Congestive heart failure causes >900,000 admissions annually in the United States with a readmission rate exceeding 20%. Many hospitals have implemented quality improvement initiatives to lower the burden of heart failure–related readmissions, and financial incentives from the Centers for Medicare and Medicaid Services for reducing such readmissions have been established recently. Despite interest in preventing heart failure admissions, novel therapies to reduce the frequency of heart failure complications have not been approved for use in United States in recent years. Neither large-scale clinical trials of novel pharmacological agents nor medical devices that detect increases in cardiac filling pressures have proven effective in decreasing heart failure hospitalizations. Digoxin, one of the oldest available treatments for heart failure, has declined in use during the past 2 decades in favor of agents with demonstrated mortality benefit but remains a common adjunctive therapy for heart failure, particularly in patients with refractory symptoms. To further curb heart failure–related hospitalizations, some recently have suggested re-evaluating digoxin’s role in contemporary heart failure treatment.

Background—Recent data on digoxin prescribing and adverse events are lacking but could help inform the management of digoxin in contemporary heart failure treatment.

Methods and Results—We determined nationally representative numbers and rates of emergency department (ED) visits for digoxin toxicity in the United States using 2005 to 2010 reports from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project and the National Ambulatory (and Hospital Ambulatory) Medical Care Surveys. Based on 441 cases, an estimated 5156 (95% confidence interval [CI], 2663–7648) ED visits for digoxin toxicity occurred annually in the United States; more than three fourths (78.8% [95% CI, 73.5%–84.1%]) resulted in hospitalization. Serum digoxin level was ≥2.0 ng/mL for 95.8% (95% CI, 93.2%–98.4%) of estimated ED visits with levels reported (n=251 cases). The rate of ED visits per 10,000 outpatient prescription visits among patients ≥85 years was twice that of patients 40 to 84 years (rate ratio, 2.4 [95% CI, 1.2–5.0]); among women, the rate was twice that of men (rate ratio, 2.3 [95% CI, 1.1–4.7]). Digoxin toxicity accounted for an estimated 1.0% (95% CI, 0.6%–1.4%) of ED visits for all adverse drug events among patients ≥40 years, but an estimated 3.3% (95% CI, 2.3%–4.4%) of ED visits and 5.9% (95% CI, 4.0%–7.9%) of hospitalizations for all adverse drug events among patients ≥85 years. Estimated annual ED visits and hospitalizations remained relatively constant from 2005 to 2010.

Conclusions—Digoxin toxicity is not declining; more careful prescribing to high-risk groups and improved monitoring of serum levels might be needed to reduce morbidity from outpatient digoxin use. (Circ Heart Fail. 2014;7:28-34.)

Key Words: digoxin ■ drug-related side effects and adverse reactions ■ emergency service, hospital ■ heart failure ■ hospitalization

Congestive heart failure causes >900,000 admissions annually in the United States with a readmission rate exceeding 20%. Many hospitals have implemented quality improvement initiatives to lower the burden of heart failure–related readmissions, and financial incentives from the Centers for Medicare and Medicaid Services for reducing such readmissions have been established recently. Despite interest in preventing heart failure admissions, novel therapies to reduce the frequency of heart failure complications have not been approved for use in United States in recent years. Neither large-scale clinical trials of novel pharmacological agents nor medical devices that detect increases in cardiac filling pressures have proven effective in decreasing heart failure hospitalizations. Digoxin, one of the oldest available treatments for heart failure, has declined in use during the past 2 decades in favor of agents with demonstrated mortality benefit but remains a common adjunctive therapy for heart failure, particularly in patients with refractory symptoms. To further curb heart failure–related hospitalizations, some recently have suggested re-evaluating digoxin’s role in contemporary heart failure treatment.

