Analyzing Gender and Racial Effects of Digoxin vs Diltiazem in Atrial Fibrillation Mortality Using Large EHR Data

Shrieraam Sathyanarayanan, M.S., Center for Health Systems Innovation, OSU Center for Health Sciences

Michael Sutton, OMS IV, College of Osteopathic Medicine, OSU Center for Health Sciences

William Paiva, PhD, M.B.A., Center for Health Systems Innovation, OSU Center for Health Sciences

Abstract

Digoxin is an atrial fibrillation (AF) rate control drug that is still in use. New randomized trial data comparing digoxin with other agents is unlikely to become available, but observational data exists in the form of large patient databases. We compared the mortality rates between Digoxin and Diltiazem using the Cerner Healthfacts Data. The study was performed on data with 52,775 U.S. patients with atrial fibrillation. The goal of the study was to assess the mortality versus survival rates between patients. Patients' characteristics were reviewed among those receiving either a calcium channel antagonist (diltiazem) or digoxin. The mortality rates for patients who took digoxin were greater than that of patients who took diltiazem and had 1.31 times the risk of mortality [5.23% vs 3.98%, RR 1.31, CI 1.21-1.42, p < 0.001]. African Americans had the highest mortality rate compared to other races [6.28%, p<0.0001]. The age (in years) of patients treated with digoxin was higher than that of patients treated with diltiazem [74.96 vs 68.45, p<0.0001]. Length of stay (in days) of patients with digoxin was also significantly higher than that of diltiazem patients [74.96 vs 68.45, p<0.0001; 5.95 vs 4.99, p<0.0001]. Within certain races, digoxin mortality rates were higher between male and female patients. The mortality rate differences show adverse outcomes and increased risk of mortality was found in patients taking digoxin.

Introduction

Digoxin is one of the oldest cardiovascular medicines in use today, being first adapted from the foxglove (*digitalis lanata)* plant in the 18th century by Dr. William Withering and utilized to treat heart failure symptoms.[1] It is used as an agent to control heart rhythm in patients with atrial fibrillation (AF). It is one of the first heart failure treatments shown to reduce hospitalizations in patients with reduced ejection fractions of ≤45%.[2] As a ventricular rate controller, Digoxin has enjoyed a longstanding place in the management of atrial fibrillation as a rate-controlling agent. However, its performance in use for rate reduction in acute atrial fibrillation is poor,[3] but it remains an acceptable rate controlling agent for atrial fibrillation in the setting of heart failure with reduced ejection fractions below 40%.[4] Digoxin's efficacy as a rate controlling agent appears to be enhanced by the concomitant use with beta-adrenergic antagonists.[5] In the digitalis investigation group (DIG),[6] the largest randomized controlled trial to evaluate heart failure mortality and hospital readmission with digoxin use, higher mortality was seen with elevated serum digoxin concentrations; however, lower overall hospitalization rates were also observed. The DIG trial helps define the role of digoxin plays in patients with heart failure and an ejection fraction less than 45%. In a post-hoc analysis of the atrial fibrillation follow-up investigation of

rhythm management (AFFIRM) study by Olshansky and colleagues, propensity matched patients all had elevated risks of both all-cause and arrhythmic mortality with digoxin use.[7] While no randomized controlled trial data appear to clearly define digoxin's role in the heart failure with reduced ejection fraction (HFrF) population with atrial fibrillation (AF), a large meta-analysis was recently completed in 2015.[8] This comprised data from 621,845 patients, albeit with limited data on cardiovascular mortality. They report the tendency for increased cardiovascular mortality seen with some observational studies[9-11] with a tendency for other trial data to suggest a neutral effect on mortality.[12-14]

Methods

Data source and preparation
This study uses the Cerner Healthfacts data comprising of 52,775 patients who were diagnosed with AF (ICD-9 CM 427.31). The patients were filtered based on the generic name of the drugs. Only patients who took either digoxin or diltiazem during their visit were considered in the data set. Later the data was cleaned carefully by analyzing patients with discrepancies in gender, race, and other demographic variables. There were a few patients who took both digoxin and diltiazem in the data set. These patients were removed from our study because the scope of the study is only to compare the two drugs separately and not to test the interaction effect. The data was then subject to intensive cleaning where the records with missing demographic information were removed, after intensive cleaning the mortality rates were calculated based on the patients who were marked as "Expired" in the discharge description of the data. Variables with too many levels were subjected to reduction of levels. The mortality rates were then compared between the patients who took one of the two drugs.

