Renal Dysfunction Predicts Major Adverse Cardiovascular Events in Black and Latino Patients Who Have Atrial Fibrillation

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Abstract

Background: Atrial Fibrillation (AF) is present in over 6 million Americans. However, AF occurs less commonly in African Americans and Latinos compared to Caucasians. Major adverse cardiovascular events (MACE) is the leading cause of death in these populations. Hypothesis: We theorize that glomerular filtration rates (GFR) is an independent risk factor for MACE in African Americans and Latinos with non-valvular AF (NVAF). Methods: The association of reduced GFR with MACE in NVAF patients was investigated by retrospective chart review. 656 patients were included: 339 with GFR <60 and 317 with GFR [?]60. A Chi-square test, two-sample t-test, or Wilcoxon Rank Sum test was used to test for differences between the two groups in terms of demographic variables and other risk factors. The association between GFR groups and myocardial infarction (MI), stroke, and/or death, was tested using binomial logistic regression. To incorporate the element of time and adjust for covariates, a Cox proportional hazards model analysis was applied for each outcome variable. Results: As compared to GFR [?]60, a GFR <60 in NVAF was an independent risk factor for MI (HR 1.88 (1.17, 3.04); p=0.009); death (HR 1.63 (1.11, 2.41); p=0.014) and MI, stroke or death ((HR 1.37 (1.05, 1.78); p=0.018). GFR <60 was not an independent risk factor for stroke (HR 1.13 (0.77, 1.65); p=0.529) Conclusion: Renal dysfunction in patients with NVAF is an independent risk factor for MI, death in and composite of MI, stroke and death in African American and Latino populations.

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Hypothesis : We theorize that glomerular filtration rates (GFR) is an independent risk factor for MACE in African Americans and Latinos with non-valvular AF (NVAF).

Methods: The association of reduced GFR with MACE in NVAF patients was investigated by retrospective chart review. 656 patients were included: 339 with GFR <60 and 317 with GFR [?]60. A Chi-square test, two-sample t-test, or Wilcoxon Rank Sum test was used to test for differences between the two groups in terms of demographic variables and other risk factors. The association between GFR groups and myocardial infarction (MI), stroke, and/or death, was tested using binomial logistic regression. To incorporate the element of time and adjust for covariates, a Cox proportional hazards model analysis was applied for each outcome variable.

Results: As compared to GFR [?]60, a GFR <60 in NVAF was an independent risk factor for MI (HR 1.88 (1.17, 3.04); p=0.009); death (HR 1.63 (1.11, 2.41); p=0.014) and MI, stroke or death ((HR 1.37 (1.05, 1.78); p=0.018). GFR <60 was not an independent risk factor for stroke (HR 1.13 (0.77, 1.65); p=0.529)

Conclusion : Renal dysfunction in patients with NVAF is an independent risk factor for MI, death in and composite of MI, stroke and death in African American and Latino populations.

Abbreviations: GFR: Glomerular filtration rate; MACE: Major adverse cardiovascular events; MI: Myocardial Infarction; HR: Hazard ratio; NVAF: Non-valvular atrial fibrillation

Atrial Fibrillation (AF) is the most prevalent sustained cardiac arrhythmia disorder. More than 6 million Americans have AF and the number of cases is expected to rise to double over the next 30 years (1). Multiple studies have demonstrated that African Americans and Latinos have a lower prevalence of AF despite having a higher burden of traditional AF risk factors when compared with Caucasians (2-5). These minority populations are often underrepresented in large scale AF trials such as AFFIRM (6). Whereas AF prevalence in the overall general population averages about 2%, the estimated prevalence of AF among patients with renal impairment has been reported up to 23% depending upon age, degree of renal impairment and method of detection for AF (7-9). Thus, there exists a large group of patients that have AF with reduced glomerular filtration rate (GFR). A unique association between AF and chronic kidney disease (CKD) is

that they share similar risk factors and comorbidities. (9-17). Non-valvular atrial fibrillation (NVAF) is an independent risk factor for cardiovascular morbidity and mortality including death (18, 19), myocardial infarction (MI) (20) and stroke. Specific risk factors have been identified which significantly increase the risk of major adverse cardiovascular events (MACE) in general population with NVAF, as delineated by the CHA_2DS_2VASc score (19, 21). However, the c statistic for such scoring systems are in the 0.6 range (19). Adding renal dysfunction to such scoring scales has also been shown to improve the positive predictive value of this scoring system (22).

It is not clear that white race confers higher AF risk or that African American and Latino race provide some form of arrhythmia protection. Renal dysfunction as defined by a GFR <60 is recognized as an independent risk factor for MACE (23-27). Traditional risk factors for MACE are more commonly seen in patients with reduced GFR and AF. There is minimal published data that establishes CKD as an independent risk factor for MACE in the African American and Latino AF population. We conducted a retrospective study, in a unique hospital population mainly of African Americans and Latinos, to investigate if reduced GFR is an independent risk factor for MACE primarily in a minority NVAF population.