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One of the important limitations to digoxin use remains its narrow therapeutic index as it contributes to the development of cardiac and noncardiac (eg, central nervous system, gastrointestinal) toxicities. Understanding the current epidemiology of digoxin toxicity could provide additional context for renewed considerations of digoxin use in heart failure. We used nationally representative public health surveillance data from the United States to estimate the frequency and rates of emergency department (ED) visits and hospitalizations for digoxin toxicity and to characterize the nature of these visits.
Methods

National estimates of the number of ED visits and subsequent hospitalizations for adverse drug events (ADEs) were based on data from the National Electronic Injury Surveillance System—Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project, an international stratified probability sample comprised of 63 hospitals in the United States and its territories; this surveillance system, including its performance characteristics, has been described previously in detail.14,15 For this analysis, only data from the 58 participating nonpediatric hospitals were used. In brief, trained abstractors at each hospital review clinical records of every ED visit to identify conditions that the attending clinician explicitly attributes to the use of a drug (ie, prescription and over-the-counter medications, vaccines, and herbs/dietary supplements) or drug-specific adverse effects. Abstractors record up to 2 medications implicated in each ADE by the treating clinician in addition to narrative descriptions of the incidents, including physician diagnosis and clinical testing. Narrative descriptions are then coded using the Medical Dictionary for Regulatory Activities, an international terminology used to analyze ADE reports.12 In this analysis, hospitalization was defined as admission to an inpatient unit of the healthcare facility, transfer to another healthcare facility, or billed as a hospital observation stay.

Patients <40 years were involved in only 6.4% of all cases of digoxin-related adverse events reported to NEISS-CADES and were excluded from the analysis. Cases of digoxin-related adverse events reported to NEISS-CADES from ED visits made between January 1 2005 and December 31 2010 were included if evidence of digoxin toxicity was present as indicated by documentation in the medical record narrative of any one of the following terms: digoxin toxicity or drug toxicity, documentation of administration of a digoxin dose greater than prescribed or intended (ie, medication error), an elevated digoxin level (>2.0 ng/mL), or ≥1 of the following signs/symptoms consistent with digoxin toxicity: cardiac dysrhythmias, gastrointestinal disturbances (anorexia, nausea, vomiting, or diarrhea), mental disturbances (anxiety, depression, delirium, hallucinations, weakness, apathy, confusion, or decreased level of consciousness), visual disturbances, or leg cramps. Clinical symptoms associated with digoxin toxicity were characterized based on Medical Dictionary for Regulatory Activity terms and grouped into hierarchical and mutually exclusive categories. To ensure that reported symptoms were related to digoxin and not another medication implicated in the ED visit, clinical symptoms were analyzed only for cases in which digoxin was the only offending medication (ie, a second implicated medication was not recorded) and ≥1 clinical symptom was provided.

National estimates of the number of ambulatory care visits at which digoxin was prescribed were based on 2 national cross-sectional surveys of ambulatory medical care services: the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS), which involve a multistage sampling design of ambulatory care visits to nonfederally employed office-based physicians and to EDs and outpatient departments of noninstitutional general and short-stay hospitals, exclusive of federal, military, and Veterans Administration hospitals.16 For this analysis, we refer to all NAMCS/NHAMCS ambulatory care visits at which digoxin was prescribed or continued as outpatient prescription visits. We used public-use data files for 2005 to 2010 to identify ambulatory care visits at which digoxin was prescribed or continued. Visits by patients <40 years comprised 5.9% of all outpatient prescription visits for digoxin reported to NAMCS/NHAMCS and were excluded from the analysis. Digoxin was identified by searching the 8 medication fields in each NAMCS/NHAMCS data set for the Multum Lexicon Drug Database codes identifying relevant generic ingredients (ie, digoxin, digoxin, and digitals).34-36 Each selected NEISS-CADES, NAMCS, and NHAMCS record was accompanied by a sample weight based on inverse probability of selection, adjusted for nonresponse and poststratified to adjust for the number of annual hospital ED visits (NEISS-CADES), and adjusted for nonresponse and population changes incorporating weight smoothing (NAMCS/NHAMCS).13,14 National estimates and percentages of ED visits and outpatient prescription visits, as well as corresponding 95% confidence intervals (CIs) were calculated using the SURVEYMEANS procedure in SAS (version 9.3; SAS Institute Inc, Cary, NC) to account for the sample weights and complex sample designs. The resulting frequency estimates and confidence limits derived from NEISS-CADES and NAMCS/NHAMCS data were divided by 2 for the time periods 2005 to 2006, 2007 to 2008, and 2009 to 2010 to obtain annual estimates representing these 3 periods and were divided by 6 for the time period 2005 to 2010 to obtain annual estimates representing the entire study period. Estimates based on small numbers of cases (<20 cases for NEISS-CADES and <30 cases for NAMCS/NHAMCS) or with a coefficient of variation >30% were considered statistically unstable and are not presented here.

