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ORIGINAL ARTICLE

Association Between Dehydration and Short-Term Risk of Ischemic Stroke in Patients with Atrial Fibrillation

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Abstract Previous cross-sectional studies have demonstrated a higher incidence of dehydration in patients admitted for stroke suggesting a possible association. However, the temporality of the association has not been well established. We examined whether dehydration increases the risk of ischemic stroke in patients with a recent hospitalization for atrial fibrillation (AF). Data was from 1994 to 2012 from the Myocardial Infarction Data Acquisition System (MIDAS), a repository of in-patient records New Jersey hospitals, for AF hospitalizations ($n = 1{,}282{,}787$). Estimates for the association between AF hospitalization with/without dehydration and ischemic stroke within 30 days post-AF discharge were determined using log-linear multivariable modeling adjusting for socio-demographic factors and comorbid conditions. Within 10 days of discharge for AF, patients 18–80 years old (YO) with comorbid dehydration had a 60 % higher risk of ischemic stroke compared to AF patients without comorbid dehydration (adjusted risk ratio (ARR) 1.60, 95 % confidence interval (CI) 1.28–2.00). Eighteen- to 80-YO patients had a 34 % higher risk of ischemic stroke in days 11–20 post-AF discharge (ARR 1.34, 95 % CI 1.04, 1.74). There was no difference in the risk of stroke in 18–80-YO patients with or without prior dehydration during days 21–30 post-AF discharge. We also found no difference in the risk of ischemic stroke during any time period in patients over 80 YO. Dehydration may be a significant risk factor for ischemic stroke in patients 18–80 YO with AF.

Keywords Ischemic stroke · Hemorrhagic stroke · Myocardial infarction · Dehydration · Cardiovascular

Introduction

Many studies have found an association between dehydration and stroke. However, the temporal sequence of the association and the underlying mechanisms are in question. Studies to date have primarily focused on the incidence of comorbid dehydration in patients admitted for ischemic stroke [1–3]. From these studies, it is not possible to determine whether ischemic stroke preceded dehydration or vice versa. Current American Heart Association guidelines do not list control of dehydration as a modifiable risk factor for stroke prevention [4]. Evidence for the association of prior dehydration with ischemic stroke would be important for guidance in the primary prevention of ischemic stroke.

The relationship between dehydration and ischemic stroke is not clear, and it is possible that both sequences, ischemic stroke leading to a dehydrated state

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and dehydration leading to ischemic stroke, may occur. In cases where ischemic stroke precedes dehydration, this may be the result of acute motor deficits leading to the inability of a patient to rehydrate. Dysphagia has been shown to be one such motor deficit leading to dehydration [5, 6]. Dehydration following stroke has been shown to increase short-term mortality rates [1, 3]. Reducing dehydration rates could be a secondary prevention measure following stroke. Circumstances may also exist where the temporal relationship between these events is reversed, when dehydration precedes and may be a factor in ischemic stroke. Dehydration may promote thrombus formation [7], and although this temporal sequence has not been demonstrated for ischemic stroke, it has been suspected in other thromboembolic events, for example in the development of deep vein thrombosis during extended air travel [8].

Although the theory behind the sequence of dehydration leading to ischemic stroke is well founded, evidence for this route has been largely circumstantial. One difficulty in observing this sequence of events is due to the lack of hydration status measurements just prior to the incidence of ischemic stroke. Studies to date have based the association between dehydration and ischemic stroke on cross-sectional analyses of hydration levels in patients after the initial presentation for ischemic stroke. An actual determination of the patient's hydration status prior to the onset of stroke would rely on chance recent laboratory testing or, at a minimum, patient recall which is prone to bias.

The objective in this study was to examine, utilizing longitudinal data, whether patients with a recent history of hospitalization for atrial fibrillation, a known risk factor for ischemic stroke, and dehydration were at an increased short-term risk of ischemic stroke. The design utilized in this study allowed us to test the temporal relationship between the two factors by examining dehydration diagnosed just prior to ischemic stroke occurrence. Our hypothesis was that as dehydration increased the coagulability of blood, patients would be at an increased risk of thrombus formation and, in turn, an increased risk of thromboembolic cerebral infarction.

