Fludrocortisone Is Associated With a Higher Risk of All-Cause Hospitalizations Compared With Midodrine in Patients With Orthostatic Hypotension

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Background—Orthostatic hypotension causes ~80 000 hospitalizations per year in the United States. Treatments for orthostatic hypotension include fludrocortisone, a mineralocorticoid analog that promotes sodium reabsorption; and midodrine, an α-1 adrenergic agonist that is a direct vasoconstrictor. Although both medications are used to treat orthostatic hypotension, few studies have compared their relative safety.

Methods and Results—We compared incidence rates of hospitalizations for all causes, and for congestive heart failure between users of fludrocortisone and users of midodrine in a retrospective cohort study of Tennessee Medicaid adult enrollees (1995–2009). Adjusted incidence rate ratios were calculated using negative binomial regression models. Subgroup analyses based on history of congestive heart failure were conducted. We studied 1324 patients initiating fludrocortisone and 797 patients initiating midodrine. Compared with fludrocortisone users, midodrine users had higher prevalence of cardiovascular conditions. Incidence rates of all-cause hospitalizations for fludrocortisone and midodrine users were 1489 and 1330 per 1000 person-years, respectively (adjusted incidence-rate ratio 1.20, 95% confidence interval, 1.02–1.40). The respective rates of heart failure–related hospitalization were 76 and 84 per 1000 person-years (adjusted incidence-rate ratio: 1.33, 95% confidence interval, 0.79–2.56). Among patients with a history of congestive heart failure, the rates of all-cause hospitalization for fludrocortisone and midodrine were 2448 and 1820 per 1000 person-years (adjusted incidence-rate ratio: 1.42, 95% confidence interval, 1.07–1.90), and the respective rates of heart failure exacerbation–related hospitalizations were 297 and 263 per 1000 person-years (adjusted incidence-rate ratio: 1.48, 95% confidence interval, 0.69–3.16).

Conclusions—Compared with users of midodrine, users of fludrocortisone had higher rates of all-cause hospitalizations, especially among patients with congestive heart failure. (J Am Heart Assoc. 2017;6:e006848. DOI: 10.1161/JAHA.117.006848.)

Key Words: fludrocortisone • heart failure • hospitalization • midodrine • orthostatic hypotension

Orthostatic hypotension (OH) is defined as a drop in systolic blood pressure >20 mm Hg or diastolic blood pressure of at least 10 mm Hg with symptoms of cerebral hypoperfusion within 3 minutes upon standing. The prevalence of OH in community dwellers 65 years or older is 16.2%, and increases with age. Severely affected patients commonly experience syncope and falls, which causes substantial disability.

Treatment for OH is aimed at improving presyncopal symptoms, and preventing syncope, falls, and related morbidity. Treatment strategies include discontinuation of medications that cause OH (diuretics, α-1 adrenergic antagonists, and tricyclic antidepressants), use of compression garments, use of countermeasures, and rapid water drinking. If these strategies fail, then drug treatment may be warranted. In 2006, the European Federation of Neurological Societies provided guidelines for the diagnosis and management of OH. These guidelines considered fludrocortisone as the first-line drug treatment, although evidence supporting its efficacy for the treatment of OH was limited. Our previous study found that fludrocortisone, a drug not US Food and Drug Administration–approved to treat OH, is prescribed more frequently for OH than is midodrine, a US Food and Drug Administration–approved drug for this condition.

Considering that fludrocortisone is a synthetic mineralocorticoid analog (aldosterone-like drug) that increases plasma...
Clinical Perspective

What Is New?

- This is the first study to evaluate the comparative safety of fludrocortisone and midodrine, 2 drugs commonly used for the treatment of orthostatic hypotension.
- Fludrocortisone use was associated with increased risk of all-cause hospitalizations, particularly among patients with prevalent history of heart failure and orthostatic hypotension.

What Are the Clinical Implications?

- Our findings should help inform healthcare providers about safety of fludrocortisone use in patients with orthostatic hypotension.
- Our findings could be used to aid healthcare providers to make treatment decisions for patients with orthostatic hypotension.
- In patients with heart failure and orthostatic hypotension, fludrocortisone should not be used.