To estimate rates of ED visits for digoxin toxicity relative to outpatient medication use, we divided the estimated number of ED visits for digoxin toxicity by the estimated number of outpatient prescription visits for digoxin. Calculation of the 95% CI for each rate incorporated variance estimates for both numerator and denominator components of the corresponding rate estimate.15 Because these components were calculated from separate surveillance systems, they were treated as independent (and, thus, as having zero covariance).

Rate ratios (RRs) were used to compare rates of ED visits for digoxin toxicity relative to outpatient medication use between different patient populations. Estimated 95% CIs for the RRs were calculated using an initial logarithmic transformation and incorporated the estimated variances of the numerators and denominators of both components.

Data collection, management, quality assurance, and analyses were determined to be public health surveillance activities by the Centers for Disease Control and Prevention and US Food and Drug Administration and, therefore, did not require human subjects review or institutional review board approval.
Among cases where the serum digoxin level was recorded (251 cases), a level ≥2.0 ng/mL was present in an estimated 95.8% (95% CI, 93.2%–98.4%) of ED visits for digoxin toxicity (Table 2). In 369 of the 441 reported cases, digoxin was considered the only offending drug related to the ED visit. Clinical symptoms were recorded for 365 of these cases (Table 3). In more than two thirds of estimated ED visits, symptoms affecting the central nervous system (25.2% [95% CI, 17.4%–33.1%]) or cardiovascular system (44.5% [95% CI, 37.3%–51.7%]) were recorded. Cases in which only gastrointestinal symptoms were recorded comprised a minority of ED visits for digoxin toxicity (9.7% [95% CI, 5.8%–15.5%]). All other types of symptoms (eg, fatigue and myalgias) were documented in an estimated 11.9% (95% CI, 8.0%–15.8%) of ED visits. Medication errors (ie, administration of a digoxin dose higher than prescribed or intended) were documented in too few cases (11 of 369 [3.0%] cases where digoxin was the only offending drug documented) to be able to report a national estimate.

Accounting for the number of outpatient prescription visits for digoxin, estimated rates of ED visits for digoxin toxicity were essentially constant throughout the study period (Table 4). However, the rates of ED visits for digoxin toxicity increased with age: the rate of ED visits per 10,000 outpatient prescription visits among patients ≥85 years was twice that of patients <85 years (10.8 [95% CI, 6.1–15.6] versus 4.5 [95% CI, 1.9–7.0] ED visits per 10,000 outpatient prescription visits; RR, 2.4 [95% CI, 1.2–5.0]); in particular, the rate was 3× that of patients 40 to 69 years (RR, 3.0 [95% CI, 1.4–6.2]). Women had twice the rate of ED visits for digoxin toxicity when compared with men (7.8 [95% CI, 4.2–11.5] versus 3.5 [95% CI, 1.5–5.4] ED visits per 10,000 outpatient prescription visits; RR, 2.3 [95% CI, 1.1–4.7]).

### Table 2. Number of Cases and National Estimates of Emergency Department Visits for Digoxin Toxicity Among Persons Aged ≥40 Years, by Serum Digoxin Levels Reported—United States, 2005–2010

<table>
<thead>
<tr>
<th>Serum Digoxin Level Reported (N=251 Cases)</th>
<th>Emergency Department Visits</th>
<th>Proportion of ED Visits Resulting in Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases, n</td>
<td>n</td>
</tr>
<tr>
<td>Level, ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.0–0.9</td>
<td>3</td>
<td>...</td>
</tr>
<tr>
<td>1.0–1.9</td>
<td>8</td>
<td>...</td>
</tr>
<tr>
<td>2.0–2.9</td>
<td>121</td>
<td>54.2</td>
</tr>
<tr>
<td>3.0–3.9</td>
<td>87</td>
<td>28.5</td>
</tr>
<tr>
<td>≥4.0</td>
<td>32</td>
<td>12.5</td>
</tr>
</tbody>
</table>

Case counts and estimates from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project, 2005–2010, Centers for Disease Control and Prevention. Estimates with case count <20 or coefficient of variation >30% are considered unstable and are not shown (...).

*Data are shown only for cases where a serum digoxin level was documented (251 of 441 cases).