Methods

A retrospective review of the patients admitted to a single center from 2005 to 2012 was performed. All patients with NVAF were selected who were on guideline directed anticoagulation therapy with warfarin (prior to approval of novel anticoagulants). Demographic, comorbidity and medical therapy data were collected and analyzed from a total sample size of 656 patients, Renal dysfunction was defined as GFR of <60 ml/min (339 patients), The MDRD method was used to calculate GFR. The patient group with GFR <60 ml/min was not further categorized into subgroups.

The selected cardiovascular outcomes of interest were myocardial infarction (MI), stroke (CVA), and death. MI was defined as NSTEMI type 1 or STEMI confirmed by in house cardiologist or by subsequent cardiac catheterization or a nuclear stress test. Patient with minimal troponin elevations in settings of demand ischemia were not labelled as having MI. Stroke was defined as radiographic evidence of non-hemorrhagic stroke or TIA confirmed by board certified neurologist at the time of discharge with the help of supporting studies done during the admission. Manual review of EMR was performed for all patients included in the study to avoid false positives and negatives.

All statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC), and statistical significance was set at 0.05. To check the distributions of all variables prior to analysis, categorical variables were summarized with frequencies and percentages while continuous variables were summarized with means, standard deviations, and medians and with histograms and normal probability plots. A Chi-square test, two-sample t-test, or Wilcoxon Rank Sum test was used to test for differences between the group of patients with renal dysfunction and the group of patients with GFR [?]60 ml/min (Table 1) in terms of demographic variables and other risk factors.

The association between GFR groups and myocardial infarction, stroke, death, or any of those events was tested using binomial logistic regression (Table 2).

To incorporate the element of time and adjust for covariates, a Cox proportional hazards model analysis was applied for each outcome variable (Table 3).

The time to the event was calculated as the time from the date of admission to the time of the event, or time of the first event in the case of the combination of all events, for patients who had an event and as the time from the date of admission to the end of the retrospective study period (12-31-2013) for patients who had no event over the course of the study period. Potential covariates were determined via a bivariate analysis of the variables listed in Table 1 with each outcome variable. Variables with a p-value <0.10 were included for model selection. Prior to model selection, the potential covariates were tested for multicollinearity using variance inflation factor (VIF) statistics, but no multicollinearity between variables was found. Various methods of model selection were then applied using the potential covariates with each outcome while always including

GFR groups in the final model to determine if it continued to have a significant effect on the outcome when adjusted for other covariates. This included stepwise selection, backward selection, forward selection, and best subsets selection using 0.15 as the entry criteria and 0.05 as the stay criteria. The results from all methods were incorporated into making a decision about the composition of the final model. Hazard ratios were used to quantify the magnitude and direction of the effect of each significant variable on the outcome.

Results

Table 1 shows baseline characteristics of the patients with GFR <60 ml/min (renal dysfunction) compared with patient with GFR [?]60 ml/min. Over 98% of the patient population were either African Americans or Latinos. Table 1 also shows the statistically significant differences in baseline characteristics. Table 2 shows incidence of myocardial Ischemia, stroke, and MI stroke or death in patients with renal dysfunction as compared to patients with GFR [?]60. Out of 339 patients with renal dysfunction, 56 (17%) had MI, 72 (21%) had stroke, 85 (25%) died and 163 (48%) had MI, Stroke or Death. In comparison, out of 317 patients with GFR [?]60, 27 (9%) patient had MI, 48 (15%) had stroke, 41 (13%) died and 99 (31%) had MI, stroke or death. Table 3 shows stepwise cox regression analysis for the time to the development of MI, Stroke, Death and MI, stroke or Death (any event).

Renal dysfunction was an independent risk factor for MI (Hazard ratio 1.88 (1.17, 3.04); p=0.009). It also shows CAD is an independent risk factor for MI (2.79 (1.78, 4.39); p<0.001) as shown in prior studies. Renal dysfunction is an independent risk factor for death (HR 1.63 (1.11, 2.41); p=0.014). In addition, age (HR 1.31 (1.13, 1.51), P value <0.001) and prior MI (HR 2.24 (1.46, 3.43); p<0.001) are also independent risk factors for death as shown in prior studies. Where renal dysfunction is not an independent risk factor for stroke (HR 1.13 (0.77, 1.65); p=0.529), age (HR 1.31 (1.13, 1.51); p<0.001) and prior stroke (HR 1.99 (1.36, 2.92), p=0.001) are independent risk factors for new stroke as demonstrated in prior studies. Renal dysfunction is an independent risk factor for MI, stroke or death (Hazard ratio 1.37 (1.05, 1.78); p=0.018). It also shows that age (HR 1.32 (1.20, 1.46); p<0.001) and prior stroke (HR 1.47 (1.11, 1.94); p=0.007) are also an independent risk factors for composite of these three events.

