantable electronic device (CIED) leads are a nidus for right atrial thrombi. Right-to-left thromboembolism across a patent foramen ovale (PFO) is a putative mechanism for ischemic stroke and PFO has been associated with stroke. We used a novel unbiased case-only study design to assess the effect modification of PFO-associated ischemic stroke risk by presence of CIED. We hypothesized that presence of CIED, as a nidus for right atrial thrombus formation, magnifies the PFO-ischemic stroke relationship; therefore, among hospitalized ischemic stroke patients we would find a higher prevalence of CIED in patients with PFO.

Methods—We included consecutive first ischemic stroke patients admitted to our hospital from 2006–2015 who were enrolled in a prospectively maintained stroke registry. PFO was ascertained from documentation on echocardiography, and presence of CIED at time of stroke was determined from chest radiography reports at or prior to hospitalization. We measured distributions of CIED within PFO and control groups and used Fisher's exact test to evaluate the PFO-CIED association among ischemic stroke patients.

Results—We included 7,089 patients (age 64.5 ± 14.9 years, 51% female). Echocardiography diagnosed PFO in 760 (10.7%) and CIED was reported on chest radiography in 752 (10.6%) patients. Prevalence of CIED was lower in the PFO (61/760, 8.0%) compared to control group (691/6329, 10.9%), $p=0.015$.

Conclusion—Among admitted ischemic stroke patients, we did not find a higher prevalence of CIED in patients with PFO compared to controls. Therefore, in the underlying source population, the presence of CIED did not increase the PFO-associated ischemic stroke risk.

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Keywords

ischemic stroke; patent foramen ovale; cardiovascular implantable electronic device; intracardiac leads; case-only study design

Introduction

Approximately 800,000 new or recurrent strokes occur annually in the United States, of which 25–40% are of undetermined etiology.^{1,2} Right-to-left thromboembolism across a patent foramen ovale (PFO) is a potential mechanism of cryptogenic ischemic stroke.^{3,4} PFO is a common embryological remnant, that can be detected on autopsy evaluation in approximately 25% of the population.⁵ Cardiovascular implantable electronic devices (CIED), such as pacemakers and defibrillators, have transvenous leads implanted in right heart chambers that can be a nidus for thrombus formation in proximity to a PFO.⁶ Mobile lead-associated thrombi thus generated in the right atrium have the potential to break off and travel across the PFO, resulting in systemic embolism and stroke. Considering the overall increasing rates of CIED implantation in the general population, it is important to consider the potential impact of thrombogenicity of CIED leads on PFO-ischemic stroke relationship.^{7,8}

PFO alone, irrespective of CIED, has been shown to be a risk factor for ischemic stroke, with higher PFO prevalence observed among stroke patients.^{3,4,9} This association is further supported by the recent randomized control trials reporting a reduction in recurrent stroke with PFO closure after the index cryptogenic ischemic stroke.^{10–12}

In patients with congenital heart disease and unrepaired intracardiac shunts (e.g. atrial or ventricular septal defects and cyanotic congenital heart defects), implantation of transvenous, but not epicardial, CIED leads has been associated with increased risk of systemic embolic events including stroke.¹³ Therefore, transvenous CIED leads are contraindicated in such patients. However, the effect modification amplifying the PFO-ischemic stroke relationship in the general population by the presence of CIED leads is not well understood. The presence of CIED lead-associated thrombi in the right heart chambers has been associated with increased pulmonary artery pressures and it has been hypothesized that this may occur due to occult pulmonary embolisms of such lead-associated thrombi.⁶ It can be further hypothesized that the elevation in pulmonary artery pressures would translate to higher right atrial pressures and promote right-to-left shunting across the PFO.