**Discussion**

In 1997, >20 million prescriptions for digoxin were written in the United States, placing it among the 20 most commonly prescribed medications. In ensuing years, after the Digoxin Investigation Group (DIG) trial found that digoxin use reduced the rate of hospitalizations in heart failure patients but had no effect on mortality, digoxin lost favor as a first-line agent in the treatment of heart failure because other medications with a demonstrated mortality benefit had emerged. The annual number of prescriptions for digoxin and admissions for digoxin toxicity subsequently declined through 2004. Our analysis indicates that ED visits for digoxin toxicity did not decrease further during 2005 to 2010, with >5000 estimated ED visits occurring annually.
These events involved considerable morbidity. More than three quarters of estimated ED visits for digoxin toxicity resulted in hospitalizations. In addition, we estimated that more than one fourth of ED visits for digoxin toxicity involved symptoms affecting the central nervous system and that arrhythmias and syncopal episodes comprised many of
the cardiovascular manifestations, the principal presentation for almost half of ED visits. Our analysis might actually underestimate the proportion of ED visits involving these severe presenting symptoms because in 47 cases only the treating clinician’s diagnosis of digoxin toxicity was recorded (without the patient’s exact presenting symptoms).

Accounting for outpatient prescription frequency, we found women and older adults to have disproportionately high rates of ED visits for digoxin toxicity. It remains debated whether women are biologically more susceptible to development of digoxin toxicity; however, our data suggest that, in practice, women are affected by digoxin toxicity at higher rates. Digoxin toxicity was also an important reason for ED visits for ADEs among older adults, accounting for >1 of 20 of such visits in adults ≥85 years. In contrast to other medications commonly implicated in emergent hospitalizations for ADEs in older adults, which lead to hospitalization in an estimated 20% to 40% of visits, we found the estimated rate of hospitalization for digoxin toxicity to be 75%. Older adults are at greater risk for adverse effects from all medications because of altered pharmacokinetics or polypharmacy. Older adults with heart failure might, furthermore, be at particular risk for developing digoxin toxicity because of concomitant comorbidities, such as hypokalemia (from diuretic use) or renal impairment.

Potential benefits of prescribing digoxin for heart failure patients have been reported based on secondary analyses of DIG trial data. New clinical trials would be needed to confirm the efficacy of digoxin as an adjunct to contemporary medical therapy for heart failure. This study does not examine the risk/benefit ratio of increased use of digoxin, but we have used public health surveillance data to focus on the risk of digoxin toxicity and provide insight into potential ways to minimize the harms resulting from digoxin use. By identifying patient subpopulations at increased risk of digoxin toxicity, our findings point to the following considerations if digoxin is to be increasingly used as an adjunctive measure to prevent heart failure admissions.

First, careful patient selection for digoxin therapy, proper initial dosing, and heightened surveillance for high-risk patients, such as women and older adults, might mitigate the burden of ED visits and hospitalizations for digoxin toxicity. Second, consistent guidance for what constitutes a therapeutic serum digoxin level might also reduce the incidence of patients presenting with toxicity. The levels reported for most ED visits for digoxin toxicity were ≥2.0 ng/mL. Clinical practice guidelines suggest that serum digoxin levels 0.5 to 0.9 ng/mL are therapeutic for heart failure and that higher levels might be harmful. However, dissemination of 0.5 to 0.9 ng/mL as the standard reference range is inconsistent; many sources still indicate 2.0 ng/mL as the upper level of the therapeutic range for serum digoxin levels. Furthermore, many hospital laboratories still consider digoxin levels of 2.0 ng/mL to be within normal range. Targeting the lower range would likely further reduce the number of patients who inadvertently experience digoxin toxicity from serum digoxin levels that are clearly supratherapeutic. Third, incorporating prevention of digoxin toxicity into current strategies for reducing heart failure readmissions represents a potential means of intervention for the at-risk population. This is corroborated by data indicating increased risk of hospitalization for digoxin toxicity after hospitalization. Existing programs for reducing heart failure readmissions focus on medication reconciliation, patient compliance with medications, electronic medical orders, and careful and close follow-up during transitions of care from the inpatient to outpatient setting. To prevent digoxin toxicity, merely ensuring that patients are taking the medication as prescribed is likely to have limited use, particularly considering that few of our reported cases were because of medication errors. However, given their potential ability to manage patients whose care is coordinated by multiple providers, readmission reduction programs may provide a framework that can be leveraged to improve monitoring and follow-up of digoxin levels.