Statistical Analysis
The mortality rates for each of the drugs were compared using Chi-Sq test. Individual comparisons were done between gender, race, and combinations of race and gender for the two drugs. The relative risk estimates were recorded between the people who expired and survived. For lower sample sizes Fisher's exact test was used. The significance was determined using the p-value cut off of 0.05. SAS® 9.4 was used to perform the data cleaning and the statistical tests.

Results

Table 1: Cohort Characteristics, N= 52775

Variable	Level	Discharged (%) N=50428	Expired (%) N=2347	P value
Drug group	Digoxin	18572(36.83)	1025(43.67)	
	Diltiazem	31856(63.17)	1322(56.33)	<0.0001
Gender	Male	25645(48.59)	1206(51.38)	
	Female	24783(49.15)	1141(48.62)	0.6156
Race	African American	3291(6.53)	138(5.88)	
	Asian	444(0.88)	16(0.68)	
	Caucasian	44220(87.69)	2072(88.28)	
	Hispanic	403(0.80)	21(0.89)	
	Native American	112(0.22)	8(0.34)	
	Other	735(1.46)	39(1.66)	
	Unknown	1223(2.43)	53(2.26)	<0.0001
Age*		70.64 (14.08)	76.13(11.60)	<0.0001
Length of Stay*		5.12 (6.70)	10.24(11.96)	<0.0001

*Used t-test to compare the means and reported standard deviation

Table 1 represents the descriptive statistics of the study cohort. There were 2347 (4.45%) expired patients out of 52,775 in the data. Digoxin-associated mortality was significantly higher than diltiazem-associated mortality [5.23% vs 3.98%, RR 1.31, CI 1.21-1.42, $p < 0.001$]. Patients who were prescribed digoxin had 1.31 times the risk of expiring than the patients who were prescribed diltiazem. While comparing overall mortality rates for race and gender, African Americans had the highest mortality rate compared to other races [6.28%, p<0.0001]. There was no significant difference in overall mortality rates between male and female [4.49% vs 4.49%, p=0.61]. Within each drug, there was no significant difference between genders. The age (in years) of patients treated with digoxin was higher than that of patients treated with diltiazem [74.96 vs 68.45, p<0.0001]. Length of stay (in days) of patients with digoxin was also significantly higher than that of diltiazem patients [74.96 vs 68.45, p<0.0001; 5.95 vs 4.99, p<0.0001].

**Table 2**: Relative risk estimates comparing Digoxin and Diltiazem mortality rates, Expired patients* N=2347

Characteristics	Relative risk (95% CI)	P
Digoxin vs Diltiazem	1.31 (1.21-1.42)	<0.0001
Male	1.33 (1.19-1.49)	<0.0001
Female	1.29 (1.15-1.45)	<0.0001
Caucasians	1.31 (1.20-1.42)	<0.0001
Female Caucasians	1.26 (1.12-1.14)	0.0002
Male Caucasians	1.35 (1.20-1.52)	<0.0001
African Americans	1.59 (1.22-2.08)	0.0008
Female African Americans	1.78 (1.14-2.79)	0.01

*Only significant results are shown in the table

When looking at each specific drug, males treated with digoxin had a higher mortality rate than males treated with diltiazem [5.33% vs 4.00%, RR 1.33, CI 1.19-1.49, p<0.0001]. In addition, female patients treated with digoxin had higher mortality rates [5.12% vs 4.00%, RR 1.29, CI 1.15-1.45, p<0.0001] than females treated with diltiazem.