Materials and Methods

We obtained data for this study from the Myocardial Infarction Data Acquisition System (MIDAS) for the years 1994–2012. MIDAS is an administrative database containing hospital records of all patients discharged from non-federal hospitals in New Jersey (NJ), USA, with a diagnosis of cardiovascular disease or invasive cardiovascular procedure [9]. Information from death certificates was linked to the hospitalization records. The data were obtained from the NJ Department of Health utilizing the NJ Discharge Data Collection System (NJDDCS) and were approved by the NJ state and the Robert Wood Johnson Medical School institutional review boards.

We identified all hospitalizations for atrial fibrillation (AF), both with and without comorbid dehydration, and examined subsequent hospitalization or death from ischemic stroke 2 to 30 days post-AF discharge. The 2-day period blanking period between AF discharge and readmissions was used to ensure that the patient was indeed released from the first hospitalization and subsequently readmitted.

To identify hospitalizations for AF, records from patients 18 years and older with a primary or secondary diagnosis of AF based on International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) discharge diagnostic codes beginning with 427.3 ($N = 1{,}431{,}161$) and were discharged to home or to a secondary care facility. Dehydration was determined through the use of ICD-9-CM codes beginning with 276.5 in any of the discharge diagnoses. These codes include 276.5 and 276.50 ("volume depletion, unspecified"), 276.51 ("dehydration"), and 276.52 ("hypovolemia"). These codes excluded hypovolemic shock, either postoperative or traumatic. The use of these codes was indicated as part of the guidelines developed by the Agency for Healthcare Research and Quality (AHRQ) for analysis of dehydration hospitalizations [10]. For the AF hospitalization, we excluded any record where one of the discharge diagnostic codes began with either 433 ("occlusion and stenosis of precerebral arteries") or 434 ("occlusion of cerebral arteries") to ensure that the hospitalization did not involve a concomitant ischemic stroke ($n = 147{,}215$, 10.3 % of records). These records were excluded to ensure that all dehydration diagnoses occurred prior to ischemic stroke. To increase the sensitivity of the dehydration diagnosis, particularly the code for hypovolemia, such that it was unlikely to be due to blood loss, we excluded patients who received a blood transfusion during the AF hospitalization ($n = 1159$, 0.09 % of remaining patients). The final count of AF hospitalizations used in this study was 1,282,787.

We utilized two sets of analyses to estimate the association between dehydration and ischemic stroke. The first analysis set was used to estimate the association between dehydration and the incidence of or mortality

from ischemic stroke in patients who were either readmitted to the hospital or suffered an out-of-hospital death from ischemic stroke within 2 to 30 days after AF discharge for ischemic stroke. For the first model in this analysis, our primary outcome, ischemic stroke, was determined by the presence of discharge diagnosis codes that included one of the following: 434.10 ("cerebral embolism without mention of cerebral infarction"), 434.11 ("cerebral embolism with cerebral infarction"), 434.90 ("cerebral artery occlusion, unspecified without mention of cerebral infarction"), or 434.91 ("cerebral artery occlusion, unspecified with cerebral infarction"). We also included ischemic strokes from patients who died from strokes within the designated time frame by including ICD, 10th Revision (ICD-10-CM) codes starting with I63 ("cerebral infarction") within the cause of death variable on the death certificate.

In addition to our primary outcome of ischemic stroke, we examined three other outcomes, also within 2–30 days of discharge for AF, as secondary outcomes with which to assess potential selection biases. First, incidence of and mortality from acute myocardial infarction (AMI) following the index AF hospitalization was used as a "positive control," as there may be an increased incidence of AMI if blood coagulability is increased. AMI was determined through discharge diagnosis codes beginning with 410, excluding codes with a fifth digit of "2," e.g., 410.02, indicating a subsequent episode of care for an AMI. We also included AMIs from patients who died from AMIs within the designated time frame by including ICD-10-CM codes beginning with "I21" within the cause of death variable on the death certificate.

Next, we examined post-AF hospitalization for two "negative control" outcomes unlikely to be positively associated with dehydration and concomitant blood hypercoagulability: hemorrhagic stroke and aortic aneurysm/dissection. Incidence of or mortality from these conditions would not have been primarily caused by increases in blood coagulability and would serve as additional control groups, i.e., admissions for these conditions should show no increased risk among AF patients with recent dehydration. Hemorrhagic strokes were determined through discharge diagnosis codes beginning with 430, 431, or 432. We also included patients who died from hemorrhagic strokes during the timeframe by including IDC-10 codes beginning with I60, I61, or I62 within the cause of death variable on the death certificate. Aortic aneurysms/dissections were determined by ICD-9 codes starting with 441 in discharge diagnosis codes and ICD-10 codes beginning with I71 in the cause of death variable.