Methods

Using TennCare data files, we assembled a retrospective cohort of patients with OH. TennCare is the State-based managed care Medicaid program in Tennessee. A robust family of linkable files allows the reconstruction of medication exposures and related outcomes among program enrollees. This study included data from 1995 through 2009. From 1995 through 2005 the medication data were provided exclusively by TennCare and from 2006 until December 2009, the TennCare medication data were supplemented with Medicare Part D (for those patients who were dually eligible for TennCare and Medicare). This study was approved by the Institutional Review Board of Vanderbilt University, and by the Bureau of TennCare.

Retrospective Cohort

Potential cohort members entered the cohort at the earliest date when the following criteria were met: (1) a prescription filled for midodrine and/or fludrocortisone, identified using pharmacy files; (2) a coded healthcare encounter for OH (International Classification of Diseases, 9th Revision, Clinical Modification: 458.0, 458.1, 458.9, 333.0); (3) age 40 years or older; (4) have at least 180 prior days of continuous enrollment in TennCare (baseline); and (5) have at least 1 or more prescriptions filled during this baseline period to assure access to medication benefits. Since OH affects mostly elderly individuals, we restricted the age group to 40 and older to avoid a younger group of patients, such as those with postural tachycardia syndrome, who are usually prescribed similar drugs. We excluded patients with baseline diagnoses for conditions that have the potential to produce acute and transient OH and patients with established serious life-threatening diseases identified during baseline, including solid organ transplantation, end-stage renal disease, and hemodialysis as previously described. Since fludrocortisone is indicated as the partial replacement therapy for primary and secondary adrenocortical insufficiency in Addison’s disease and for the treatment of salt-losing adrenogenital syndrome, we also excluded patients with those conditions.

New episodes of either midodrine or fludrocortisone use began on the date of the earliest prescription for either of these medications without use of either of those drugs during the prior 180 days. Follow-up began on that date \( t_0 \) and continued through the earliest of the following dates: death, loss of enrollment, study outcome, end of the study, date of transplant of end-stage renal disease/hemodialysis or the fill of a different OH medication. Patients initiating both OH drugs simultaneously were excluded from this assessment. Patients who left the cohort could subsequently re-enter and contribute to new episodes of medication use if they fulfilled all selection criteria again.

Exposures

Study exposures were current use of midodrine or fludrocortisone. A previous study reported similar but relatively short
persistence on study medications after treatment initiation among older adults. Therefore, for this study, each person-day of follow-up was classified in prespecified medication exposure categories using pharmacy information. Current use represented person-time with medications available (ie, period covered by the prescription’s days of supply). Indeterminate use was defined as up to 180 days without medication available, following any current use. This category was used to reduce exposure misclassification as adherence could be imperfect and medication effects could extend beyond the last day of medication use. Nonuse represented any person-time not classified in the previously described categories.

Outcomes
The main study outcome was all-cause hospitalization. A secondary outcome was CHF-related hospitalizations. These CHF-related hospitalizations were identified with a primary discharge diagnosis for CHF (International Classification of Diseases, 9th Revision, Clinical Modification code 428.*), which previously showed an estimated positive predictive value of 97.4%, using medical chart reviews as the criterion standard.

Statistical Analyses
Incidence rates were calculated and compared using incidence rate ratios. We measured relevant covariates during the baseline period and adjusted for their influence on our assessments using multivariable negative binomial regression models. These models are preferred when more traditional Poisson regression models show evidence of data over dispersion. Relevant covariates in the 180 days before drug initiation included markers of patient frailty: number of hospitalizations, outpatient and emergency room visits, and number of different medication prescriptions filled; and specific medication use and clinical diagnoses as markers of comorbidity, recorded as dichotomous variables. Medications included anticonvulsants, bronchodilators, antipsychotics, antidepressants, sedatives and hypnotics, antihypertensives, gastroprotective medications (proton pump inhibitors and histamine-2 receptor antagonists), anti-arrhythmics, anticoagulants, aspirin and other platelet inhibitors, antiinfectives, antimicrobials, digoxin, lipid-lowering agents, loop diuretics and nitrates; and clinical diagnoses included chronic lung disease, congestive heart failure, myocardial infarction, angina, rheumatic heart disease, atrial fibrillation, smoking-related diagnoses, excessive alcohol consumption, cerebrovascular disease, hypertension, and diabetes mellitus. Since the study covered several years, we also accounted for trends in availability and use of the study medications during the study period by including indicator variables for calendar years in the regression models. Since patients could contribute more than 1 episode of medication use (with an updated set of covariates), we accounted for these additional correlations using the Huber-White “sandwich” variance estimator and calculated robust SE for all estimates.

