

from RCTs. Examination of the reasons behind this contradiction by the regulatory agency may help to improve the reliability of this new program.

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Editor's Note

Multiple Data Sources, the Best Way to Gather Safety Information About Medications

The US Food and Drug Administration's (FDA) Mini-Sentinel Program is an important initiative to identify adverse effects of new medications during the postapproval period. The system links electronic data from a variety of health care providers so as to rapidly determine the safety of medications in use.

The system is especially useful for identifying adverse effects that might not be apparent in randomized clinical trials because they are rare, occur in patient groups not

included in the trials, occur when used in settings less controlled than randomized trials, or occur in patients taking the medications for periods of time longer than the length of the trial. Nonetheless, it must be remembered that analysis of the data in this surveillance system, however rich, may suffer from the limitations of any observational study.

Sipahi et al used a systematic search and meta-analysis of randomized clinical trials to estimate the rate of gastrointestinal tract bleeding with dabigatran vs warfarin. Their data support a very different conclusion than that of the FDA Mini-Sentinel Program. While the Mini-Sentinel Program found that gastrointestinal tract bleeding rates were no higher with dabigatran than warfarin, the randomized clinical data showed a significantly increased risk of gastrointestinal tract bleeding compared with warfarin.

It is not surprising, or uncommon, for different methodologies to reveal different answers. Using electronic data from health care settings is a smart and efficient method of learning more about medications in real-world settings. However, new data, especially from observational studies, which are prone to confounding and underreporting, must always be judged in the context of biologic plausibility and other data sources.

Mitchell H. Katz, MD

Digitalis Use in Contemporary Clinical Practice: Refitting the Foxglove

Over 200 years after William Withering wrote the classic monograph, *An Account of the Foxglove and Some of Its Medicinal Uses*,¹ the indications for and optimal dosing of digitalis glycosides (primarily prescribed as digoxin) continue to be debated. Convincing evidence regarding the purported benefits of digoxin was unavailable until the Digitalis Investigation Group (DIG) trial, published in 1997.² This study was approved by the institutional review board at each participating center.

The DIG trial was a large-scale, international, prospective trial that randomized 6800 ambulatory adult patients with systolic heart failure (HF) to digoxin treatment or placebo. Enrolled patients were receiving concomitant HF therapy with diuretics (81% of patients) and angiotensin-converting enzyme (ACE) inhibitors (94% of patients). Notably, patients with atrial fibrillation were excluded from the trial. Treatment with digoxin had no significant reduction in all-cause mortality, although it led to a 28% relative risk reduction for hospital admission for worsening HF within a mean follow-up of approximately 3 years (Box).

Little is known about the patterns of digoxin use for the treatment of HF since the publication of the DIG trial, and the use of digoxin in HF therapy remains controversial. Concern about digitalis toxicity, along with the advent of other agents shown to confer a mortality benefit, such as

Box. Summary of the Digitalis Investigation Group Trial²

Inclusion Criteria

Ambulatory patients in sinus rhythm
 LVEF of 45% or lower^a
 History of HF^b
 Eligible patients allowed to be taking digoxin

Exclusion Criteria

Age younger than 21 y
 Atrial fibrillation or atrial flutter (with or without pacemaker)
 MI, cardiac surgery, or PTCA within 4 wk
 Unstable or refractory angina within 1 mo
 Second- or third-degree AV block (without a pacemaker)
 Cor pulmonale
 Acute myocarditis
 Hypertrophic cardiomyopathy
 Amyloid cardiomyopathy
 Constrictive pericarditis^c
 Pre-excitation syndromes
 Current treatment with IV inotropes
 Hypokalemia/hyperkalemia (range, 3.2-5.5 mmol/L)
 Need for cardiac surgery^d or PTCA in near future^c
 Listed for cardiac transplant
 SSS without pacemaker
 Recognizable noncardiac causes of HF
 Renal insufficiency (creatinine level, >3.0 mg/dL)
 Hepatic insufficiency
 Any noncardiac disease with life expectancy less than 3 years
 Baseline LVEF not available
 Unlikely to comply with study protocol

Primary Outcome

All-cause mortality

Secondary Outcomes

Mortality from CV causes
 Mortality from worsening HF
 Hospitalization for worsening HF
 Hospitalization for other causes (including digoxin toxicity)
 Results (digoxin, n=3397; placebo, n=3403)
 34.8 vs 35.1%: Mortality with digoxin vs placebo (RR, 0.99; 95% CI 0.91-1.07; *P* = .80)
 29.9 vs 29.5%: CV mortality with digoxin vs placebo (RR, 1.01; 95% CI, 0.93-1.10; *P* = .78)
 11.6 vs 13.2%: Mortality from worsening HF with digoxin vs placebo (RR, 1.14; 95% CI, 0.77-1.01; *P* = .06)
 49.9 vs 54.4%: CV hospitalization with digoxin vs placebo (RR, 0.87; 95% CI, 0.81-0.93; *P* < .001)
 26.8 vs 34.7%: Hospitalization for worsening HF with digoxin vs placebo (RR, 0.72; 95% CI, 0.66-0.79; *P* < .001)

