analysis of the effects on BP lowering (24-hour BP measurements) and its effect on cardiac performance, important because of the high prevalence of cardiac disease in CKD, is required.

Pharmacokinetic data on atrasentan show a half-life of 21 hours in patients without renal disease,[18] but pharmacokinetics may be different in proteinuric nephropathy. The preliminary data show negative effects in patients with preexisting cardiac disease, and more data on the safety of atrasentan in patients with CKD and cardiac changes will be required. On the basis of the available information, one can already state specifically that major diastolic heart failure is a contraindication.

DISCLOSURES

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REFERENCES

1. Yanagisawa M, Kurihara H, Kimura S, Tomobe Y, Kobayashi M, Mitsui Y, Yazaki Y, Goto K, Masaki T: A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature* 332: 411–415, 1988
2. Ahn D, Ge Y, Stricklett PK, Gill P, Taylor D, Hughes AK, Yanagisawa M, Miller L, Nelson RD, Kohan DE: Collecting duct-specific knockout of endothelin-1 causes hypertension and sodium retention. *J Clin Invest* 114: 504–511, 2004
3. Pavlov TS, Chahdi A, Ilatovskaya DV, Levchenko V, Vandewalle A, Pochynyuk O, Sorokin A, Staruschenko A: Endothelin-1 inhibits the epithelial Na+ channel through betaPix/14-3-3/Nedd4-2. *J Am Soc Nephrol* 21: 833–843, 2010
4. Ge Y, Bagnall A, Stricklett PK, Strait K, Webb DJ, Kotelevtsev Y, Kohan DE: Collecting duct-specific knockout of the endothelin B receptor causes hypertension and sodium retention. *Am J Physiol Renal Physiol* 291: F1274–F1280, 2006
5. Packer M, McMurray J, Massie BM, Caspi A, Charlon V, Cohen-Solal A, Kiowski W, Kostuk W, Krum H, Levine B, Rizzon P, Soler J, Swedberg K, Anderson S, Demets DL: Clinical effects of endothelin receptor antagonism with bosentan in patients with severe chronic heart failure: Results of a pilot study. *J Card Fail* 11: 12–20, 2005
6. Anand I, McMurray J, Cohn JN, Konstam MA, Notter T, Quitzau K, Ruschitzka F, Luscher TF: Long-term effects of darusentan on left-ventricular remodeling and clinical outcomes in the Endothelin A Receptor Antagonist Trial in Heart Failure (EARTH): Randomised, double-blind, placebo-controlled trial. *Lancet* 364: 347–354, 2004
7. Schildroth J, Rettig-Zimmermann J, Kalk P, Steege A, Fahling M, Sendeski M, Paliege A, Lai EY, Bachmann S, Persson PB, Hocher B, Patzak A: Endothelin type A and B receptors in the control of afferent and efferent arterioles in mice. *Nephrol Dial Transplant* September 2, 2010 [epub ahead of print]
8. Ong AC, Jowett TP, Firth JD, Burton S, Karet FE, Fine LG: An endothelin-1 mediated autocrine growth loop involved in human renal tubular regeneration. *Kidney Int* 48: 390–401, 1995
9. Wenzel RR, Littke T, Kuranoff S, Jurgens C, Bruck H, Ritz E, Philipp T, Mitchell A: Avosentan reduces albumin excretion in diabetics with macroalbuminuria. *J Am Soc Nephrol* 20: 655–664, 2009
10. Mann JF, Green D, Jamerson K, Ruilope LM, Kuranoff SJ, Littke T, Viberti G: Avosentan for overt diabetic nephropathy. *J Am Soc Nephrol* 21: 527–535, 2010
11. Kohan DE, Pritchett Y, Molitch M, Wen S, Garimella T, Audhya P, Andress DL: Addition of atrasentan to renin-angiotensin system blockade reduces albuminuria in diabetic nephropathy. *J Am Soc Nephrol* 22: 763–772, 2011
12. Kohan DE: Biology of endothelin receptors in the collecting duct. *Kidney Int* 76: 481–486, 2009
13. Weber MA, Black H, Bakris G, Krum H, Linas S, Weiss R, Linseman JV, Wiens BL, Warren MS, Lindholm LH: A selective endothelin-receptor antagonist to reduce blood pressure in patients with treatment-resistant hypertension: A randomised, double-blind, placebo-controlled trial. *Lancet* 374: 1423–1431, 2009
14. Shiigai T, Shichiri M: Late escape from the antiproteinuric effect of ACE inhibitors in nondiabetic renal disease. *Am J Kidney Dis* 37: 477–483, 2001
15. Sato A, Hayashi K, Saruta T: Antiproteinuric effects of mineralocorticoid receptor blockade in patients with chronic renal disease. *Am J Hypertens* 18: 44–49, 2005
16. Parving HH, Persson F, Lewis JB, Lewis EJ, Hollenberg NK: Aliskiren combined with losartan in type 2 diabetes and nephropathy. *N Engl J Med* 358: 2433–2446, 2008
17. de Zeeuw D, Agarwal R, Amdahl M, Audhya P, Coyne D, Garimella T, Parving HH, Pritchett Y, Remuzzi G, Ritz E, Andress D: Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): A randomised controlled trial. *Lancet* 376: 1543–1551, 2010
18. Zonnenberg BA, Groenewegen G, Janus TJ, Leahy TW, Humerickhouse RA, Isaacson JD, Carr RA, Voest E: Phase I dose-escalation study of the safety and pharmacokinetics of atrasentan: An endothelin receptor antagonist for refractory prostate cancer. *Clin Cancer Res* 9: 2965–2972, 2003
19. Gagliardini E, Corna D, Zoja C, Sangalli F, Carrara F, Rossi M, Conti S, Rottoli D, Longaretti L, Remuzzi A, Remuzzi G, Benigni A: Unlike each drug alone, lisinopril if combined with avosentan promotes regression of renal lesions in experimental diabetes. *Am J Physiol Renal Physiol* 297: F1448–F1456, 2009

