

and thereby greater statistical power to detect true differences; incorrect specification leads to bias and may render findings meaningless.¹⁵ Therefore, application of AFT models is advisable done in consultation with an experienced statistician.

Argyropoulos *et al.* did not compare results from AFT to those from time-updated proportional hazards models, which are less subject to violations of the proportional hazards assumption than standard, baseline proportional hazards models. Time-updated proportional hazards models may be particularly relevant to observational studies such as CHOICE—in which exposure (Kt/V_{urea}) is not fixed according to randomization but instead varies as the result of therapeutic titrations—given that time-updating reduces the potential for exposure misclassification bias. Further work is needed to clarify the relative merits of AFT *versus* time-updated proportional hazards approaches.

In summary, the study by Argyropoulos *et al.* suggests the use of AFT models instead of proportional hazards models in studies where risk may vary over time because of cumulative exposure. This represents an important analytical consideration in future studies measuring the association of dialysis dose and clinical outcomes.

ACKNOWLEDGMENT

The author thanks Gary Curhan, MD, ScD, for his thoughtful review of this paper.

DISCLOSURES

S.M.B. receives financial support from the National Institute of Diabetes and Digestive and Kidney Diseases (K23DK079056) and has received consulting fees from C.B. Fleet Company.

REFERENCES

1. NKF-K/DOQI Hemodialysis Adequacy Work Group Members: NKF-K/DOQI clinical practice guidelines for hemodialysis adequacy: Update 2000. *Am J Kidney Dis* 37: S7–S64, 2001
2. Gotch FA, Sargent JA: A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). *Kidney Int* 28: 526–534, 1985
3. Owen WF Jr, Lew NL, Liu Y, Lowrie EG, Lazarus JM: The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing hemodialysis. *N Engl J Med* 329: 1001–1006, 1993
4. Saran R, Bragg-Gresham JL, Levin NW, Twardowski ZJ, Wizemann V, Saito A, Kimata N, Gillespie BW, Combe C, Bommer J, Akiba T, Mapes DL, Young EW, Port FK: Longer treatment time and slower ultrafiltration in hemodialysis: associations with reduced mortality in the DOPPS. *Kidney Int* 69: 1222–1228, 2006
5. Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, Allon M, Bailey J, Delmez JA, Depner TA, Dwyer JT, Levey AS, Levin NW, Milford E, Ornt DB, Rocco MV, Schulman G, Schwab SJ, Teehan BP, Toto R: Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med* 347: 2010–2019, 2002
6. Depner T, Daugirdas J, Greene T, Allon M, Beck G, Chumlea C, Delmez J, Gotch F, Kusek J, Levin N, Macon E, Milford E, Owen W, Star R, Toto R, Eknoyan G: Dialysis dose and the effect of gender and body size on outcome in the HEMO Study. *Kidney Int* 65: 1386–1394, 2004
7. Argyropoulos C, Chang CH, Plantinga L, Fink N, Powe N, Unruh M: Considerations in the statistical analysis of hemodialysis patient survival. *J Am Soc Nephrol* 20: 2034–2043, 2009
8. Cortez AJ, Paulson WD, Schwab SJ: Vascular access as a determinant of adequacy of dialysis. *Semin Nephrol* 25: 96–101, 2005
9. Astor BC, Eustace JA, Powe NR, Klag MJ, Fink NE, Coresh J: Type of vascular access and survival among incident hemodialysis patients: the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) Study. *J Am Soc Nephrol* 16: 1449–1455, 2005
10. Lowrie EG: Prescribing and monitoring hemodialysis dose. *Kidney Int* 74: 262–264, 2008
11. Eloot S, Van Biesen W, Dhondt A, Van de Wynkele H, Glorieux G, Verdonck P, Vanholder R: Impact of hemodialysis duration on the removal of uremic retention solutes. *Kidney Int* 73: 765–770, 2008
12. Cox DR: Regression models and life-tables. *J R Stat Soc Ser B* 34: 187–220, 1972
13. Abrahamowicz M, Mackenzie T, Esdaile JM: Time-dependent hazard ratio: Modelling and hypothesis testing with application in Lupus Nephritis. *J Am Stat Assoc* 91: 1432–1439, 1996
14. Orbe J, Ferreira E, Nunez-Anton V: Comparing proportional hazards and accelerated failure time models for survival analysis. *Statist Med* 21: 3493–3510, 2002
15. Bradburn MJ, Clark TG, Love SB, Altman DG: Survival analysis part II: Multivariate data analysis—an introduction to concepts and methods. *Br J Cancer* 89: 431–436, 2003

See related article, “Considerations in the Statistical Analysis of Hemodialysis Patient Survival,” on pages 2034–2043.