A large retrospective study of over 6000 patients with CIED leads in right heart chambers reported over a 3-fold higher stroke/transient ischemic attack (TIA) risk in patients with a PFO compared to those without a PFO.¹⁴ The results of this study, however, could have been biased due to misclassification of PFO, residual confounding and differences in ascertainment of stroke/transient ischemic attack. Another retrospective cohort study of approximately 3000 patients with PFO suggests that CIED implantation does not increase stroke/TIA risk compared to the control group without CIED implantation.¹⁵ In light of such conflicting results, unbiased epidemiologic studies are needed to determine the true impact of intracardiac CIED leads on the PFO-ischemic stroke relationship. We sought to

investigate the effect modification by CIED leads on the association between PFO and ischemic stroke. We use an unbiased case-only study design to assess the association of PFO and CIED among patients hospitalized with ischemic stroke as a proxy for the effect modification by CIED of the PFO-ischemic stroke association. Case-only methodology has previously been used in epidemiologic research on rare disorders to demonstrate gene-environment interactions.^{16–22}

Methods

A case-only study design was used to determine the effect modification by CIED leads on PFO-ischemic stroke association. The validity of this design requires the two variables of interest (i.e. PFO and CIED) to be independent of one another in the source population.^{16–19} There is no known association between presence of PFO and CIED; nor is PFO currently an indication or contraindication for the implantation of CIED.²³ In fact, the presence of a PFO is greatly underdiagnosed in the general population. Therefore, we can safely assume the absence of any correlation between the prevalence of PFO and presence of CIED in the general population. Even though both PFO and CIED independently may be associated with stroke, we should not expect to see any correlation between PFO and CIED in patients presenting with ischemic stroke akin to their lack of association in the source general population. However, if risk of PFO-associated ischemic stroke is amplified by CIED leads (effect modification), there will be an overrepresentation of patients with both PFO and CIED within the population of incident ischemic stroke cases.

Mathematically, where CIED+ and CIED- refers to the population with and without CIED respectively, and PFO+ and control refers to the population with and without PFO respectively, and N refers subgroups of the source general population while n refers to subgroups of the ischemic stroke population derived from the source population, Effect modification by CIED of PFO-ischemic stroke association

$$\begin{aligned}
 &= \frac{\text{risk of ischemic stroke in PFO+,CIED+}}{\text{risk of ischemic stroke in control,CIED+}} \div \frac{\text{risk of ischemic stroke in PFO+,CIED-}}{\text{risk of ischemic stroke in control,CIED-}}, \\
 &= \frac{\frac{n_{\text{PFO+ , CIED+}}/N_{\text{PFO+ , CIED+}}}{n_{\text{control, CIED+}}/N_{\text{control, CIED+}}}}{\frac{n_{\text{PFO+ , CIED-}}/N_{\text{PFO+ , CIED-}}}{n_{\text{control, CIED-}}/N_{\text{control, CIED-}}}}, \\
 &= \frac{\frac{n_{\text{PFO+ , CIED+}}/n_{\text{PFO+ , CIED-}}}{n_{\text{control, CIED+}}/n_{\text{control, CIED-}}}}{\frac{N_{\text{PFO+ , CIED+}}/N_{\text{PFO+ , CIED-}}}{N_{\text{control, CIED+}}/N_{\text{control, CIED-}}}}, \\
 &= \frac{\text{odds of CIED in PFO+ ischemic stroke cases}}{\text{odds of CIED in control ischemic stroke cases}} \div \frac{\text{odds of CIED in PFO+ population}}{\text{odds of CIED in control population}}.
 \end{aligned}$$

Assuming independence of PFO and CIED in general population, i.e.

$$\frac{\text{odds of CIED in PFO+ population}}{\text{odds of CIED in control population}} = 1.$$

Then, Effect modification by CIED of PFO-ischemic stroke association

$$= \frac{\text{odds of CIED in PFO+ ischemic stroke cases}}{\text{odds of CIED in control ischemic stroke cases}},$$

or odds ratio of CIED in PFO vs. controls in ischemic stroke case-only study.

In other words, under the assumption of independence of PFO and CIED in the source general population, an observed PFO-CIED association among ischemic stroke cases would reflect the effect modification of the PFO-ischemic stroke association by presence of CIED (a hypothetical example is included as Supplementary Figure 1). We therefore hypothesized that among patients hospitalized with ischemic stroke, the prevalence of CIED is greater in patients with PFO compared to those without PFO.