See related article, "Addition of Atrasentan to Renin-Angiotensin System Blockade Reduces Albuminuria in Diabetic Nephropathy," on pages 763–772.

Aspirin and Arteriovenous Graft Thrombosis in Hemodialysis: Just What the Doctor Ordered?

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The Center for Medicare and Medicaid Services' (CMS) *Fistula First* initiative has changed dialysis practice. In 2003, more

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than one third (37%) of patients on hemodialysis (HD) used prosthetic arteriovenous grafts (AVGs), slightly more than the 35% using native AV fistulas (AVFs). By 2010, fewer than 20% of prevalent patients on HD used AVGs.

In this issue of *JASN*, baseline aspirin (ASA) use in the Dialysis Access Consortium (DAC) Graft Trial was shown to be associated with a marginal extension in AVG longevity.[1] Although some might suggest that the marginal extension (supported by a marginal *P* value) is of marginal importance, any therapeutic strategy that might enhance AVG performance in any way would be welcome. A large fraction of patients in the United States fail to develop a mature, usable AVF (as the DAC Fistula Trial confirmed[2]), such that a larger fraction of prevalent patients remain dependent on tunneled catheters for permanent vascular access. An inexpensive and safe therapy that might add even a few weeks of uninterrupted long-term HD access deserves our close attention.

Dixon *et al.*[3] meticulously performed a secondary analysis of data from the DAC Graft Trial, in which 649 patients were assigned to either placebo or twice-daily extended-release dipyridamole (200 mg) and ASA (25 mg; ERDP/ASA) after AVG placement. The primary outcome—loss of primary unassisted patency—was defined as the first occurrence of AVG thrombosis or any procedure (angioplasty or surgery) to treat AVG stenosis. Patients who were assigned to ERDP/ASA experienced an absolute risk reduction of 5% (28 *versus* 23% with primary unassisted patency at 1 year), corresponding to an adjusted relative risk reduction of 18% (95% confidence interval [CI] 2 to 32%). Rates of hemorrhage and other adverse events were similar across randomized groups, and other retrospective studies of HD patients[4] suggested marginal risk for ASA exposure in this setting (1.06; 95% CI 1.01 to 1.11).