Does a Statistical Method Suggest a New Pathobiology for Hemodialysis Patients?

Edmund G. Lowrie

Cape Neddick, Maine

J Am Soc Nephrol 20: 1867–1869, 2009.
doi: 10.1681/ASN.2009060649

You will find elsewhere in these pages of *JASN*¹ a paper by Argyropoulos *et al.* entitled “Considerations in the Statistical Analysis of Hemodialysis Patient Survival.” The claim of this work—a comparative statistical analysis—is that the authors have proven their *a priori* hypothesis that the natural history of

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Edmund G. Lowrie, 511 Shore Road, Cape Neddick, ME 03902. Phone: +207-361-2920; Fax: +207-361-1242; E-mail: edlowrie@prodigy.net

Copyright © 2009 by the American Society of Nephrology

dialysis patients proceeds in an accelerating fashion. As such, they say their chosen statistical method, the accelerated failure time model (AFTM), should be used when evaluating survival on dialysis. The evidence and its interpretation, however, are weak, and both should be considered critically and viewed skeptically. I have several reasons for this view.

Contrary to the authors' assertions, there is widespread agreement that dialysis dose is important to the survival of dialysis patients. The National Cooperative Dialysis Study² proved many years ago that small molecule–directed dialysis is important. Later analyses using those data, but ignoring length of dialysis (t),³ suggested that a K_t/V of 0.9 was a suitable initial threshold. The Hemodialysis Study⁴ used higher K_t/V values, but even so, there remains the implication that women had worse survival in the low than the high K_t/V arm.^{4,5} More to the point, there is widespread transnational agreement that dose is important.^{5–9} Although some might argue about the best formula for describing dose, opinion converges on a K_t/V ratio of 1.2 to 1.4 per session.^{6–9}

Furthermore, the authors' database is quite small¹—only 491 patients evaluated—and thus insufficient to prove their point. Nearly 24% of the parent sample lacked a dose measurement any time during their first 3 mo of treatment (Table 1, last row, of Argyropoulos *et al.*)— K_t/V was the primary target here. This fact suggests either poor patient care or poor data management. The latter possibility is far more likely than the first and raises serious concerns about the quality of the data. Furthermore, patients were followed for up to 9 yr—median follow-up of approximately 4 yr—and it is difficult to imagine, let alone prove, that K_t/V does not change during those interval years. No follow-up dose measurements are included in the paper, although they must have been collected by the dialysis facilities given current regulatory requirements. Those data would allow evaluation of changing dose for use in routine, time-varying, proportional hazards models^{10,11} or to prove that dose did not change. The current data are inadequate for either purpose.

Next, some of the analyses are suspect. Supplementary Tables 1 and 2 from the study of Argyropoulos *et al.* show that six AFTMs were evaluated. K_t/V is significantly associated with survival in only two ($P = 0.04$; last rows). Such “multiple dipping” is usually frowned on, because they lead to claims of new discovery when none exist in statistical fact. Here is a simple example: we have a 1 in 20 chance of randomly drawing a green ball mixed in a bowl with 19 red balls ($P = 0.05$). The chance of drawing red is 0.95. If one dips into the bowl three times, the chance of drawing all red is $0.95^3 = 0.86$. This means the chance of drawing at least one green ball is 0.14—greater than the magic P value of <0.05 to which we are accustomed. In other words, the chance of encountering a type I error, declaring significance when none exists, becomes large unless one accounts for such multiple sampling. That was not done here. Indeed, one can estimate the chances of finding at least one “nonsignificant” significant P value in six tries like this are approximately 26%. Multiple testing in search of P values to support hypotheses is an unwelcome approach.

One might argue that each of these six tries used a different

statistical distribution. Following that line, one would say the complex pathobiology of dialysis patients not only follows an accelerated failure time model but also is constrained to a particular statistical distribution, that is to say, a Log-Normal but not a Weibull distribution, a Log-Logistic distribution, and so forth because K_t/V is not associated with survival for those distributions (Supplementary Tables 1 and 2 from the study of Argyropoulos *et al.*). That argument may seem reasonable to a statistician but dubious to a clinical nephrologist.

