Digitalis and Hemodialysis Is a Bad Combination

David R. Thiemann
Division of Cardiology, Department of Medicine, Johns Hopkins Medical Institutions, Baltimore, Maryland


Two centuries after its discovery, digitalis remains perennially controversial, even as it is largely supplanted by newer, safer drugs. For atrial fibrillation, β blockers and calcium channel blockers offer better rate control than digoxin; for congestive heart failure (CHF), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers, β blockers, and aldosterone antagonists have a proven survival advantage. Consensus guidelines have become increasingly cautious: In 2005, the American Heart Association/American College of Cardiology Heart Failure guidelines downgraded digoxin from a class 1 recommendation (in 2001) to class IIa; the 2009 update added special cautions about dosing and levels. Overall use has declined from approximately 80% of patients with systolic heart failure to 30%, yet no less a scientist and statesman than Eugene Braunwald recently urged a large National Institutes of Health–sponsored trial of low-dosage digoxin for acute CHF.

The basic clinical facts about digoxin for nondialysis patients come from two venerable randomized trials. In the Randomized Assessment of Digoxin on Inhibitors of Angiotensin-Converting Enzyme (RADIANCE) trial of 178 patients, withdrawal of digoxin from patients who had an ejection fraction of ≤35% and were tolerating the drug well (an important caveat—these were survivors already) carried a 5.9-fold relative risk for worsening heart failure. In the Digitalis Investigation Group (DIG) trial of 6801 patients, the addition of digoxin to patients who had an ejection fraction of ≤35% and were tolerating the drug well (an important caveat—these were survivors already) carried a 5.9-fold relative risk for worsening heart failure. In the Digitalis Investigation Group (DIG) trial of 6801 patients, the addition of digoxin (with levels from 0.5 to 2.0) to ACEIs and diuretics had no survival benefit or detriment: Reduced rates of heart failure admission and death from pump failure were neutralized by increased rates of other cardiovascular death, presumably from arrhythmias. Subsequent analyses of this and other studies suggested that serum levels of digoxin <1.0 ng/dl are sufficient for inotropic benefit, whereas lethal arrhythmias occur predominantly at levels >1.0 ng/dl.

For nephrologists, the role of digoxin in hemodialysis patients would seem less controversial. The narrow therapeutic window, long half-life, and the potential for lethal arrhythmias of the drug—especially in the context of hypokalemia—are
widespread. Because hemodialysis inevitably involves large
potassium fluxes, digoxin and dialysis would seem to be a bad
combination. All previous major digoxin trials excluded pa-
tients with renal insufficiency, yet theory and practice often
diverge, as shown by Chan et al. in this issue of JASN. Of the
120,864 patients in their Fresenius Medical Care database, rep-
resenting patients who started hemodialysis in 2001 through
2006, 4% were treated with digoxin. Only 44% of these patients
had monitoring of serum levels during the first 90 days of dialysis.
Of those monitored, 53% were supratherapeutic by current stan-
dards, with serum levels ≥1.0 ng/ml, yet dosage adjustment was
rare. Although the study presumably does not reflect monitoring
elsewhere by internists or cardiologists, the impression of hapha-
azard monitoring of a potentially lethal drug in the vulnerable dial-
ysis population is disconcerting.

The study by Chan et al. compares patients with and with-
out digoxin treatment, using proportional hazards and pro-
pensity methods, but this approach is unconvincing to me de-
spite good statistical analyses. Comparing digoxin and nondigoxin patents mostly just compares patients with and
without heart failure and/or atrial fibrillation, with great risk
for unmeasured confounding by severity and other cardiac co-
morbidities. The 40 covariates of the model include laboratory
and dialysis details but lack vital variables such as ejection frac-
tion and functional heart failure status. A far more persuasive
finding is that digoxin levels >1.0 ng/dl are associated with
substantial excess mortality (adjusted hazard ratio 1.19 [95% con-
fidence interval 1.05 to 1.35] per 1.0-ng/ml increase in
digoxin level; Table 3), particularly in conjunction with predi-
alysis levels of serum potassium <4.3 mg/dl. Paradoxically,
patients with exemplary dietary compliance in potassium re-
striction may be at greatest risk!

The study by Chan et al. nicely illustrates the promise and the
pitfalls of specialty-centric observational comparative effective-
ness research, one component of a renewed federal commit-
tment to patient-centered outcome studies. For all of its strengths, the
rich Fresenius database underlying the study necessarily is disease
defined: The inception cohort begins with dialysis enrollment,
and the variables are largely related to dialysis; although the study
can compare patients according to digoxin levels, it cannot reli-
ably measure digoxin indications or predialysis CHF manage-
ment and cannot match patients who have CHF or atrial fibrilla-
tion and are treated with digoxin with those who are treated with
other agents, such as ACEIs and β blockers; that is, there may be
immortal time bias in the data set.

Although disease-specific registries are the source of many
great studies, for comparative effectiveness research, their in-
herent temporal and content limitations are crippling com-
pared with the integrated clinical databases maintained by sev-
eral European governments and in the United States by the
Veterans Administration and a few large health maintenance
organizations. Even these databases have inherent data com-
pleteness and validity challenges compared with a dedicated
research registry or a randomized trial.