2.0 vs 0.9%: Hospitalization for suspected digoxin toxicity with digoxin vs placebo (RR, 2.17; 95% CI, 1.42-3.32; *P* < .001)^e

Professional Society Recommendations

ESC (class IIb, level of evidence B): May be considered to reduce the risk of HF hospitalization in patients in sinus rhythm with an LVEF of 45% or lower who are unable to tolerate a β -blocker. Patients should also receive an ACE inhibitor (or ARB) and an MRA (or ARB). May be considered to reduce the risk of HF hospitalization in patients with an EF of 45% or lower and persisting symptoms (NYHA class II-IV) despite treatment with a β -blocker, ACE inhibitor (or ARB), and an MRA (or ARB).⁴

ACC/AHA (class IIa, level of evidence B): Digoxin can be beneficial in patients with HF with reduced LVEF, unless contraindicated, to decrease hospitalizations for HF. Clinicians may consider adding digoxin in patients with persistent symptoms of HF with reduced LVEF during GDMT. Digoxin may also be added to the initial regimen in patients with severe symptoms who have not yet responded symptomatically during GDMT. Alternatively, treatment with digoxin may be delayed until the patient's response to GDMT has been defined and may be used only in patients who remain symptomatic despite therapy with neurohormonal antagonists. If a patient is taking digoxin but not an ACE inhibitor or a β -blocker, treatment with digoxin should not be withdrawn, but appropriate therapy with the neurohormonal antagonists should be instituted.⁵

Heart Failure Society of America (NYHA class II-III, level of evidence B; NYHA class IV, level of evidence C). Digoxin may be considered to improve symptoms in patients with LVEF \leq 40% who have signs or symptoms of HF while receiving standard therapy, including ACE inhibitors and β -blockers.⁶

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AV, atrioventricular; CI, confidence interval; CV, cardiovascular; EF, ejection fraction; ESC, European Society of Cardiology; GDMT, guideline-directed medical therapy; HF, heart failure; IV, intravenous; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PTCA, percutaneous transluminal coronary angiography; RR, relative risk; SSS, sick sinus syndrome.

SI conversion factors: To convert creatinine to micromoles per liter, multiply by 88.4; to convert digoxin to nanomoles per liter, multiply by 1.281.

^a Ancillary study of 988 patients with an LVEF greater than 45% performed, with combined primary outcome of death of hospitalization due to worsening HF, with results consistent with main trial.

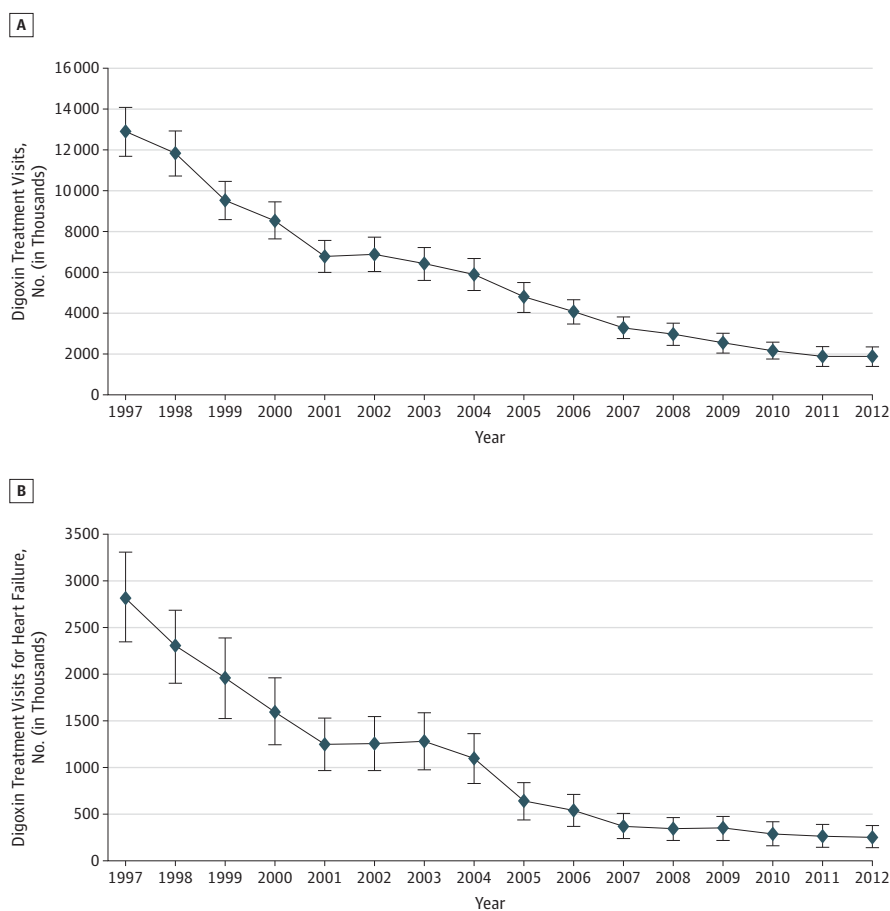
^b Current or past symptoms (limitation of activity, fatigue, dyspnea, orthopnea) or signs (edema, elevated jugular venous pressure, rales, S3 gallop), or radiologic evidence of pulmonary congestion.