For the analyses of CHF-related hospitalizations, the number of events was small relative to the number of study covariates, so we summarized those using exposure propensity scores, an analytic strategy commonly used to control confounding in this scenario. A separate multivariable logistic regression model was built using the OH medication exposures as the dependent variable, and baseline covariates as independent variables. The linear predictor of the logistic regression model representing the likelihood of selecting an OH medication over the other based on baseline covariates was computed and categorized into deciles. The propensity score deciles were then incorporated into the final outcome models together with the main exposure OH medications.

Planned subgroup analyses were conducted by history of CHF. Inpatient or outpatient recorded diagnosis qualified the patient as having a history of CHF. For all-cause hospitalizations, stratified estimates for patients with history of CHF were obtained with the addition of an interaction term to the outcome multivariable model. For CHF hospitalizations, we recalculated the propensity scores for the subset of patients with history of CHF, and the recalculated deciles were included in the outcome model as previously described. Finally, to explore the potential role of changing prescribing preferences during the study years, we conducted a post-hoc subgroup analysis of all-cause hospitalizations, stratifying the study period in 2 subgroups with similar number of observations in each: 1995–2002 and 2003–2009. All analyses were conducted in Stata (StataCorp, College Station, TX).

Results
Orthostatic Hypotension Cohort
During the study period, 2121 patients with OH (1324 initiators of fludrocortisone, and 797 initiators of midodrine) met our selection criteria and were included in our analyses. A total of 54 patients who initiated use of midodrine and fludrocortisone simultaneously were also identified, and excluded from the study. The baseline characteristics of study patients according to their exposure OH medication are shown in Table 1. The median age at baseline was 67 years among fludrocortisone initiators and 66 years among midodrine initiators. Most patients (≈80%) were white, and 54% of fludrocortisone initiators were female, compared with 57% of midodrine initiators.

The median number of different medications used during the baseline 180 days was 13 (interquartile range [IQR], 8–
Relative Safety of Orthostatic Hypotension Drugs

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Table 1. Baseline Profile of Orthostatic Hypotension Drug Users

| Parameters                              | Fludrocortisone (N=1324) | Midodrine (n=797) | P Value |
|-----------------------------------------|---------------------------|-------------------|---------|
| Age*, y, (IQR)                          | 67 (56–77)                | 66 (55–77)        | 0.700   |
| Sex, %                                  |                           |                   |         |
| Female                                  | 54.2                      | 57.3              | 0.150   |
| Race, %                                 |                           |                   |         |
| White                                   | 80.3                      | 79.9              | 0.098   |
| Black                                   | 10.7                      | 13.0              |         |
| Other                                   | 9.0                       | 7.0               |         |
| Health care use during baseline         |                           |                   |         |
| Nursing home residents†, %             | 15.9                      | 16.7              | 0.650   |
| Disability†, %                          | 54.4                      | 53.7              | 0.760   |
| Number of outpatient visits, median (IQR)* | 5 (2–9)                | 5 (1–9)           | 0.18    |
| Medication use during the past 6 mo†, median (IQR) | 13 (8–19)           | 14 (9–21)         | 0.002   |
| Hospital admission in the past 30 d, %  | 62.5                      | 66.4              | 0.069   |
| Hospital admission in past 31 d to 6 mo, % | 56.1                      | 59.7              | 0.100   |
| Emergency visit in past 30 d†, %       | 48.0                      | 52.9              | 0.026   |
| Emergency visit in past 31 d to 6 mo, % | 56.9                      | 56.7              | 0.940   |

IQR indicates interquartile range.
*Median, (IQR), and P values for Mann–Whitney test for marked row/section.
†Proportions and P values for χ² tests, unless otherwise specified.