African American patients with digoxin had a higher mortality than African American patients with diltiazem [8.63% vs 5.41%, p=0.0008; RR 1.59, CI: 1.22-2.08]. Mortality rates of female and male patients were compared within each race. Female African Americans who took digoxin had higher mortality [5.94% vs 3.33%, p=0.01] and 1.78-fold [RR 1.78, CI- 1.14-2.79] higher risk of mortality than those treated with diltiazem. There was no significant difference in mortality rates amongst male African Americans. But amongst all African American population who took Digoxin, female had higher mortality than male patients [5.94% vs 3.26%, p=0.0216, RR 1.82, CI 1.08-3.07]. No such difference in mortality rates were observed for patients with diltiazem.

Figure 1
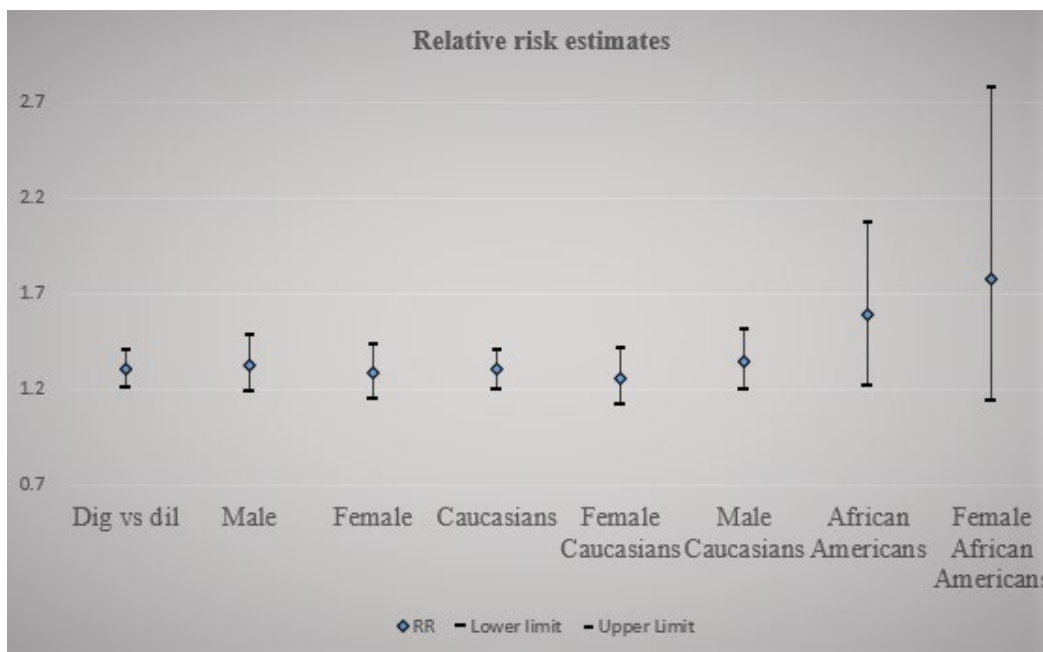
Caucasian patients with digoxin had a higher mortality than Caucasian patients taking diltiazem [5.25% vs 4.02%, p<0.0001; RR 1.31, CI: 1.20-1.42]. Caucasian females treated with digoxin had higher rate and risk of mortality than Caucasian females treated with diltiazem [5.03% vs 3.98%, p=0.0002; RR 1.26, CI: 1.12-1.43]. In addition, Caucasian males treated with digoxin also showed a higher rate and risk of mortality [5.47% vs 4.06%, p<0.0001; RR 1.35, CI: 1.20-1.52]. There were no differences in mortality rates between male and female among Caucasian patients who took Digoxin. The same is observed for patients who took Diltiazem as well.