Because 43% of patients who entered the trial were taking ASA before randomization (typically 81 mg/d), the authors were able to compare outcomes associated with ASA use across and within randomized groups assigned to either ERDP/ASA or placebo. Patients who were taking ASA before randomization were older (62.5 *versus* 55.1 years) and had a higher prevalence of diabetes (74 *versus* 54%). Unadjusted rates of loss of primary unassisted patency were 81 and 82% in the prerandomization ASA and non-ASA groups, respectively. After adjustment for unbalanced baseline covariates, there was a relative difference of 17% (95% CI −1 to 32%) in favor of patients who were taking ASA before randomization. Although the interaction (randomized group × prerandomization ASA exposure) was not significant, it is noteworthy that the estimated relative risk reduction associated with prerandomization ASA use was 27% (95% CI 3 to 45%) in patients who were randomly assigned to placebo and 10% (95% CI −22 to 33%) in patients who were randomly assigned to ERDP/ASA.

To gauge the importance of these observations, recall that AVGs fail for several reasons. Intimal hyperplasia at the venous anastomosis is the most common reason for AVG thrombosis; eventually flow declines sufficiently to result in thrombosis and AVG failure. Others occlude suddenly after functioning well with no demonstrable structural abnormalities. These latter events are probably multifactorial; extrinsic compression may play a role, as could intradialytic hypotension and/or thrombophilia. The prosthetic luminal surface of an AVG, lacking endothelium, is vulnerable to both stasis and hypercoagulability. Because thrombosis is the final common pathway, anticoagulant or antiplatelet agents would seem to be logical prophylactic strategies. Controlled trials of warfarin proved ineffective and hazardous[5]; small studies of antiplatelet agents have shown mixed results. In the current analysis, enhanced AVG longevity was achieved with low-dosage ASA without excess bleeding. Also noteworthy was the lower percentage of AVGs that clotted unexpectedly after performing well without underlying venous stenosis: 13% failed in patients who were taking ASA at baseline compared with 20% in patients who were not taking ASA (adjusted hazard ratio 0.60; 95% CI 0.38 to 0.95).

The overall poor performance of AVGs in the DAC Trial is sobering. In current practice, patients typically undergo AVG placement because of risk factors for nonmaturation, including advanced age, female gender, peripheral arterial disease, and obesity[6] or after failure of one or more AVFs. The percentage of patients with functional AVFs may rise further in coming years with ongoing payer and provider emphasis on AVF creation and enhanced surgical skill and experience; AVF usage to initiate dialysis is now twice as likely in facilities operated by the Department of Defense or Veterans Affairs.[7,8] However, a plateau is foreseeable. There will be an ongoing role for AVGs; thus, no viable approach to enhance AVG longevity should be dismissed. Indeed, despite the mantra of *Fistula First*, AVGs may be preferable to AVFs when life expectancy is relatively short or in patients with a low likelihood of fistula maturation, in the latter case, to limit person-months of tunneled catheter exposure.

Venous intimal hyperplasia remains unsolved despite years of basic and translational research; however, promising therapeutics are on the horizon. The antiproliferative effects of dipyridamole may have been responsible for the modest benefit observed in the parent DAC trial[9]; other systemic or locally applied antiproliferative agents may ultimately prove more effective. Spontaneously self-assembling nitric oxide–releasing nanofiber gels applied to injured rat carotid arteries reduce intimal hyperplasia.[10] Heparin-bonded grafts are in widespread use, and new biologically active grafts can be anticipated.[11] A completely tissue-engineered vascular autograft has had limited success in a small clinical trial.[12]

Roughly 50 years after the advent of the Scribner shunt, it is dispiriting to reflect on the lack of reliable means for establishing long-term vascular access for HD. Bioengineering programs take note: We have nothing shiny and new just yet. While we await the paradigm shift, we must comfort ourselves with old-fashioned technology and low-cost, modestly effective interventions. For the meantime, low-dosage daily ASA may be just what the doctor ordered.

DISCLOSURES

None.