Discussion

In 2014, 8.0% of all Medicare Fee-For-Service beneficiaries had a diagnosis of AF (28). In the 65 and older population, AF prevalence was higher among males (10.5%) than females (8.4%) and was highest among Non- Hispanic Whites (10.2%), followed by American Indians/Alaska Natives (5.9%), Hispanics (5.0%), Blacks/African Americans (5.1%), and Asian Pacific Islanders (4.9%). The cause of these differences in prevalence is unknown but recent study suggests that there may be some genetic protection against AF in minority populations (29).

Several additional reports have evaluated the prevalence of AF in CKD patients but few have studied if CKD in AF patients independently increases MACE when adjusted for previously defined traditional risk factors for MACE. Our study is one of the first to assess the effects of CKD on MACE in an African American and Latino NVAF population and provides evidence that a decreased GFR was an independent risk factor for MI, Death and MI, stroke and death among these patients. Our data reinforces other studies that have identified renal dysfunction as an added predictor of MACE, although our data is unique in that it is predominantly from a non-Caucasian population.

Different than other studies in non- African Americans and Latinos, our data showed that a decreased GFR was not an independent risk factor for stroke in our patient population. In a recent large prospective cohort study of AF patients, Go et al found that a lower level of estimated glomerular filtration rate was associated with a graded, increased risk of ischemic stroke and other systemic embolism, independently of known risk factors in AF (30). A study performed in Japan evaluated if CKD constitutes a risk for stroke and it concluded that decreased kidney function increases the risk of first symptomatic stroke events in a general Japanese population (31). Piccini et al reported that adding impaired renal function to standard stroke risk scoring scale was a potent predictor for stroke and systemic embolism in a predominantly white population (22).

Multiple studies have demonstrated that stroke rates are higher in AF patients with renal dysfunction. Vazquez et al demonstrated a 9.8-fold increased risk of ischemic stroke among patients undergoing dialysis who had AF compared those who maintained sinus rhythm during dialysis (32). In the U.S. Renal Data System study, patients with end-stage renal failure and AF had a 1.8-fold higher rate of ischemic strokes, whereas hemorrhagic stroke rates were comparable to end-stage renal failure patients in sinus rhythm (33). Conversely, in the Rotterdam study (34), decreased GFR did not significantly increase the risk of ischemic stroke, but was a strong predictor of hemorrhagic stroke. Genovesi et al demonstrated that AF was associated with greater total and cardiovascular mortality among hemodialysis patients and was more notable for cardiovascular than non-cardiovascular mortality (8). Nakagawa et al demonstrated that combined eGFR and $CHADS_2$ score could be an independent powerful predictor of cardiovascular events and mortality in patients with NVAF (35). Long-term mortality, cardiac events, and stroke risk were >8 times higher when decreased eGFR was present with higher $CHADS_2$ score ([?]2).

The mechanism by which chronic kidney disease (CKD) increases the risk of MACE is not known. CKD increases vascular calcification, inflammation, valve problems, and fluctuation in electrolytes, sympathetic nervous system activation and modulation of renin angiotensin system. Tanaka (36) noted an inverse relationship of eGFR to thrombin-antithrombin (TAT) and fibrin D-dimer levels, both indexes of thrombogenesis. Shlipak demonstrated that renal insufficiency was independently associated with elevations in inflammatory and pro-coagulant biomarkers (37). These findings lend support to the notion that enhanced coagulation activation appears to be related to a reduction in residual renal function in patients with AF (38).

A manual review of EMR was performed for all patients included in the study to avoid false positives and negative. However, our study has several limitations. It was completed at one center and was done primarily on African American and Latino patient population. The Latino/Hispanic population was not sub-stratified further and there have been differences in prevalence in various subgroups (5). This was a retrospective analysis of such patients. The contradictory result for CKD being an independent risk factor for stroke could be due to our unique patient population, or a relatively small sample size of patients with paroxysmal AF mistakenly excluded from study.

A prospective study in minority AF patients with renal dysfunction should be done in the future to provide further evidence regarding ischemic neurological events in this patient population and verify our findings of MACE.