19) for fludrocortisone, and 14 (IQR, 9–21) for midodrine. The median number of baseline outpatient visits was 5 for both exposure groups. Of note, the prevalence of several cardiovascular conditions (coronary artery disease, CHF, hypertension, arrhythmia, and syncope) and endocrine conditions (diabetes mellitus, hyperlipidemia) was higher in patients initiating midodrine than in patients initiating fludrocortisone. On the other hand, the prevalence of neurological conditions such as cerebrovascular disease, parkinsonism, and multiple system atrophy was similar in both groups, although patients initiating midodrine had a higher prevalence of history of syncope than patients initiating fludrocortisone (Table 2). New midodrine users also had a higher prevalence of use of diuretics, other antihypertensives, antidiabetics, narcotics, and antidepressants than new fludrocortisone users (Table 2).

All-Cause and CHF Hospitalizations

Fludrocortisone users had 617 all-cause hospitalizations (404 events per 1000 person-years of follow-up) compared with 323 all-cause hospitalizations (1330 events per 1000 person-years of follow-up) in midodrine users. The median duration of follow-up for fludrocortisone and midodrine users was 30 days (IQR: 28–55) and 30 days (IQR 28–37), respectively. During periods of no study medication use (nonuse person-time following periods of use, as defined above), there were 270 all-cause hospitalizations (404 events per 1000 person-years of follow-up). In multivariable analyses, fludrocortisone use was associated with a higher rate of all-cause hospitalizations, compared with midodrine use (adjusted incidence-rate ratio [aIRR]: 1.20, 95% confidence interval [CI], 1.02–1.40). There were only 2 patients who contributed more than 1 all-cause hospitalization to the analysis, and their exclusion did not materially affect these results (data not shown).

The number of CHF-related hospitalizations for fludrocortisone and midodrine initiators was 57 and 33, respectively. The median duration of follow-up for fludrocortisone and midodrine users was 30 days (IQR: 28–55) and 30 days (IQR 25–40), respectively. The respective incidence rates were 76 and 84 per 1000 person-years. In multivariable analyses, there was no statistically significant difference in the incidence of CHF-related hospitalization between fludrocortisone and midodrine initiators (aIRR: 1.23, 95% CI, 0.71–2.13) (Figure [A]).

Subgroup Analyses

We performed planned subgroup analyses on study outcomes based on CHF history. Among patients with history of CHF, the number of all-cause hospitalizations for fludrocortisone and midodrine initiators was 161 and 109, respectively. The rates of all-cause hospitalization for fludrocortisone and
midodrine were 2448 and 1820 per 1000 person-years (aIRR: 1.42, 95% CI, 1.07–1.90); the P value for the interaction term was 0.540. The number of CHF-related hospitalizations for fludrocortisone and midodrine initiators was 33 and 25, respectively. The respective rates of CHF exacerbation-related hospitalizations were 297 and 263 per 1000 person-years (aIRR: 1.48, 95% CI, 0.69–3.16) (Figure [B]).

Among patients with no history of CHF, the number of all-cause hospitalizations for fludrocortisone and midodrine initiators was 456 and 214, respectively. The rates of all-cause hospitalization for fludrocortisone and midodrine were 1308 and 1169 per 1000 person-years (aIRR: 1.11, 95% CI, 0.91–1.35). The number of CHF-related hospitalizations for fludrocortisone and midodrine initiators was 24 and 8, respectively. The respective rates for CHF exacerbation-related hospitalization were 38 and 27 person-years (aIRR: 1.44, 95% CI, 0.58–3.54).

In the post hoc subgroup analysis of all-cause hospitalizations by study period, the incidence rate ratio was 1.17 (95% CI, 0.89–1.55) and 1.21 (95% CI, 0.98–1.48) in the 1995–2002 and 2003–2009 periods, respectively. There was no significant difference in the estimates for these periods (P=0.300).

**Discussion**

In this retrospective cohort study of patients with OH, the initiation of fludrocortisone was associated with an increased...
risk of all-cause hospitalizations compared with initiation of midodrine. Importantly, this increased risk was more prominent among patients with history of CHF.