REFERENCES

1. Dixon BS, Beck GJ, Dember LM, Vazquez MA, Greenberg A, Delmez JA, Allon M, Himmelfarb J, Hu B, Greene T, Radeva MK, Davidson IJ, Ikizler TA, Braden GL, Lawson JH, Cotton, Jr. JR, Kusek JW, Feldman HI: Use of aspirin associates with longer primary patency of hemodialysis grafts. *J Am Soc Nephrol* 22: 773–781, 2011
2. Dember LM, Beck GJ, Allon M, Delmez JA, Dixon BS, Greenberg A, Himmelfarb J, Vazquez MA, Gassman JJ, Greene T, Radeva MK, Braden GL, Ikizler TA, Rocco MV, Davidson IJ, Kaufman JS, Meyers CM, Kusek JW, Feldman HI, Dialysis Access Consortium Study Group: Effect of clopidogrel on early failure of arteriovenous fistulas for hemodialysis: A randomized controlled trial. *JAMA* 299: 2164–2171, 2008
3. Dixon BS, Beck GJ, Vasquez MA, Greenberg A, Delmez JA, Allon M, Dember LM, Himmelfarb J, Gassman JJ, Greene T, Radeva MK, Davidson IJ, Ikizler TA, Braden GL, Fenves AZ, Kaufman JS, Cotton JR Jr, Martin KJ, McNeil JW, Rahman A, Lawson JH, Whiting JF, Hu B, Meyers CM, Kusek JW, Feldman HI, DAC Study Group: Effect of dipyridamole plus aspirin on hemodialysis graft patency. *N Engl J Med* 360: 2191–2201, 2009
4. Chan KE, Lazarus JM, Thadhani R, Hakim RM: Anticoagulant and antiplatelet usage associates with mortality among hemodialysis patients. *J Am Soc Nephrol* 20: 872–881, 2009
5. Crowther MA, Clase CM, Margetts PJ, Julian J, Lambert K, Sneath D, Nagai R, Wilson S, Ingram AJ: Low-intensity warfarin is ineffective for the prevention of PTFE graft failure in patients on hemodialysis: A randomized controlled trial. *J Am Soc Nephrol* 13: 2331–2337, 2002
6. Miller PE, Tolwani A, Luscy CP, Deierhoi MH, Bailey R, Redden DT, Allon M: Predictors of adequacy of arteriovenous fistulas in hemodialysis patients. *Kidney Int* 56: 275–280, 1999
7. Hurst FP, Abbott KC, Raj D, Krishnan M, Palant CE, Agodoa LY, Jindal RM: Arteriovenous fistulas among incident hemodialysis patients in Department of Defense and Veterans Affairs facilities. *J Am Soc Nephrol* 21: 1571–1577, 2010
8. Schwab SJ, Brown KD: Immature public policy for vascular access. *J Am Soc Nephrol* 21: 1420–1421, 2010
9. Himmelfarb J, Couper L: Dipyridamole inhibits PDGF- and bFGF-induced vascular smooth muscle cell proliferation. *Kidney Int* 52: 1671–1677, 1997
10. Kapadia MR, Chow LW, Tsihlis ND, Ahanchi SS, Eng JW, Murar J, Martinez J, Popowich DA, Jiang Q, Hrabie JA, Saavedra JE, Keefer LK, Hulvat JF, Stupp SI, Kibbe MR: Nitric oxide and nanotechnology: A novel approach to inhibit neointimal hyperplasia. *J Vasc Surg* 47: 173–182, 2008
11. Davidson I, Hackerman C, Kapadia A, Minhajuddib A: Heparin bonded hemodialysis e-PTFE grafts result in 20% clot free survival benefit. *J Vasc Access* 10: 153–156, 2009
12. McAllister TN, Maruszewski M, Garrido SA, Wystrychowski W, Dusserre N, Marini A, Zagalski K, Fiorillo A, Avila H, Manglano X, Antonelli J, Kocher A, Zembala M, Cierpka L, de la Fuente LM, L'heureux N: Effectiveness of haemodialysis access with an autologous tissue-engineered vascular graft: A multicentre cohort study. *Lancet* 373: 1440–1446, 2009

See related article, "Use of Aspirin Associates with Longer Primary Patency of Hemodialysis Grafts," on pages 773–781.