The study population included prospectively collected consecutive first ischemic stroke patients admitted to our hospital from January 2006 to December 2015 and enrolled in the Stroke Management and Rehabilitation Team (SMART) Stroke Registry maintained by the Washington University Cognitive Rehabilitation and Recovery Group. Patient medical records were deidentified and assigned a unique patient identifier. Only the first ischemic stroke admission for each patient was included. Presence of ischemic stroke was determined by International Classification of Disease Codes, which were used to differentiate between ischemic and hemorrhagic etiologies. The unique identifiers were used to cross reference individuals to the Washington University Clinical Investigation and Data Exploration Repository (CIDER). CIDER was used to obtain chest radiography reports and echocardiography studies. Chest radiographs obtained prior to or within 5 days of the stroke admission were included. All available transthoracic and transesophageal echocardiography reports were included. Patients without a qualifying chest radiograph or any available echocardiogram were excluded.

The echocardiography reports were obtained directly from our echocardiography lab database. Doppler evaluation for PFO is a standard component of routine transthoracic and transesophageal echocardiography at our institution. A language query tool was used to search echocardiography reports for mention of “PFO” in the findings and comments/summary sections. Reports with sentences containing “PFO” in the summary comments were searched for negative qualifiers, such as “no”, “without”, “w/o”, or “negative”, suggesting the absence of PFO. Patients with any echocardiography report containing “PFO” and absence of a negative qualifier were assigned to the PFO-positive group. All other patients were assigned to the control group (Figure 1).

All chest radiography reports dated on or prior to 5 days post date of index ischemic stroke hospitalization were queried for selected terms suggesting the presence of CIED, including “pacemaker”, “defibrillator”, “ICD”, or “leads”. Those containing such terms were classified as CIED positive and those without these terms classified as CIED negative. A random

sample of chest radiography and echocardiography reports was selected for manual review to assess the classification accuracy.

Baseline patient demographics for the ischemic stroke study population were obtained from the prospectively maintained SMART Stroke Registry. Clinical data such as age, gender, history of prior stroke or TIA, use of antiplatelet agent or anticoagulation at the time of stroke admission, cardiovascular disease history, and pertinent comorbidities were used for statistical analysis. Our primary outcome was the prevalence of CIED within PFO-positive versus control groups.

The primary unadjusted association between PFO and CIED among ischemic stroke patients was determined using Fisher's exact test. Two-sided confidence level 95% (1- α) was used as the threshold for statistical significance.

Univariate analyses were performed to identify variables with a significant difference between PFO-positive and control groups, and CIED-positive and CIED-negative groups. Continuous variables were compared using two-sided t-tests for independent groups and categorical variables compared with Fisher's exact tests. Continuous variables with non-normal distributions were summarized by the median (1st quartile, 3rd quartile) and compared using Mann-Whitney U test. An exploratory multivariable logistic regression model was developed to further examine the association between PFO and CIED after adjusting for variables correlated to both. Clinically relevant variables and variables in the univariate analyses with $p \leq 0.10$ for differences based on both PFO and CIED status were included in the multivariable model.

All statistical analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

Results

There were 14,927 ischemic stroke patients admitted to our hospital from 2006 to 2015. Of these, 434 patients were excluded due to unavailability of the unique patient identifier, 1520 patients were excluded for non-first stroke admission, and an additional 5884 patients were excluded due to the absence of any qualifying chest radiography and echocardiography reports available for review. Thus, our study included 7,089 first ischemic stroke patients (Figure 1).

Comprehensive transthoracic echocardiography (TTE) with Doppler or transesophageal echocardiography (TEE) with Doppler were used for evaluation of PFO in greater than 98% of patients and limited TTE without Doppler in the remaining 1–2% patients. TEE was performed in 39.8% of cases. Additionally, saline bubble study was performed in 73.4% of echocardiograms. Review of 100 randomly selected echocardiography reports for internal validation of query system for PFO classification revealed positive predictive value of 98% and negative predictive value of 100%. Review of 100 randomly selected chest radiography reports showing CIED-positive language query result yielded a 96% positive predictive value for presence of intracardiac CIED leads.

Baseline characteristics are presented in Table 1. We had 760 patients who were determined to be PFO-positive, of whom 61 (8.0%) PFO patients were determined to have a CIED and 699 (92.0%) did not have a CIED. We had 6,329 controls, of whom 691 (10.9%) were CIED-positive and 5638 (89.1%) were CIED-negative. These findings are detailed in the 2×2 contingency table (Figure 2).

