

DISCLOSURES

None.

REFERENCES

1. Glassock RJ, Winearls C: Screening for CKD with eGFR: Doubts and dangers. *Clin J Am Soc Nephrol* 3: 1563–1568, 2008
2. Baxmann AC, Ahmed MS, Marques NC, Menon VB, Pereira AB, Kirsztajn GM, Heilberg IP: Influence of muscle mass and physical activity on serum and urinary creatinine and serum cystatin C. *Clin J Am Soc Nephrol* 3: 348–354, 2008
3. Rule AD, Gussak HM, Pond GR, Bergstralh EJ, Stegall MD, Cosio FG, Larson TS: Measured and estimated GFR in healthy potential kidney donors. *Am J Kidney Dis* 43: 112–119, 2004
4. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J: A new equation to estimate glomerular filtration rate. *Ann Intern Med* 150: 604–612, 2009
5. Shlipak MG, Katz R, Sarnak MJ, Fried LF, Newman AB, Stehman-Breen C, Seliger SL, Kestenbaum B, Psaty B, Tracy RP, Siscovick DS: Cystatin C and prognosis for cardiovascular and kidney outcomes in elderly persons without chronic kidney disease. *Ann Intern Med* 145: 237–246, 2006
6. Shlipak MG, Sarnak MJ, Katz R, Fried LF, Seliger SL, Newman AB, Siscovick DS, Stehman-Breen C: Cystatin C and the risk of death and cardiovascular events among elderly persons. *N Engl J Med* 352: 2049–2060, 2005
7. Astor BC, Levey AS, Stevens LA, Van Lente F, Selvin E, Coresh J: Method of glomerular filtration rate estimation affects prediction of mortality risk. *J Am Soc Nephrol* 20: 2214–2222, 2009
8. Ishani A, Grandits GA, Grimm RH, Svendsen KH, Collins AJ, Prineas RJ, Neaton JD: Association of single measurements of dipstick proteinuria, estimated glomerular filtration rate, and hematocrit with 25-year incidence of end-stage renal disease in the multiple risk factor intervention trial. *J Am Soc Nephrol* 17: 1444–1452, 2006
9. Gansevoort RT, de Jong PE: The case for using albuminuria in staging chronic kidney disease. *J Am Soc Nephrol* 20: 465–468, 2009
10. Dhamidharka VR, Kwon C, Stevens G: Serum cystatin C is superior to serum creatinine as a marker of kidney function: A meta-analysis. *Am J Kidney Dis* 40: 221–226, 2002
11. Stevens LA, Coresh J, Schmid CH, Feldman HI, Froissart M, Kusek J, Rossert J, Van Lente F, Bruce RD 3rd, Zhang YL, Greene T, Levey AS: Estimating GFR using serum cystatin C alone and in combination with serum creatinine: A pooled analysis of 3,418 individuals with CKD. *Am J Kidney Dis* 51: 395–406, 2008
12. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 351: 1296–1305, 2004
13. den Hartog JR, Reese PP, Cizman B, Feldman HI: The costs and benefits of automatic estimated glomerular filtration rate reporting. *Clin J Am Soc Nephrol* 4: 419–427, 2009
14. Fried LF: Creatinine and cystatin C: What are the values? *Kidney Int* 75: 578–580, 2009
15. Knight EL, Verhave JC, Spiegelman D, Hillege HL, de Zeeuw D, Curhan GC, de Jong PE: Factors influencing serum cystatin C levels other than renal function and the impact on renal function measurement. *Kidney Int* 65: 1416–1421, 2004

See related article, “Method of Glomerular Filtration Rate Estimation Affects Prediction of Mortality Risk,” on pages 2214–2222.

Warfarin and Stroke Outcomes in Hemodialysis Patients with Atrial Fibrillation

Simonetta Genovesi* and Antonio Santoro[†]

*Department of Clinical Medicine and Prevention, University of Milano-Bicocca, Milano, Italy, and Nephrology Unit, San Gerardo Hospital, Monza, Italy; and [†]Nephrology, Dialysis and Hypertension Department, University of Bologna and S. Orsola-Malpighi Hospital, Bologna, Italy

J Am Soc Nephrol 20: 2090–2092, 2009.
doi: 10.1681/ASN.2009070754

The prevalence of atrial fibrillation in ESRD is extremely high, reaching 27%,¹ and fibrillation, as in the general population, also is associated with increased mortality in hemodialysis patients.² A large number of trials show the usefulness of oral anticoagulation therapy¹ for primary and secondary prevention of stroke in patient populations with atrial fibrillation absent ESRD.³ Recently, a large study demonstrated the superiority of oral anticoagulation therapy compared with the combination of clopidogrel plus aspirin with regard to stroke prevention, with no added risk of bleeding.⁴ Even trials performed in patients with high hemorrhagic risk who took warfarin, particularly the elderly, show that benefits of treatment exceed the risks when the international normalized ratio (INR) is monitored correctly.

The decision to use oral anticoagulation therapy, particularly warfarin, in patients with atrial fibrillation involves weighing the risk of a thromboembolic event without therapy, or with inadequate anticoagulation, against the risk of a hemorrhagic event on therapy, particularly over-anticoagulation. Efficacy and safety of anticoagulation in atrial fibrillation depend on maintaining the INR between 2 and 3,⁵ as recommended by most practice guidelines.⁶ Recently an INR of 3.0 to 3.4 has been proposed to achieve optimal anticoagulation intensity in patients with atrial fibrillation.⁷ However, dialysis populations are different from the general population.