We considered several covariates as possible confounders for these analyses based on prior literature. We utilized socio-demographic variables including age at admission (categorized as ≤60 years old (YO), 61–70 YO, 71–80 YO, and ≥81 YO), sex, race/ethnicity (categorized as non-Hispanic White, non-Hispanic Black, Hispanic, and Other), neighborhood income based on home zip code and 2000 and 2010 census information [11] (categorized as median household incomes ≤$50,000 and >$50,000), and health insurance (categorized as Commercial, Medicare, Medicaid, and other/uninsured). We also adjusted for several comorbid conditions, either concurrent with or prior to AF admission, determined to be risk factors for ischemic stroke based on prior studies. The comorbid conditions we included as covariates were history of myocardial infarction, stroke, hypertension, diabetes, hyperlipidemia, cancer, chronic renal disease, chronic obstructive pulmonary disease (COPD) or asthma, heart failure, ischemic heart disease, deep vein thrombosis, peripheral vascular disease, atherosclerosis, upper respiratory infection, sepsis and/or septicemia, and chronic liver disease. We also adjusted for two prior surgical procedures as possible confounders, percutaneous coronary intervention (PCI), and coronary artery bypass graft (CABG). In a sensitivity analysis, we adjusted for the CHA_2DS_2-VASc score for stroke risk in atrial fibrillation patients [12]. We utilized the score as an adjustment measure replacing the individual elements of age, sex, and history of heart failure, hypertension, stroke, peripheral vascular disease, and diabetes.

Our second analysis was utilized to determine if the association between dehydration and hospitalization for ischemic stroke changed over time from AF discharge. For this analysis, the outcome of ischemic stroke was determined through the use of the same ICD-9-CM codes discussed previously. In the first model of this analysis, we included a dehydration-time interaction term to determine whether the effect of dehydration decreased with time from AF discharge. In the second model, we stratified the analysis by time periods, 2–15, 16–30, and 31–45 days post-AF discharge. In this analysis, we also tested for effect modification of dehydration by age based on differences found in bivariate analyses for both dehydration and ischemic stroke. For ischemic stroke, the effect modification term was statistically significant for those over 80 YO compared those 80 years or younger. Due to this heterogeneity of effect by age, we analyzed ischemic stroke utilizing a two-level stratified method. One stratum consisted of those patients 80 YO and younger; the other stratum

consisted of those older than 80 YO. These models were also adjusted for all covariates as in the first analysis.

Statistical Analysis

We calculated the incidence risk ratio (RR) as:

$$\text{Incidence Risk Ratio} = \frac{\text{Incidence Rate ischemic stroke following AF + D}}{\text{Incidence Rate ischemic stroke following AF − D}}$$

Incidence risk ratios were calculated in an analogous manner for AMI, hemorrhagic stroke, and aortic aneurysm/dissection.

We calculated the mortality risk ratio (RR) as:

$$\text{Mortality Risk Ratio} = \frac{\text{Mortality Rate ischemic stroke following AF + D}}{\text{Mortality Rate ischemic stroke following AF − D}}$$

Mortality risk ratios were calculated in an analogous manner for AMI, hemorrhagic stroke, and aortic aneurysm/dissection.

We estimated the incidence and mortality risk ratios conditional on possible confounders using log-linear regression with the GENMOD procedure in SAS V9.3 (SAS Corporation, Cary, NC, USA). Parameter estimates were determined utilizing generalized estimating equations (GEE) with robust variances for repeated measures accounting for multiple AF admissions per study subject [13, 14]. We utilized a compound symmetry working correlation matrix to fit the regression models for this unbalanced longitudinal data.

The level for statistical significance for all tests was set at two-sided P values <0.05.