The prevalence of CIED in the PFO-positive group was not significantly increased compared to control group (odds ratio, 0.71; 95% confidence interval, 0.54–0.94, $p=0.015$). A similar result was obtained with the subsequent multivariable model (odds ratio, 0.74; 95% confidence interval, 0.56–0.99, $p=0.045$). Findings of multivariable logistic regression model are provided in Table 2.

Discussion

In a large retrospective study of ischemic stroke patients admitted to our hospital, we did not observe an increase in CIED prevalence among PFO-positive compared to control patients, counter to what we had hypothesized. Based on our sample size, as well as frequencies of PFO and CIED in the study sample, we had an 80% power to detect a 1.37 ratio in the odds of CIED in PFO-positive compared to control patients (two-tailed α 0.05). An odds-ratio of 1.37 in our analysis would symmetrically translate to a 1.37-fold higher *odds ratio of ischemic stroke in PFO-positive vs. controls among CIED-positive* compared to *odds ratio of ischemic stroke in PFO-positive vs. controls among CIED-negative* (see Case-only Study Design in Methods section). In fact, a significant negative association between the presence of PFO and CIED was observed. Based on these findings, we conclude that the presence of CIED does not increase the risk of ischemic stroke associated with a PFO.

Formation of thrombus on CIED leads and migration across a PFO has been previously described in the literature.^{6,24,25} We proposed that CIED leads should increase the risk of ischemic stroke in patients with PFO; therefore, in our stroke population, we had hypothesized that the prevalence of CIED should be higher among PFO-positive compared to control patients. Among ischemic stroke patients, we observed a lower CIED prevalence in the PFO-positive group. This finding contradicts our hypothesized interaction between PFO and CIED in the pathogenesis of ischemic stroke. We do not believe that our observed statistical difference suggests a finding of clinical significance. There is no logical mechanism for CIED to directly predispose to a lower risk of cardioembolic stroke due to the presence of a PFO (or other intracardiac shunt). Therefore, the relative underrepresentation of CIED within the PFO-positive group is more likely to be explained by random chance (e.g. 5 additional patients in PFO-positive group with CIED would have resulted in statistical insignificance). Alternatively, our statistical association can be explained by the presence of CIED reducing sensitivity of PFO detection by echocardiography. The difference in mean age between PFO-positive and control groups could be a potential confounder in our study. Individuals in the PFO-positive group were 4.5 years younger on average than those in the control group. Within the general population, the prevalence of CIED increases with advancing age.⁷ Therefore, the increased prevalence of CIED within the control group we observed may be partly due to the higher average age of

individuals in this group. However, the negative association persisted despite the multivariable logistic model adjusting linearly for age.

Our results are consistent with the findings of a previous retrospective study among patients with a PFO. Poddar et al. studied patients with a PFO and observed no difference in the occurrence of first time ischemic stroke/TIA in those with a CIED as compared to patients without CIEDs.¹⁵ Conversely, the retrospective study by DeSimone et al. among CIED patients showed an increased risk of stroke or TIA in the presence of PFO.¹⁴ The findings of both studies are limited by their retrospective design and risk of bias, confounding, and unadjusted variability. Additionally, the study by DeSimone et al. does not directly address the question of additional stroke risk attributable to CIED-PFO interaction, as it does not include patients without CIED. It is quite possible that in their CIED population, the relationship between PFO and stroke/TIA is explained by a combination of the baseline increased stroke risk due to a PFO in the general population,^{3,4,9} as well as residual confounding and biases in the detection of predictor (PFO) and outcome (stroke/TIA). We detected a PFO prevalence of 10.9% in our study sample, which is similar to PFO detection rate using TEE in prior retrospective studies,²⁶ though less than the prevalence of approximately 25% based on autopsy and prospective TEE studies.^{5,27,28} The diagnosis of PFO in our study was limited by the retrospective retrieval of echocardiography data. Internal validation with manual review of the query system yielded a false negative rate of 0%. Thus, the risk of underestimating PFO prevalence due to ineffective language query of the echocardiography reports is unlikely. Prevalence may have been reduced by the echocardiography technique used to evaluate for PFO. TTE, TEE, and limited TTE reports were used to diagnose PFO in our study.