This study’s findings should be interpreted in the context of the limitations of public health surveillance data. First, NEISS-CADES only captures ADEs resulting in ED visits or emergent hospitalizations. Thus, clinical episodes of digoxin toxicity resulting in lower levels of care (eg, physician office visits) or direct admissions to the hospital would not have been identified. In addition, digoxin toxicity might go unrecognized during an ED visit and would not be reported if it was diagnosed during hospitalization after the ED visit. NEISS-CADES does not include data on length of stay for patients hospitalized for digoxin toxicity. Second, NAMCS/NHAMCS imperfectly measure outpatient prescribing frequency as they exclude prescriptions initiated by phone and e-mail contacts, as well as prescriptions initiated in nursing homes, in ambulatory surgery centers, or provided at hospital discharge. However, we would not expect this to affect the relative magnitude of the risks of digoxin toxicity between sexes. Although NAMCS/NHAMCS data may be underestimates of outpatient prescription visits for older adults, previous studies have also found older adults to be at higher risk of digoxin toxicity compared with younger patients. Third, we did not have sufficient information from all cases to ascertain the indication for digoxin use; thus these data might include patients being treated for indications other than heart failure (eg, atrial fibrillation). Fourth, we did not have information in all cases about such variables as electrolyte levels, renal function, and concomitant medications and thus could not fully characterize factors leading to digoxin toxicity. This is important in that digoxin might be currently considered more often for patients with advanced heart failure, who have the greatest risk for renal impairment and thus digoxin toxicity. Fifth, we do not have a record of the indication for hospitalization in our cases. As patients with heart failure have high rates of hospitalization in general, some of the hospitalizations described could have been for patients’ underlying illnesses rather than digoxin use per se. However, given that the incident ED visits were related to use of digoxin, it is likely that most of the subsequent hospitalizations were related to digoxin use as well.

Digoxin continues to have a niche in the treatment of patients with symptomatic heart failure who are refractory to other treatments. National public health surveillance data indicate that digoxin use and the burden of digoxin toxicity as measured by ED visits and hospitalizations did not decline from 2005 through 2010. The lack of decline in digoxin toxicity during this time period could be because of
several reasons, including unchanged frequency of digoxin prescribing during this time, continued use of high reference ranges (eg, an upper limit of 2.0 ng/mL) for serum digoxin levels, or lack of effective strategies targeted at safely managing digoxin therapy among patients at highest risk of adverse events. Efforts to minimize morbidity from toxicity when digoxin use is considered might require prevention strategies focused on identifying the patient populations most likely to benefit from digoxin therapy, carefully prescribing to high-risk populations (ie, women and older adults) and improving monitoring and management of digoxin levels, including promoting adherence to lower ranges (eg, 0.5–0.9 ng/mL) for serum digoxin levels.

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Disclosures
None.

References


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**CLINICAL PERSPECTIVE**

Recent studies report potential benefits for prescribing digoxin for heart failure. However, contemporary data regarding digoxin prescribing and adverse events are lacking and could be useful to inform safer prescribing of digoxin. We report nationally representative estimates for emergency department (ED) visits and rates (accounting for outpatient digoxin use) for digoxin toxicity in the United States from 2005 to 2010 using national survey data. More than 5000 ED visits for digoxin toxicity occurred annually with a high hospitalization rate (79%), a trend that remained constant during the time period studied. The serum digoxin level was $\geq 2.0$ ng/mL for most ED visits (95.8%) with a level reported. Accounting for prescribing frequency, women had twice the rate of ED visits for digoxin toxicity compared to men. The rate of ED visits for digoxin toxicity increased with age, and patients aged 85 years or older had twice the rate compared to younger patients. These results suggest that safer prescribing for digoxin should focus on identifying patient populations most likely to benefit from therapy and improving monitoring and management of digoxin levels in outpatient settings, including promoting adherence to and awareness of guideline-directed lower reference ranges for therapeutic serum digoxin levels (eg, ranges of 0.5–0.9 ng/mL). These implications have particular relevance when prescribing digoxin to patients at higher risk for development of digoxin, such as women and older adults.
Emergency Department Visits and Hospitalizations for Digoxin Toxicity: United States, 2005 to 2010
Isaac See, Nadine Shehab, Scott R. Kegler, S. Raja Laskar and Daniel S. Budnitz

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