Given meager data on digoxin in hemodialysis patients,
what should a nephrologist do? Opting not to start digoxin is
simple and unarguable, absent extenuating circumstances
such as end-stage cardiomyopathy. Decisions are more com-
plicated for patients who are already taking digoxin, partic-
ularly because the original indication often is unclear. If the
patient has a left ventricular ejection fraction of >30%, then
the drug probably should be stopped. For patients with CHF,
afterload reduction and β blockade should be optimized. For
antiarrhythmic indications, principally atrial fibrillation, con-
sultation for alternative agents is indicated; digoxin is at best
a second-line drug for rate control, slowing resting rate without
controlling adrenergic exercise-mediated tachycardia.

For patients with severe systolic dysfunction, ejection frac-
tion <30%, discretion may be the better part of valor because
the RADIANCE trial and clinical experience show rebound
CHF exacerbation when digitalis is discontinued. Such pa-
tients should be maintained on low digoxin dosages (e.g., 0.125
mg every 2 to 3 days), with periodic monitoring of serum lev-
els; monitoring is particularly important for women and for
patients with low body mass. A level of ≥1.0 ng/dl should be
considered toxic. There is no defined subtherapeutic level for
CHF, so digitalis dosages should rarely be increased, although
the usual target is approximately 0.7 ng/dl.

Chan et al. conclude with the obligatory nod to safety eval-
uation in randomized trials. Unfortunately niche dialysis-spe-
cific trials for a generic drug never will happen. The method-
ologic issues are daunting. The population involved is tiny
from a clinical trials enrollment perspective, with very high
mortality, many competing risks, and complicating time-de-
pendent factors such as kidney transplantation. Lacking per-
fected evidence, the best guides are common sense and the fam-
iliar 19th-century Latin injunction *primum non nocere.*

**DISCLOSURES**

None.

**REFERENCES**

1. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats
   TG, Konstam MA, Mancini DM, Rahko PS, Silver MA, Stevenson LW,
   Yancy CW. 2009 focused update: ACCF/AHA Guidelines for the Di-
   agnosis and Management of Heart Failure in Adults: a report of the
   American College of Cardiology Foundation/American Heart Associ-
   ation Task Force on Practice Guidelines: developed in collaboration
   with the International Society for Heart and Lung Transplantation.

2. Gheorghiade M, van Veldhuisen DJ, Colucci WS. Contemporary use
   of digoxin in the management of cardiovascular disorders. Circulation
   113: 2556–2564, 2006

3. Gheorghiade M, Braunwald E. Reconsidering the role of digoxin in
   the management of acute heart failure syndromes. JAMA 302: 2146–
   2147, 2009

4. Packer M, Gheorghiade M, Young JB, Costantini PJ, Adams KF, Cody
   RJ, Smith LK, Van Voorhees L, Gourley LA, Jolly MK. Withdrawal of
   digoxin from patients with chronic heart failure treated with angioten-
Long-term reliable access to the circulation remains the largest technical barrier to successful long-term HD. The cumulative data as derived by the Dialysis Outcome Quality Initiative (DOQI) reveal that elective AVFs before initiation of dialysis are the most complication-limited, reliable, and long-lived form of vascular access.5,6 Forming an AVF nonelectively after the initiation of HD requires placement of a venous HD catheter while awaiting AVF maturation. The mortality and morbidity of extended catheter use are well described.7 The successful increase in late AVF use in the prevalent patient population of the United States is also associated with a substantial increase in catheter use, a result at least in part of non-preemptive AVF placement. Preemptive placement of AVFs eliminates the cost and risk associated with prolonged catheter-based dialysis.7

How did we get to this situation, and can we fix this problem? We arrived here on the basis of groundbreaking public policy first passed into law in 1972 as an amendment to the Social Security Act that afforded dialysis care to many Americans when they reached a stage of renal failure requiring replacement therapy. Finally, in 1990, the Americans with Disabilities Act opened the door to dialysis for all Americans regardless of age or comorbidity. This public policy did not provide preventive care, but rather, like catastrophic insurance, it insured for the catastrophe itself.

The unintended consequences of this landmark action are not trivial. We now have a public policy that treats a catastrophic illness such as renal failure but does not act to prevent or ameliorate that catastrophe earlier, a setting in which political force has already expanded this catastrophic care to all Americans. The demographics of these patients who start HD now reflect an aging population with diabetes, who, as a consequence of their age and disease, are progressively more unlikely to have commercial insurance, which is the entity that seems most interested in preventive care to limit costs, especially of catastrophic illness such as renal failure.

The placement of native AVFs months in advance of the start of dialysis will improve morbidity and mortality and decrease costs.6,7 This special form of preventive care, to be seen and treated by both a nephrologist and a vascular surgeon before the determination of dialysis dependence, is not covered by CKD reimbursement from Medicare, a carrier that supports most coverage for dialysis. In contrast, capitated care organizations, such as the Department of Defense and the Veterans Administration, receive direct incentives to reduce the costs of catastrophic illness by ameliorating complications and prevention of CKD progression including early referral as a matter of financial policy.

Thus, a farsighted and compassionate public policy for long-term dialysis care has unintended consequences.8 The solution to this dilemma is business-simple but politically difficult. From a business standpoint, it makes medical and financial sense to extend Medicare coverage to those with advancing renal impairment. In this manner, both proper preparations for HD by creation of AVFs and indeed preventive therapies to