The predominant use of TTE compared to TEE for evaluation of PFO in our study population is also a limitation of our study. TEE is the most sensitive technique for PFO detection and is considered the gold standard for evaluation of a cardioembolic source in cryptogenic stroke, but was available only for approximately two-fifths of the patients included in our analysis.^{29–31} According to the American Society of Echocardiography, contrasted TTE with bubble study and Doppler evaluation is the standard initial diagnostic modality for the evaluation of PFO.³² TEE however is needed for further characterization as TTE image quality is inadequate to thoroughly evaluate the intraatrial septum. PFO is echocardiographically defined by the presence of right-to-left shunting by bubble study or color Doppler. It is important to note that a PFO is not a true deficiency of the atrial septal tissue, but rather a potential space between the septum primum and secundum. Therefore, the prevalence of hemodynamically significant PFO detected by bubble study or color Doppler on echocardiography is less than the autopsy estimated prevalence of 20–25%. Although bubble study was only performed in 73.4% of TTEs, color Doppler was utilized in all echocardiography studies, and our overall PFO detection rate (10.7%) is comparable to prior echocardiographic studies.^{29–31}

The association between PFO and stroke also remains a topic of debate. Several early studies demonstrate an increased prevalence of PFO among patients with ischemic stroke compared to non-stroke control.^{3,4,9} PFO prevalence is also increased among cryptogenic ischemic stroke patients compared to patients with stroke of known etiology.^{4,9} On the contrary, there

is equal evidence arguing against the association between PFO and cryptogenic stroke. The SPARC study, consisting of randomly sampled subjects who underwent transesophageal echocardiography (TEE), failed to find a significant difference in the composite primary outcome of future cerebrovascular events (i.e. TIA, cerebral infarct, or death) between subjects with PFO and those without.^{27,28}

New evidence showing the benefit of PFO closure in addition to medical therapy for the prevention of recurrent ischemic stroke supports the association between PFO and cryptogenic ischemic stroke.^{10–12} These findings contradict prior negative studies regarding benefit of PFO closure.^{33–35} Long term follow up of three randomized controlled trials show a marginally significant reduction in recurrent stroke, but wide confidence intervals and a higher dropout rate in the medical therapy arm undermine the clinical significance of this finding.^{10–12}

The strength of our case-only study design lies in its unbiased primary analysis, free of confounding common in retrospective analyses. We did not assess for a retrospective association between a putative risk factor (PFO or CIED) and outcome (stroke), where confounders associated with diagnosis of both the predictor and outcome may bias towards a false positive result. In fact, our entire study population had the outcome of stroke (case-only design). Both of our study variables, PFO and CIED, are independently allowed to have an association with stroke, but this does not translate to a false-positive result. A positive result, necessarily depends on an interaction between PFO and CIED on the stroke risk in the source general population from which our study population is derived. Case-only methodology has been described in the investigation of gene-environment interactions, particularly in cancer biology and epigenetics, but is novel to the field of cardiovascular research.^{18–21} Validity of case-only study design strongly hinges on the assumption that the two variables assessed are independent of each other within the general population.^{16–18} If this assumption is true then the case-only method is more efficient and more reliable than a case-control study design. Our study expands upon case-only methodology of genetics research by investigating the interaction between a “genotype” of interest (i.e. PFO) and an “environmental exposure” (i.e. CIED leads). In general, retrospective methodology carries the risk of misclassification and confounding bias as discussed above. This bias can be partially attributed to inadequate controls. Case-only design reduces this risk as its validity is not dependent on the integrity of a control. Fault within the independence assumption is the primary source of bias for case-only design.^{18,22}

There are some limitations to our study methodology. We do not have the denominator source population from which our stroke cases are derived. We thus cannot obtain the absolute prevalence of PFO or CIED in the population nor their association with the risk of stroke. We are only limited to the assessment of the effect modification by CIED of the PFO-stroke association (i.e. the ratio of odds ratio of stroke in PFO-positive vs. controls among CIED-positive vs. odds ratio of stroke in PFO-positive vs. controls among CIED-negative). Our analysis is conditional on the assumption that presence of PFO and that of CIED in the source population is independent of each other. Ultimately, our ability to accurately detect PFO and CIED is limited by the accuracy of the clinician performing the study, and this data was collected in a retrospective fashion from clinical medical records.