^c Eligible after surgery/revascularization.

^d Severe valvular disease, planned coronary artery bypass surgery.

^e Mean serum digoxin concentration of 0.80 ng/mL at the 12-month visit, with 88.3% of digoxin group within the range of 0.5 to 2.0 ng/mL.

Figure. Digoxin Treatment Visits



β -blockers, ACE inhibitors and aldosterone antagonists, may have contributed to waning digoxin use.³ We hypothesized that digoxin use for systolic HF has decreased during the past 15 years, despite clinical guidelines supporting its use.⁴⁻⁶

Methods | We used the IMS Health National Disease and Therapeutic Index, an ongoing audit of office-based US physicians that provides nationally representative information regarding disease patterns and treatment. This project was not human subjects research and therefore did not require institutional review board approval. Our primary unit of analysis was a treatment visit, defined as an office visit where digoxin was used for a specific clinical indication. We quantified digoxin use from 1997 through 2012 among all subjects as well as among patient subpopulations. All statistical analyses were performed using SAS 9.2 (SAS Institute Inc). This project was not human subjects research and, as such, did not require institutional review board approval.

Results | Digoxin treatment visits declined by 86%, from 12.9 million visits in 1997 to 1.87 million visits in 2012 (Figure, A). Declines were greater between 1997 and 2001 (12.9 to 6.8

million visits, averaging a 10% decrease per year over 5 years [$P < .001$ for trend]) than subsequent years (6.9 to 1.9 million visits, averaging a 6% decrease per year over 11 years [$P < .001$ for trend]). For patients with HF, digoxin treatment visits declined by 91% overall (Figure, B), averaging an 11.2% decrease per year between 1997 and 2001 and a 7% decrease per year from 2002 through 2012. There were no statistically significant differences in these trends based on patient sex or physician specialty. Of note, 23% of treatment visits for digoxin use over the course of the study period were due to HF, compared with 20% for atrial fibrillation or flutter.

Discussion | There has been a marked reduction in ambulatory digoxin use in the United States since 1997, with the largest declines in use observed from 1997 through 2001, and especially for patients with HF. Our study is limited by the lack of data prior to 1997, and there are a number of potential causes of the declines that we have illustrated. An increasing number of evidence-based therapies for HF, the perceived toxic effects and challenges of digoxin dosing, and the negative results of the DIG trial with respect to its primary end point of all-cause mortality, may all have contributed to reductions in digoxin use. However, the

DIG trial demonstrated a significant decrease in hospital admissions for HF in ambulatory patients receiving digoxin therapy. These changes may be particularly salient to contemporary clinical practice in clinical and policy efforts to reduce inpatient health care utilization for HF. However, whether digoxin use will have any direct effect on hospital readmission for HF remains unclear, given that readmissions were not directly measured. As such, this hypothesis merits caution. Unfortunately, new prospective randomized trials of digoxin are unlikely, leaving its fate as an integral part of HF therapy in contemporary practice uncertain.

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Contemporary Data About Hospital Strategies to Reduce Unplanned Readmissions: What Has Changed?

Almost 1 in 5 hospitalized Medicare beneficiaries will experience an unplanned readmission within 30 days, with an estimated cost to Medicare of more than \$17 billion annually.¹ In response, many hospitals have enrolled in quality collaboratives or campaigns to implement evidence-based strategies to reduce readmission rates. However, we have little information on the changes in practice that have occurred among the nation's hospitals. Such information is important to understand hospital responses to the policy changes.

Methods | We examined changes from 2010 to 2012 in the use of commonly recommended strategies to reduce unplanned readmissions in a national sample of hospitals participating in the Hospital to Home Quality Improvement Initiative,² an initiative of the American College of Cardiology and Institute of Healthcare Improvement to reduce readmissions of patients with cardiovascular disease. Of the 594 hospitals that had enrolled in the initiative between October 1, 2009, and July 1, 2010, 537 (90.4%) completed the baseline web-based survey, which was conducted from November 2010 to May 2011. A total of 437 of these hospitals (81.4%) completed a follow-up survey approximately 12 to 18 months later from November 2011 to October 2012. We determined differences in implementation of recommended strategies between the 2 time points using McNemar χ^2 tests and Bowker tests of symmetry, with a significance threshold of $P < .01$ to account for multiple comparisons. About 35% of the hospitals were teaching hospitals, 30% had 400 or more beds, 5% were rural, 73% were part of a multihospital system, and 22% were for-profit. Institutional review board approval was obtained for the surveys.

Results | Statistically significant changes of substantial magnitude were apparent for several specific strategies (Table 1). At the follow-up survey, significantly more hospitals were partnering with other local hospitals to reduce readmissions (30.7% vs 22.9%; $P = .002$), were discharging patients with a follow-up appointment already made (61.1% vs 52.4%; $P = .005$), and were tracking the percentage of patients who were