Results

The socio-demographic and comorbid factors in patients with AF + D and those with AF − D are described in Table 1. Based on our patient selection criteria, there were a total of 1,284,729 AF admissions between January 1, 1994, and December 31, 2012. Of those admissions, 116,437 (9 %) included comorbid dehydration diagnoses (AF + D) and 1,168,292 (91 %) did not (AF − D). The AF + D group was less likely to have AF as the primary reason for admission, was older, and had a higher percentage of women than the AF − D group. In accordance with the age differences, the AF + D group was more likely to have Medicare as their primary source of health insurance. Other potentially important differences between the groups were in the comorbid rates of hyperlipidemia (AF + D lower than AF − D), prior stroke (AF + D higher than AF − D), chronic renal disease (AF + D higher than AF − D), sepsis and/or septicemia (AF + D higher than AF − D), and in the use of PCI and CABG (AF + D lower than AF − D).

We first examined the association between dehydration and the incidence of or mortality from ischemic stroke after AF discharge (Table 2). We found that in AF + D patients, there was a 21 % increase in the risk of ischemic stroke within days 2 to 30 after AF discharge compared to AF − D patients after adjustment for socio-demographic factors and comorbid conditions (adjusted risk ratio (ARR) 1.21, 95 % confidence interval (CI) 1.11, 1.32). We also found that the risk of death from ischemic stroke was about 2.3 times greater in AF + D patients compared to AF − D patients (ARR 2.33, 95 % CI 1.67, 3.26). We also utilized this analysis to estimate the incidence and mortality risks for three additional outcomes, AMI, hemorrhagic stroke, and aortic aneurysm and dissection. We found a 25 % increase in the incidence of AMI in AF + D patients compared to AF − D patients (ARR 1.25, 95 % CI 1.18, 1.33) and a 59 % increase in AMI mortality in AF + D compared to AF − D patients (ARR 1.59, 95 % CI 1.47, 1.72). We also found a significant 16 % decrease in the incidence of hemorrhagic stroke in AF + D patients compared to AF − D patients (ARR 0.84, 95 % CI 0.71, 0.99) and no difference in aortic aneurysm and dissection (ARR 0.91, 95 % CI 0.80, 1.04). We found no significant differences in the risk of mortality from either hemorrhagic stroke or aortic aneurysm and dissection during days 2–30 post-AF discharge in AF + D patients compared to AF − D patients.

In our second series of analyses, we examined changes in risk of ischemic stoke over time in AF + D and AF − D patients (Table 3). Modeling the risk of ischemic stroke stratified by time period, we found the greatest relative difference in risk of ischemic stroke associated with dehydration during the 2–10-day time period post-AF discharge. During this period, 80-year-old and younger patients with AF + D were at 60 % higher risk of hospitalization for ischemic stroke compared to AF − D patients (ARR 1.60, 95 % CI 1.28, 2.00). In the next time period, days 11–20 post-AF discharge, the risk of ischemic stroke in AF + D patients was 34 % higher than in AF − D patients (ARR 1.34, 95 % CI 1.04, 1.74), somewhat less than in days 2–10 post-AF discharge. The effect of dehydration was no longer evident in the 21–30-day time period; the risk of ischemic stroke during this period was similar in the AF + D and AF − D patients (ARR 1.05, 95 % CI 0.77, 1.42). There was no relative difference in risk among those over 80 years of age with AF + D versus AF − D during any of the time periods studied. We also developed a model where time was included as a continuous log-transformed covariate to determine the

Table 1 Distribution of patient socio-demographic and comorbid conditions in atrial fibrillation admissions with and without comorbid dehydration from 1994 to 2012 in the Myocardial Infarction Data Acquisition System ($N = 1{,}282{,}787$)