Further, any misclassification of PFO or CIED has the risk of biasing our analysis towards a null result.

Conclusion

We sought to investigate the effect-modification by CIED leads of the PFO-stroke association in the general population, using a case-only design that is novel to cardiovascular epidemiology. In our cases with ischemic stroke, we did not observe an increased prevalence of CIED among patients with a PFO. This implies absence of the hypothesized effect-modification by CIED of any underlying PFO-stroke association. Our results do not support avoidance of intracardiac CIED lead implantation in patients with PFO due to consideration for an increased risk of stroke, nor the preemptive closure of PFO in patients without prior stroke.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Derivation of ischemic stroke study population. Schematic demonstrating selection of cases from original SMART Stroke Registry and subsequent cross-referencing within echocardiography and chest radiography databases to yield final sample population. * Negative qualifiers include “no”, “without”, “w/o”, and “negative”.

	CIED-	CIED+	Total
PFO+	699 (92.0%)	61 (8.0%)	760 (10.7%)
Control	5638 (89.1%)	691 (10.9%)	6329 (89.3%)
Total	6337 (89.4)	752 (10.6%)	7089

Figure 2.

The distribution of PFO and CIED within included first stroke patients. The boldly outlined area depicts the 2×2 contingency table, tabulating stroke patients by PFO and CIED status. The measured association between PFO and CIED yielded $p=0.015$. The last row shows the total number (percent total) of CIED-negative and CIED-positive patients. The last column shows the total number (percent total) of control and PFO-positive patients within the sample.

Table 1.

Baseline characteristics of the ischemic stroke study population, as well of control and PFO-positive subgroups. Age demonstrates mean $\pm$ standard deviation. Categorical variables (i.e. gender and comorbidities) are summarized by frequency count and percent. Length of stay is reported by median number of days, as well as the 1st and 3rd quartiles.

Variable, N= 7089	Overall	Control	PFO Positive	P-value
Age, y	64.5 $\pm$ 14.9	65.0 $\pm$ 14.6	60.6 $\pm$ 16.7	<.001
Female, n (%)	3600 (51%)	3215 (51%)	385 (51%)	1.00
Smoking, n (%)	1753 (25%)	1522 (24%)	231 (30%)	<.001
Hypertension, n (%)	3483 (49%)	3124 (49%)	359 (47%)	0.28
Diabetes mellitus, n (%)	1129 (16%)	1024 (16%)	105 (14%)	0.09
Atrial fibrillation, n (%)	677 (10%)	615 (10%)	62 (8%)	0.19
Congestive heart failure, n (%)	685 (10%)	627 (10%)	58 (8%)	0.04
Peripheral vascular disease, n (%)	357 (5%)	322 (5%)	35 (5%)	0.66
Depression, n (%)	652 (9%)	567 (9%)	85 (11%)	0.05
Length of stay, Median days (Q1, Q3)	4.0 (2.0, 9.0)	4.0 (2.0, 10.0)	3.0 (2.0, 8.0)	0.001

Multivariable logistic regression model. Odds ratios of CIED are reported for each included variable, along with lower and upper limit of 95% confidence interval and p-value. The final sample size was reduced, N=7051, due to missing patient data.

Table 2.

Variable, N= 7051	Odds Ratio	95% Confidence Interval	P-value
PFO yes (vs. no)	0.744	(0.558, 0.994)	0.045
Age (per 1 year increase)	1.012	(1.006, 1.018)	<.001
Female yes (vs. no)	0.589	(0.500, 0.694)	<.001
Smoking yes (vs. no)	0.838	(0.678, 1.036)	0.10
Hypertension yes (vs. no)	0.622	(0.507, 0.762)	<.001
Diabetes yes (vs. no)	0.853	(0.677, 1.075)	0.18
Cardiac Disease yes (vs. no)	3.080	(2.276, 4.168)	<.001
Coronary Artery Disease yes (vs. no)	2.492	(2.021, 3.073)	<.001
Congestive Heart Failure yes (vs. no)	3.481	(2.797, 4.332)	<.001
Depression yes (vs. no)	1.053	(0.803, 1.380)	0.71
Drugs yes (vs. no)	0.816	(0.522, 1.276)	0.37
Length of Stay (per 1 day increase)	1.008	(1.003, 1.012)	<.001