The most favorable AFTM (lowest P value associated with K_t/V) was selected for comparison with the Cox model (Table 2 from the study of Argyropoulos *et al.*).¹ The usual requirement for Cox models—proportionality of hazard over time—is not met here as stated by the authors and shown in Supplementary Table 3 from the study of Argyropoulos *et al.* Perhaps this is because the hazards of dose are not consistently proportional over time as the authors suggest. Or perhaps K_t/V changes with time in patients so it was not the same in year 4, for example, as during those first 3 mo. That dynamic is clinically quite likely. Time-varying Cox models¹¹ can easily manage both possibilities, as well as obviate the proportionality concern¹⁰ raised by these authors.¹ Unfortunately, these data are insufficient to the purpose because, as noted earlier, follow-up K_t/V data are not evaluated. The lack of adequate data simply cannot drive conclusions about pathobiology or the relative value of AFTMs *versus* Cox models.

I have constrained my observations thus far by assuming that K_t/V , and this algebraic estimate of it, is an optimum survival-associated expression of hemodialysis dose. However, K_t/V may be a suboptimum expression of hemodialysis dose,¹² in part because of its compound nature, dividing one measure associated with survival (K_t) by another (body size or V). The proposals of the study of Argyropoulos *et al.*¹ become doubly problematic if that argument holds and is deemed true.

Finally, this new paper¹ is an excellent subject for academic journal club review. There are many reasons. For example, the urea kinetics paradigm (K_t/V) is not grounded in a model for the pathophysiology of uremia that depends on cumulative exposure to the uremic milieu claimed here as a premise.¹ To the contrary, urea kinetics was conceived as a method simply to control blood concentrations of substances in dialysis patients assuming that “the control of blood concentrations of various toxic or inhibiting substances to some maximum (peak) value is required for adequate treatment (emphasis added).”¹³ There is nothing in the derivation of the urea kinetic equations, either there¹³ or elsewhere,^{2–4} suggesting a cumulative or additive damage model for uremic pathobiology.

In summary, it seems that the stated premises, the statistical methods, and the analyses themselves are constructed to support a particular preconception about the pathobiology of dialysis patients. Perhaps the authors are constrained by the lack of follow-up data on dialysis dose or did not seek to later collect the information from medical records to complete their existing database. However, those possible dynamics aside, al-

though it is reasonable to experiment with AFTMs,¹⁴ this information that is based only on two *P* values of *P* = 0.04 can not yet be used to inform changes in either current concepts about patient physiology on dialysis or the statistical methods used by the renal community.

DISCLOSURES

None.