There were interesting trends in other races but the results were not statistically significant. Hispanic population within the two genders had larger variations in mortality rates [Male - digoxin vs diltiazem: 8.54% vs 2.92%, p=0.065, RR 2.92, CI: 0.88-9.68; Female- digoxin vs diltiazem: 4.65% vs 5.04%, p=0.89, RR 0.922, CI: 0.27-3.17]. Hispanic females treated with diltiazem had

a higher associated mortality than Hispanic females treated with digoxin; however, the result was not statistically significant. Asian males had a similar trend like Hispanic females with diltiazem mortality rate higher than that of digoxin [p=0.3655, 1.05% vs 2.76%, RR 0.38, CI: 0.04-3.36], whereas, the female population had the opposite trend [p=0.1632, 7.79% vs 3.50%, RR 2.23, CI: 0.70-7.07]. The Native American population had higher mortality rates for both the genders [Male - digoxin vs diltiazem: 7.69% vs 0%, p=0.0824; Female- digoxin vs diltiazem: 11.11 % vs 10.53%, p=0.94, RR 1.06, CI: 0.21-5.24].

Discussion

The analysis continues the work into the efficacy of digoxin in the treatment of atrial fibrillation and expands upon it by investigating if gender or race has an effect on mortality rates of patients treated with digoxin compared to patients treated with diltiazem. Our research demonstrates that mortality was higher in patients treated with digoxin. This is consistent with other studies investigating digoxin including secondary analysis from the AFFIRM study and ARTISTOTLE study.[16-17] The increased overall mortality rate for digoxin patients is also consistent with the meta-analysis conducted by Vamos et al.[18] In addition, the AFFIRM study demonstrated that regardless of gender digoxin mortality was higher and likewise, the research presented in this paper also confirms that regardless of gender that digoxin mortality is higher.

There are studies that find the use of digoxin does not have an increased association with mortality. Allen et.al found there is a neutral association between digoxin and outcomes amongst patients with atrial fibrillation.[19] In addition, the Stockholm Cohort study found that digoxin is not associated with mortality, and the reason for the increased rate of mortality in digoxin is that patients tend to be older and frailer.[20] The research in this paper examines race and gender to see possible reasons for mortality rate variation. The research presented in this study shows it is evident that Caucasians with atrial fibrillation treated with digoxin have a higher mortality rate regardless of gender. In addition, African American females treated with digoxin have a higher mortality rate. African American males also have a higher mortality rate, however the value was not statistically significant. The data is consistent with the study done by Adedinsewo et.al, which found that digoxin use in African Americans lead to increased mortality rates.[21]

However, our data for Hispanic and Asian populations was not as decisive. Our research demonstrates that Hispanic women actually have a lower mortality rate when treated with digoxin compared to Hispanic women treated with diltiazem. Although the data is not statistically significant, the data calls to question if gender within the Hispanic population plays a role in mortality rates. Like Hispanic women, Asian males treated with diltiazem also had a higher mortality than Asian males treated with digoxin. Once again, the data was not statistically significant, but it begs the question if gender plays a role in the mortality rate of digoxin. Our data for Asian males is inconsistent with the research presented by Chao et al, who demonstrated that digoxin has an increased mortality rate in Asian populations compared with beta blockers and calcium channel blockers.[22]

For Caucasians and African American, the research is consistent with current American College of Cardiology guidelines that diltiazem is a better choice than digoxin for the treatment of atrial fibrillation.[23] The results of the analysis suggest that more investigation needs to be done to

analyze if gender in Hispanic and Asian populations plays a role in the mortality rate of patients treated with digoxin compared to diltiazem. As the use of digoxin continues to decline in healthcare practices, it is worthwhile to continue to examine if gender or race play a role in the efficacy of digoxin. This key question could unlock the therapeutic value of digoxin and allow physicians to utilize it to its maximal potential. This study mainly focuses on AF patients, but some of the studies considered AF patients with heart failure. It might be critical to analyze if difference in drug treatments for patients with heart failure have different mortality rates. Due to the limitations in EHR data, the reason for death is unknown for the study population which might yield more insights on drug treatments.

Conclusion

We used a large EHR data to analyze the effectiveness of administering Digoxin and Diltiazem. Among the patients with AF in the Cerner Healthfacts data, digoxin associated mortality was significantly higher than that of diltiazem associated mortality. There were no significant difference in digoxin and diltiazem mortality rates between male and female patients. Data from large EHR databases can be an effective way of analyzing efficacy of drugs. This study reflected the concerns raised for the use of Digoxin by many studies using a large observational data.

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