	All AF admissions	AF admissions without dehydration	AF admissions with dehydration
Number of AF admissions	1,282,787	1,166,631 (91.0 %)	116,156 (9.0 %)
AF primary reason for admission (%)	18.1	19.2	7.1
Age			
Mean (SD)	76.0 (12.6)	75.5 (12.7)	81.0 (10.1)
≤60YO (%[a])	11.9	12.6	4.3
61–70 YO (%)	15.1	15.8	8.7
71–80 YO (%)	30.9	31.3	27.4
≥81 YO (%)	42.1	40.3	59.6
Length of stay (days), median (IR)	5 (2, 8)	5 (2, 8)	7 (4, 11)
Female (%)	52.9	52.3	58.6
Race/ethnicity			
NonH White (%)	82.7	82.5	84.1
NonH Black (%)	7.8	7.9	7.1
Hispanic (%)	5.1	5.1	4.5
Other (%)	4.4	4.4	4.3
NH income ≥ $50,000/year (%)	64.6	64.5	65.7
Health insurance			
Commercial (%)	21.7	22.5	13.1
Medicare (%)	75.3	74.3	85.3
Medicaid (%)	1.3	1.4	0.9
Other/uninsured (%)	1.7	1.8	0.7
Prior/comorbid conditions and procedures			
Hypertension (%)	82.1	82.3	79.7
Diabetes (%)	34.1	34.2	32.4
Hyperlipidemia (%)	41.9	42.9	31.7
Prior AMI (%)	15.5	15.6	14.6
Prior stroke (%)	16.0	15.7	20.0
Cancer (%)	26.7	26.4	29.7
Chronic renal disease (%)	24.4	23.6	32.7
COPD/asthma (%)	41.9	42.0	40.7
Heart failure (%)	56.6	56.6	57.4
Ischemic heart disease (%)	62.9	63.1	60.7
Deep vein thrombosis (%)	7.6	7.5	8.7
Peripheral vascular disease (%)	17.1	17.1	17.2
Chronic liver disease (%)	2.9	2.9	2.5
Upper respiratory infection (%)	0.4	0.4	0.3
Sepsis and/or septicemia (%)	3.8	3.2	9.6
PCI (%)	11.0	11.3	7.7
CABG (%)	10.2	10.4	7.6
CHA_2DS_2-VASc, median (IR)	4 (3, 5)	5 (3, 6)	4 (3, 5)

AF atrial fibrillation, *SD* standard deviation, *IR* interquartile range, *YO* years old, *NonH* non-Hispanic, *AMI* acute myocardial infarction, *NH* neighborhood, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass graft surgery, *CHA_2DS_2-VASc* the Birmingham 2009 schema for stroke risk in patients with atrial fibrillation

[a] Percent of AF admissions

level of effect modification of time on the association between dehydration and ischemic stroke. Utilizing this model, we found a 10 % reduction in the effect of dehydration per 10-day period (ARR 0.90, 95 % CI 0.84, 0.97).

There were large differences in the proportion of AF + D patients with prior stroke, chronic renal disease, and sepsis and/or septicemia compared to AF − D patients. In addition to the previously described analyses,

Table 2 Adjusted incidence and mortality rate ratios for ischemic stroke, acute myocardial infarction, hemorrhagic stroke, and aortic aneurysm and dissection 2 to 30 days after hospital discharge for atrial fibrillation with or without comorbid dehydration from 1994 to 2012 in the Myocardial Infarction Data Acquisition System ($N = 1,282,787$)

Outcome	Adjusted[a] incidence risk ratio AF + D vs. AF − D (95 % CI)	*P* value	Adjusted[a] mortality risk ratio AF + D vs. AF − D (95 % CI)	*P* value
Ischemic stroke	1.21 (1.11, 1.32)	<0.0001	2.33 (1.67, 3.26)	<0.0001
Acute myocardial infarction	1.25 (1.18, 1.33)	<0.0001	1.59 (1.47, 1.72)	<0.0001
Hemorrhagic stroke	0.84 (0.70, 0.44)	0.04	1.02 (0.68, 1.55)	0.9
Aortic aneurysm and dissection	0.91 (0.80, 1.04)	0.2	0.89 (0.65, 1.20)	0.4

AF atrial fibrillation, *AF + D* atrial fibrillation with dehydration, *AF − D* atrial fibrillation without dehydration, *CI* confidence interval

[a] Adjusted for age, sex, race/ethnicity, health insurance type, neighborhood income, and history of the following: acute myocardial infarction, stroke, ischemic heart disease, hypertension, diabetes, hyperlipidemia, cancer, chronic renal disease, chronic obstructive pulmonary disease, heart failure, cardiac arrhythmias, deep vein thrombosis, chronic liver disease, peripheral vascular disease, sepsis/septicemia, upper respiratory infection, percutaneous coronary intervention, and coronary artery bypass graft surgery

we performed sensitivity analyses where we excluded patients with prior stroke, chronic renal disease, or sepsis/septicemia. The results of these analyses were similar to the analyses where we adjusted for these covariates. We also performed sensitivity analyses excluding patients where AF was the primary reason for admission as the proportion was much higher in AF − D patients compared to AF + D patients. In these analyses, we again found similar results to the original analyses. We also performed a sensitivity analysis where we utilized the CHA_2DS_2-VASc score in place of the component risk factors. The results of these analyses yielded similar results to those observed in the original models.