REFERENCES

- Argyropoulos C, Chang CCH, Plantinga L, Fink N, Powe N, Unruh M: Considerations in the statistical analysis of hemodialysis patient survival. *J Am Soc Nephrol* 20: 2034–2043, 2009
- Lowrie EG, Laird NM, Parker TF, Sargent JA: Effect of the hemodialysis prescription on patient morbidity. Report from the National Cooperative Dialysis Study. *N Engl J Med* 305: 1176–1181, 1981
- Gotch FA, Sargent J: A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). *Kidney Int* 28: 526–534, 1985
- Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, Allon M, Bailey J, Delmez JA, Depner TA, Dwyer JT, Levey AS, Levin NW, Milford E, Ornt DB, Rocco MV, Schulman G, Schwab SJ, Teehan BP, Toto R: Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med* 347: 2010–2019, 2002
- Depner T, Daugirdas J, Greene T, Allon M, Beck G, Chumlea C, Delmez J, Gotch F, Kusek J, Levin N, Macon E, Milford E, Owen W, Star R, Toto R, Eknoyan G: Dialysis dose and the effect of gender and body size on outcome in the HEMO study. *Kidney Int* 65: 1386–1394, 2004
- National Kidney Foundation: Clinical practice guidelines for hemodialysis adequacy, update 2006. *Am J Kidney Dis* 48[Suppl 1]: S2–90, 2006
- European Renal Association–European Dialysis and Transplant Association: European best practice guidelines. *Nephrol Dial Transplant* 17: 17–21, 2002
- Goldstein MB, Deziel C, Hirsch DJ, Hoult P, Levin A, Sohi P, Taub KJ, Watson D: Clinical practice guidelines for the delivery of hemodialysis: Canadian Society of Nephrology clinical practice guidelines. *J Am Soc Nephrol* 10: S306–S310, 1999
- Kerr P, Perkovic V, Petrie J, Agar J, Disney A: *Dialysis Adequacy (HD) Guidelines—Dose of Haemodialysis. CARI Guidelines*. Council of the Australian and New Zealand Society of Nephrology and the Board of Kidney Health Australia, 2005. Available at http://www.cari.org.au/DIALYSIS_adequacy_published/dose_of_hemodialysis_jul_2005.pdf. Accessed July 25, 2009
- Collett D: Time-dependent variables. In: *Modelling Survival Data in Medical Research*, London, Chapman & Hall/CRC, 1999, pp 223–236
- Allison PD: *Survival Analysis Using the SAS System—Time-Dependent Covariates*, Cary, NC, SAS Publishing Cary, NC, 1995
- Lowrie EG, Li Z, Ofsthun N, Lazarus JM: The online measurement of hemodialysis dose (Kt): Clinical outcome as a function of body surface area. *Kidney Int* 68: 1344–1354, 2005
- Sargent JA, Gotch FA: The analysis of concentration dependence of uremic lesions in clinical studies. *Kidney Int* 7: S35–S44, 1975
- Collett D: Some other parametric models for survival data. In: *Modelling Survival Data in Medical Research*, London, Chapman & Hall/CRC, 1999, pp 199–222

See related article, “Considerations in the Statistical Analysis of Hemodialysis Patient Survival,” on pages 2034–2043.

Metabolic Acidosis and Progression of Chronic Kidney Disease

Lynda A. Frassetto and Chi-yuan Hsu

Department of Medicine, University of California San Francisco, San Francisco, California

J Am Soc Nephrol 20: 1869–1870, 2009.

doi: 10.1681/ASN.2009070710

The concentration of hydrogen ion is normally managed by several buffering and elimination systems, including the kidney. Consequently, progressive renal failure is accompanied by an increasing inability to excrete metabolites of fuel consumption, lower blood pH, and reduced plasma bicarbonate levels,^{1,2} but is the inverse true? Can correcting this chronic metabolic acidosis slow or prevent progressive kidney damage?

An elegant series of experiments several years ago by Mitch and colleagues^{3–6} found that metabolic acidosis in the rat activates the ubiquitin-proteasome pathway, leading to increased protein breakdown to amino acids, including glutamate, which is excreted by the proximal tubule as ammonium. Nath *et al.*⁷ observed even earlier that nitrogen nucleophiles such as ammonia are injurious to the kidney and stimulate chronic tubulointerstitial inflammation through a complement-mediated pathway. Both findings together suggest a deleterious multisystem mechanism contributing to progression of chronic kidney disease (CKD).

Data from studies of rats on the effects of alkali therapy in CKD have been contradictory: Some studies posit alkali therapy is protective^{5,8} or neutral,⁹ whereas others suggest the opposite—that metabolic acidosis is protective.^{10,11} Investigation of this issue in humans also reveals divergent results. In an early report from 1931, Lyon and Stewart¹² treated 17 patients with moderate renal failure for periods of several weeks to months with both low-acid diets and sufficient oral supplementation with sodium bicarbonate and potassium citrate to maintain an alkaline urine pH. This work advanced the notion that lightening of an acid load on the kidney stabilizes or temporarily improves renal function. Since then, there have been only limited numbers of short-term studies in small groups of humans with CKD.^{13–15}

In this issue of *JASN*, Ashurst *et al.*¹⁶ make a significant contribution to this field by performing a randomized, placebo-controlled trial of oral sodium bicarbonate supplementation (approximately 21 mmol/d in divided doses) in 134 adults with stages 4 to 5 CKD (GFR 15 to 30 ml/min per 1.73 m²) and levels of serum bicarbonate between 16 and 20 mmol/L. Primary end points following intention to treat were rates of decline in creatinine clearance and development of ESRD that required dialysis. Recruited patients were a heterogeneous mix of race, gender, and cause of renal failure on typical medications used in advanced CKD, including renin-angiotensin