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Table 1- Baseline characteristics of patients with GFR <60 vs. patients with GFR [?]60

Variable	**GFR <60 N = 339**	**GFR [?]60 N = 317**	**p value**
Age (years)*	73.6 ± 13.3	67.1 ± 15.4	<0.001
Gender			0.015
Men	154 (45%)	174 (55%)	
Women	185 (55%)	143 (45%)	
African-American	271 (80%)	258 (81%)	0.639
Latino	61 (18%)	51 (16%)	0.517
BMI (kg/m^2)+	27.5 (9.5)	27.6 (9.1)	0.433
Hypertension	315 (93%)	255 (80%)	<0.001
Dyslipidemia	136 (40%)	117 (37%)	0.383
Smoking	116 (35%)	145 (46%)	0.003
DM	134 (40%)	85 (27%)	<0.001
CAD	80 (24%)	56 (18%)	0.067
PVD	34 (10%)	27 (9%)	0.506
CHF	113 (34%)	90 (29%)	0.198
Prior stroke	77 (23%)	54 (17%)	0.076
CHADVasc2			<0.001
0	5 (1%)	22 (7%)	
1	18 (5%)	41 (13%)	
>1	316 (93%)	254 (80%)	
Oral Hypogly	65 (19%)	43 (14%)	0.053
Insulin	46 (14%)	13 (4%)	<0.001
Aspirin	140 (41%)	129 (41%)	0.850
Plavix	24 (7%)	15 (5%)	0.204
Statins	124 (37%)	112 (35%)	0.739
B-Blockers	155 (46%)	136 (43%)	0.447
ACEI/ARB	146 (43%)	144 (45%)	0.543
Coumadin/AC	133 (39%)	135 (43%)	0.383
% Time on AC+	62.7 (43.0)	60.4 (33.0)	0.551
Digoxin	42 (12%)	37 (12%)	0.778
Amiodarone	8 (2%)	3 (1%)	0.159
BiDil	20 (6%)	7 (2%)	0.017
CCB-DH	82 (24%)	64 (20%)	0.218

CCB-NonDH	45 (13%)	25 (8%)	0.026
Abbreviations: ACEI Angiotensin converting enzyme; ARB Angiotensin receptor blocker; BMI body mass index; GFR glomerular filtration rate. * Mean ± SD, Two-sample t-test + Median (IQR), Wilcoxon Rank Sum test N (%), Chi-square test otherwise	Abbreviations: ACEI Angiotensin converting enzyme; ARB Angiotensin receptor blocker; BMI body mass index; GFR glomerular filtration rate. * Mean ± SD, Two-sample t-test + Median (IQR), Wilcoxon Rank Sum test N (%), Chi-square test otherwise	Abbreviations: ACEI Angiotensin converting enzyme; ARB Angiotensin receptor blocker; BMI body mass index; GFR glomerular filtration rate. * Mean ± SD, Two-sample t-test + Median (IQR), Wilcoxon Rank Sum test N (%), Chi-square test otherwise	Abbreviations: ACEI Angiotensin converting enzyme; ARB Angiotensin receptor blocker; BMI body mass index; GFR glomerular filtration rate. * Mean ± SD, Two-sample t-test + Median (IQR), Wilcoxon Rank Sum test N (%), Chi-square test otherwise

Table 2- Incidence of myocardial Ischemia, stroke, and MI stroke or death in patients with GFR <60 vs. patients with GFR [?]60

Outcome	**GFR <60 N = 339**	**GFR [?]60 N = 317**	**p value***
Myocardial infarction	56 (17%)	27 (9%)	0.002
Stroke	72 (21%)	48 (15%)	0.044
Death	85 (25%)	41 (13%)	<0.001
MI, Stroke or Death	163 (48%)	99 (31%)	<0.001
Binomial logistic regression model Abbreviations: MI: Myocardial Infarction; GFR: Glomerular filtration rate	* Binomial logistic regression model Abbreviations: MI: Myocardial Infarction; GFR: Glomerular filtration rate	* Binomial logistic regression model Abbreviations: MI: Myocardial Infarction; GFR: Glomerular filtration rate	* Binomial logistic regression model Abbreviations: MI: Myocardial Infarction; GFR: Glomerular filtration rate

Table 3- Cox Proportional Hazard Regression Analysis for the Time to the Development of Myocardial Infarction, Stroke, Death, or any of these events among patients with GFR <60 vs. patients with GFR [?]60

Outcome	**Prognostic Factor**
Myocardial infarction	GFR <60
	CAD
Stroke	GFR <60
	Age (per 10 years)
	Prior stroke
Death	GFR <60
	Age (per 10 years)
	Oral hypoglycemics
	Insulin
	Myocardial infarction
Any event	GFR <60
	Age (per 1 year)
	Prior stroke
Cox proportional hazards regression model Abbreviations: GFR: Glomerular filtration rate; CAD: Coronary artery disease	* Cox proportional hazards regression mo Abbreviations: GFR: Glomerular filtration