Discussion

Our results indicate a positive association between prior dehydration and ischemic stroke in patients with atrial fibrillation. We also found that the effect of dehydration on ischemic stroke risk diminishes within a relatively short period of time. To the best of our knowledge, this study is the first to demonstrate a temporal relationship between prior dehydration and ischemic stroke.

Dehydration is a readily preventable condition that is a prevalent diagnosis on hospital discharge records. The rate of dehydration in AF patients in this study was approximately 9 %. The reasons for the development of dehydration vary. Dehydration may be from gastrointestinal losses, including

Table 3 Time trends for adjusted rate ratios of ischemic stroke hospitalizations following hospital discharge for atrial fibrillation with or without comorbid dehydration from 1994 to 2012 in the Myocardial Infarction Data Acquisition System ($N = 1,282,787$)

	Adjusted[a] AF + D vs. AF − D incidence risk ratio (95 % CI)	*P* value
≤80 YO		
2–10 days[b]	1.60 (1.28, 2.00)	<0.0001
11–20 days	1.34 (1.04, 1.74)	0.03
21–30 days	1.05 (0.77, 1.42)	0.8
EM	0.90 (0.84, 0.97)	0.004
>80 YO		
2–10 days	1.16 (0.99, 1.38)	0.1
11–20 days	0.93 (0.76, 1.14)	0.5
21–30 days	1.00 (0.81, 1.23)	0.9
EM	0.98 (0.94, 1.04)	0.5

AF atrial fibrillation, *AF + D* atrial fibrillation with dehydration, *AF − D* atrial fibrillation without dehydration, *CI* confidence interval, *EM* effect modification (dehydration-time)

[a] Adjusted for age, sex, race/ethnicity, health insurance type, neighborhood income, and history of the following: acute myocardial infarction, stroke, ischemic heart disease, hypertension, diabetes, hyperlipidemia, cancer, chronic renal disease, chronic obstructive pulmonary disease, heart failure, cardiac arrhythmias, deep vein thrombosis, chronic liver disease, peripheral vascular disease, sepsis/septicemia, upper respiratory infection, percutaneous coronary intervention, and coronary artery bypass graft surgery

[b] Days postdischarge AF admission

those due to gastroenteritis [15], renal losses (commonly due to diuretic therapy), and insufficient fluid intake, where behavior may play an important role. According to studies of NHANES survey data, US adults are drinking less water than is recommended by the CDC guidelines [16, 17]. In particular, men are more likely to be insufficiently hydrated as are those over age 70 [16]. Regardless of the cause of dehydration, the effects of dehydration on changes in blood coagulability due to hemoconcentration would likely be similar.

There are a number of biologically plausible mechanisms for increased blood clotting following dehydration. Biochemical factors have been extensively examined. von Willebrand factor (vWF) has been suggested as a factor that is increased during dehydration and promotes blood clotting [18]. Dmitrieva et al. found that in dehydrated mice, plasma levels of vWF and the number of microthrombi in capillaries both increased [19]. They hypothesize that increased extracellular sodium, as would occur during dehydration, acts as the trigger for increased vWF production. Physical factors have also been considered. Reduction in cerebral blood flow has been proposed as one mechanism. Harrison hypothesized that increases in hematocrit decrease cerebral blood flow through increases in blood viscosity [20]. Reduction in cerebral blood flow after standing has also been shown following dehydration combined with heat stress [21]. Pollock et al. found that higher hematocrits produced larger cerebral infarcts following partial cerebrovascular occlusion in a gerbil model [22]. Increased levels of factors involved in the blood clotting cascade, such as fibrinogen and platelets, would also occur following dehydration due to hemoconcentration [23]. The dehydration-induced promotion of blood clotting may have a role in ischemic stroke.