There are at least 2 different interpretations for our findings. It is possible that midodrine exerts a protective effect against hospitalizations in patients with OH, particularly those with heart failure. Small studies have suggested that the use of midodrine may allow for up-titration of neurohormonal antagonist therapy such as angiotensin-converting enzyme inhibitors and β-blockers, leading to improved outcomes in patients with advanced CHF. 22 This, however, has not been demonstrated in large clinical trials. On the other hand, fludrocortisone may indeed increase the risk of hospitalizations in OH patients through a number of different pharmacological mechanisms. For instance, fludrocortisone increases renal sodium reabsorption and expands plasma volume through its mineralocorticoid activity; it also potentiates the vasoconstrictive effect of norepinephrine through enhanced norepinephrine release from sympathetic neurons. Fludrocortisone has been reported to produce supine hypertension in a small study involving patients with autonomic failure. 23 Hypokalemia develops in nearly 50% of patients, and it can appear rapidly, within the first week of treatment. Hypomagnesemia occurs in about 5% of patients. These electrolyte abnormalities could further increase the risk of complications such as arrhythmias in a patient population highly susceptible such as those with prevalent heart failure, and thus increase the risk of hospitalization in this population.

In addition, previous studies suggest that use of fludrocortisone might have a volume-independent mechanism that could predispose patients to CHF. For instance, in animal models, the administration of aldosterone promoted cardiac fibrosis through the induction of oxidative stress and endothelial dysfunction. 13,14 In hypertensive patients, increased plasma aldosterone concentrations are associated with decreased arterial compliance, and patients with primary hyperaldosteronism exhibit a greater degree of endothelial dysfunction than patients with essential hypertension. 24

Our findings complement previous small case series reports and anecdotal observations that indicate that there is a high prevalence of CHF in patients with OH receiving fludrocortisone. Four case series studies included collected data on 121 patients with OH. Of the 121 patients, 45% reported adverse events, with heart failure being the most frequent, affecting 11%. 10,11,15,16 Furthermore, our findings also suggest a gap in knowledge about the use of these OH agents in clinical practice, particularly because we observed potential use of these agents in combination with other pharmacologic agents that antagonize their actions (ie, midodrine combined with α-blockers, or fludrocortisone combined with diuretics). We have addressed this observation in a previous publication. 12

Our study has several limitations. First, some clinical information such as functional status or specific measurements of OH severity are not recorded in our study databases, and although we made extensive efforts to control confounding, residual confounding cannot be ruled out. However, our analyses adjusted for several surrogate variables that are correlated with those unmeasured factors, minimizing their potential confounding effect. Second, we based our exposure classification on pharmacy refill data, but we cannot demonstrate that patients were actually taking the dispensed medications. Nevertheless, automated pharmacy records are an excellent source of prescription medication data because

![Figure. Fludrocortisone use and risk of all-cause hospitalization in orthostatic hypotension patients. Forest plot with individual estimates of incidence rate ratios on a logarithmic scale and 95% confidence interval for all cause-hospitalizations and CHF-related hospitalizations in fludrocortisone users (reference: midodrine users) (A). Subgroup analyses on study outcomes based on previous history of heart failure (B). CHF indicates congestive heart failure; CI, confidence interval.](https://doi.org/10.1161/JAHA.117.006848)
these records are not subject to incomplete patient reporting or recall bias and have concordance of better than 90% with patient self-reports of medication use.25–27 Furthermore, our study classified exposure into categories designed to minimize exposure classification and facilitate the comparison of periods of current use of study medications. As OH is a chronic condition with periodic exacerbation periods, it would be challenging to compare periods of current use with periods of no medication use using an observational study design. Third, we used retrospective records to identify our study outcomes. However, we relied on validated computerized definitions for identification of CHF-related hospitalizations,19 which should reduce concerns about outcome misclassification. Fourth, the number of CHF hospitalizations was small, and limited the precision of some estimates. Our study was not powered to study less frequent outcomes, such as mortality. Fifth, we used all-cause hospitalization as a proxy for healthcare need, but the analysis was not designed to assess specific causes of hospitalization. Lastly, our study population overrepresents patients with low income, and high prevalence of comorbidities and disabilities. Additional studies in other populations would be useful to complement our observations.

Conclusion
In patients with OH, the initiation of fludrocortisone was associated with an increased risk of all-cause hospitalizations compared with initiation of midodrine. Importantly, this increased risk was more prominent among patients with a history of CHF.

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Disclosures
Shibao serves as consultant, speaker and member of the advisory committee for Lundbeck Pharmaceuticals. Biaggioni has served as consultant for Lundbeck and Theravance Biopharma.

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