

Digitalis and Hemodialysis Is a Bad Combination

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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.1 Overall use has declined from approximately 80% of patients with systolic heart failure to 30%, yet no less a scientist and statesman than Eugene Braunwald3 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,4 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,5 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,5 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
widely known. Because hemodialysis inevitably involves large potassium fluxes, digoxin and dialysis would seem to be a bad combination. All previous major digoxin trials excluded patients with renal insufficiency,9 yet theory and practice often diverge, as shown by Chan et al.7 in this issue of JASN. Of the 120,864 patients in their Fresenius Medical Care database, representing 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 standards, with serum levels $\geq 1.0$ ng/ml, yet dosage adjustment was rare. Although the study presumably does not reflect monitoring elsewhere by internists or cardiologists, the impression of haphazard monitoring of a potentially lethal drug in the vulnerable dialysis population is disconcerting.

The study by Chan et al.7 compares patients with and without digoxin treatment, using proportional hazards and propensity methods, but this approach is unconvincing to me despite good statistical analyses. Comparing digoxin and nondigoxin patients mostly just compares patients with and without heart failure and/or atrial fibrillation, with great risk for unmeasured confounding by severity and other cardiac comorbidities. The 40 covariates of the model include laboratory and dialysis details but lack vital variables such as ejection fraction 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% confidence interval 1.05 to 1.35] per 1.0-ng/ml increase in digoxin level; Table 3), particularly in conjunction with predialysis levels of serum potassium $<4.3$ mg/dl. Paradoxically, patients with exemplary dietary compliance in potassium restriction may be at greatest risk!

The study by Chan et al.7 nicely illustrates the promise and the pitfalls of specialty-centric observational comparative effectiveness research, one component of a renewed federal commitment to patient-centered outcome studies.8 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 reliably measure digoxin indications or predialysis CHF management and cannot match patients who have CHF or atrial fibrillation and are treated with digoxin with those who are treated with other agents, such as ACEIs and $\beta$ blockers; that is, there may be immortal time bias in the data set.9

Although disease-specific registries are the source of many great studies, for comparative effectiveness research, their inherent temporal and content limitations are crippling compared with the integrated clinical databases maintained by several European governments and in the United States by the Veterans Administration and a few large health maintenance organizations. Even these databases have inherent data completeness 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 complicated for patients who are already taking digoxin, particularly 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 $\beta$ blockade should be optimized. For antiarrhythmic indications, principally atrial fibrillation, consultation 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 fraction $<30\%$, discretion may be the better part of valor because the RADIANCE trial and clinical experience show rebound CHF exacerbation when digitalis is discontinued. Such patients should be maintained on low digoxin dosages (e.g., 0.125 mg every 2 to 3 days), with periodic monitoring of serum levels; monitoring is particularly important for women10 and for patients with low body mass. A level of $\geq 1.0$ 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.7 conclude with the obligatory nod to safety evaluation in randomized trials. Unfortunately niche dialysis-specific trials for a generic drug never will happen. The methodologic issues are daunting. The population involved is tiny from a clinical trials enrollment perspective, with very high mortality, many competing risks, and complicating time-dependent factors such as kidney transplantation. Lacking perfect evidence, the best guides are common sense and the familiar 19th-century Latin injunction primum non nocere.

DISCLOSURES
None.

REFERENCES
The article by Hurst et al. in this issue of JASN demonstrates a much greater proportion of patients with chronic kidney disease (CKD) initiate hemodialysis (HD) with a native arteriovenous fistula (AVF) when they are patients of the Veterans Administration or Department of Defense, federally capitated systems, versus patients in the US Renal Data System, who receive care in the commercial market. The problems of evaluating retrospective databases are widely known. Nonetheless, the magnitude of the difference described here argues for the validity of the observation. We accept both the premise that this measured event, preemptive AVF formation, and the Fistula First Initiative are critically important for patient outcome and that the differences described in the databases are real. Thus, the key question becomes what accounts for these differences; some of them are socioeconomic or racially demographic but not all.

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 almost 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