The reason for our finding of a lack of effect of dehydration in those over 80 years of age is unclear. While it is possible that changes in blood coagulability due to dehydration may be less pronounced in those over 80, this seems unlikely. There may have been greater misclassification of dehydration in this older age group. Thomas et al. found that overdiagnosis of dehydration occurred more frequently in older patients [24]. They found that physicians tended to rely more on physical appearance than on laboratory test results in making this diagnosis. If the specificity of the dehydration diagnosis was lower in this age group, the estimated association between dehydration and ischemic stroke would have been reduced. It is also possible that patients over 80 years old were more likely to die from ischemic stroke prior to hospitalization. In MIDAS, the ICD-10-CM codes for out-of-hospital death from stroke were nonspecific. In our study, when we included nonspecific out-of-hospital death from stroke in our data, we found that that AF + D patients over 80 years of age were at 28 % higher risk of stroke than AF − D patients (ARR 1.28, 95 % CI 1.17, 1.39, data not shown).

The present study has a number of strengths. We were able to examine the effect of dehydration on four overlapping sets of stroke outcomes based on ICD-9-CM coding and found our hypothesis of dehydration leading to a greater propensity for thromboembolic events to be supported. We were also able to test a number of outcomes in our patient dataset. The risks of two of these outcomes, ischemic stroke and AMI, were more likely to increase if our hypothesis was correct, whereas the risks of the other two control outcomes, hemorrhagic stroke and aortic aneurysm/dissection, would be unlikely to increase with a greater propensity for thrombus formation. The data on these four outcomes following admission for AF supported our hypothesis. Understanding the time trends for ischemic stroke risk also provided important information in support of our hypothesis. We conducted our study in a large dataset that has been validated for two of our four outcomes of interest, ischemic stroke and AMI. Utilizing a repeated measure statistical methodology, allowing multiple hospitalizations per patient, also likely increased the strength of our inferences in the study.

This study has a number of limitations. While our study demonstrated a recent history of dehydration prior to stroke, we cannot be certain that the patient was, in fact, dehydrated just prior to the onset of the ischemic stroke. However, patients with AF + D were about 24 times more likely to be diagnosed with dehydration during the subsequent admission for ischemic stroke compared to the AF − D group in strokes that occurred within 15 days of AF discharge (data not shown). In addition, it is known that intracardiac thrombi (particularly in the left atrial appendage) may persist over extended periods of time, in some cases despite therapeutic anticoagulation [25, 26]. This raises the possibility that some thrombi may have developed or increased in size during periods of dehydration, with subsequent embolization following discharge for AF. The use of hospital discharge data has been shown to be a source of misclassification due to data entry errors as well as data omission. While the MIDAS data set has undergone validation for accuracy of stroke and AMI, there may have been misclassification for dehydration. While one study demonstrated an overuse of the dehydration diagnosis, especially in the elderly, our study used a more specific definition of dehydration, which may reduce misclassification. Considering that there is no "gold standard" [27] for hydration status, dehydration may actually have been underreported in our dataset, especially in those without other risk factors for dehydration. It has been suggested that physicians may rely on physical signs of dehydration such as skin turgor or sunken eyes, signs of extreme dehydration, rather than evaluating laboratory data, which may or may not be available by the time of patient discharge [24]. Our dataset did not contain information on drug treatments. There may have been differences in anticoagulant use between the AF + D and AF − D patients possibly due to, for example, renal impairment or history of stroke. The sensitivity analysis performed where we found similar results after excluding those with chronic renal disease or prior stroke may somewhat address the

question of residual confounding due to differential anticoagulant use.

Conclusion

Our results indicate that dehydration may be a significant risk factor for the physically and economically costly outcome of ischemic stroke. The Agency for Healthcare Research and Quality, a division of the US Department of Health and Human Services, has cited reducing the dehydration admission rate as one of the top prevention quality indicators for health care organizations. However, in the MIDAS dataset covering all hospital admissions in NJ involving cardiovascular disease, there does not appear to be any significant reductions in admissions for dehydration over the past 15 years. This study reinforces the need to better understand how dehydration increases the risk of ischemic stroke especially in patients at higher risk of stroke due to comorbid conditions such as atrial fibrillation.

Authors' Contributions JS conceived of the study, performed the statistical analyses, and drafted the manuscript. TJ, WK, AF, NC, and JK participated in study design and in the draft of the manuscript. All authors read and approved the final manuscript.

Compliance with Ethical Standards

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Conflict of Interest Joel N. Swerdel declares that he has no conflict of interest. Teresa M. Janevic declares that she has no conflict of interest. William J. Kostis declares that he has no conflict of interest. Ambarina Faiz declares that she has no conflict of interest. Nora M. Cosgrove declares that she has no conflict of interest. John B. Kostis declares that he has no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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