The association between renal dysfunction and bleeding has long been recognized, even as long as 200 yr ago,⁸ and morbidity and mortality from bleeding remain a significant clinical problem in ESRD. Impaired platelet function is one of the main determinants of uremic bleeding. This impairment is multifactorial and includes defects that are intrinsic to platelets and abnormal platelet–endothelial interactions. Uremic toxins and anemia also play a role.⁹ Moreover, hemodialysis patients, unlike other patient settings, are exposed to continuous

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

Correspondence: Dr. Simonetta Genovesi, Dipartimento di Medicina Clinica e Prevenzione, Via Cadore 48, Monza, Milano 20052, Italy. Phone: +390392332426; Fax: +390392332376; E-mail: simonetta.genovesi@unimib.it

Copyright © 2009 by the American Society of Nephrology

anticoagulation with heparin during the course of hemodialysis. Therefore, the problem of how to anticoagulate dialysis patients with atrial fibrillation is a truly huge concern.

In this issue of *JASN*, Chan *et al.*¹⁰ report an increased risk of stroke (presumably hemorrhagic) associated with warfarin use in dialysis patients with atrial fibrillation. The authors stress the risk of unmonitored anticoagulation in this subpopulation and caution the careful use of warfarin in these patients. Although the study was performed in a large number of patients, it contains various limitations, as do all association studies—association studies are hypothesis generating: There is no formal documentation of arrhythmias (and thus a correct indication for anticoagulation therapy); in many cases, the exact nature of the strokes (ischemic or hemorrhagic) is not identified; the number of patients on warfarin treatment without INR monitoring is high; and the INR value at the moment of the stroke is often unknown. All of these factors limit the strength of the results and the conclusions of the work.

However, the study confirms the importance of identifying patients at special risk for warfarin-associated stroke to optimize the risk/benefit of anticoagulation therapy. Risk of ischemic stroke in the general population is best estimated with the CHADS2 score (congestive heart failure, hypertension, age ≥ 75 yr, diabetes, 1 point each; prior stroke or transient ischemic attack, 2 points). For patients with atrial fibrillation and a CHADS2 score ≥ 2 , anticoagulation with warfarin is recommended, although the sensitivity of this scoring system for dialysis populations is unclear.¹¹ Access to high-quality monitoring of anticoagulation is crucial in the decision to use warfarin. The use of warfarin without adequate monitoring is more dangerous than the choice not to use it, even in the presence of increased thromboembolic risk, and this seems to apply particularly to patients with ESRD. It should be emphasized that dialysis patients already demonstrate an ischemic or hemorrhagic stroke prevalence that is much higher than that of the general population, and the magnitude of this excess stroke risk is greater for ischemic stroke than that for hemorrhagic stroke.^{12,13} Thus, it is also difficult to understand which percentage of strokes reported by Chan *et al.*¹⁰ really had a thromboembolic cause, perhaps preventable by proper warfarin therapy, and which percentage of the hemorrhagic strokes would have occurred regardless of such treatment.

Nevertheless, the study by Chan *et al.*¹⁰ poses another important question that nephrologists have to deal with frequently in light of the growing importance of cardiovascular comorbidities in hemodialysis patients: *Are the anticoagulation guidelines for the general population at risk for stroke applicable to patients who concomitantly suffer from cardiovascular disease and ESRD?* The Chan *et al.*¹⁰ study raises concern about offering standard medical treatments established for heart disease patients without renal failure and then translating them to dialysis patients with cardiac diseases. This issue urges the development of a prospective clinical trial where dialysis patients with documented atrial fibrillation are randomized to treatment with oral anticoagulation therapy or placebo to evaluate

the efficacy of anticoagulant therapy in this population. An evidence-based answer to the issue is urgently needed.

In conclusion, in our opinion and for the moment, dialysis patients with atrial fibrillation should be treated with oral anticoagulation only if they have a CHADS score ≥ 2 and after carefully weighing the risk/benefit ratio. In subjects on renal replacement therapy, proper anticoagulation control along with aggressive BP management is also important to minimize the risk of stroke in these high-risk patients. Careful INR monitoring is already feasible, because dialysis treatment requires most patients to be in contact with medical staff more than once a week. However, even these cautious measures of monitoring may not protect our patients from the risk of stroke, and on this issue we are in agreement with Chan *et al.*¹⁰ The future also could be brighter for dialysis patients. We need antithrombotic agents that are more effective than aspirin and safer to use than adjusted-dose warfarin. Additional options for stroke prevention may be on the horizon. Several large, randomized trials are currently testing novel oral anticoagulants, such as dabigatran and combinations of antiplatelet agents,^{14,15} but for the time being, given the ongoing epidemic of atrial fibrillation in ESRD, all nephrologists should be aware of this common and possibly iatrogenic cause of preventable stroke.

DISCLOSURES

None.

REFERENCES

- Genovesi S, Pogliani D, Faini A, Valsecchi MG, Riva A, Stefani F, Acquistapace I, Stella A, Bonforte G, DeVecchi A, DeCristofaro V, Buccianti G, Vincenti A: Prevalence of atrial fibrillation and associated factors in a population of long-term haemodialysis patients. *Am J Kidney Dis* 46: 897–902, 2005
- Genovesi S, Vincenti A, Rossi E, Pogliani D, Acquistapace I, Stella A, Valsecchi MG: Atrial fibrillation and morbidity and mortality in a cohort of long-term hemodialysis patients. *Am J Kidney Dis* 51: 255–262, 2008
- Reynolds MW, Fahrback K, Hauch O, Wygant G, Estok R, Cella C, Nalysnyk L: Warfarin anticoagulation and outcomes in patients with atrial fibrillation. A systemic review and metaanalysis. *Chest* 126: 1938–1945, 2004
- Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): A randomised controlled trial. *Lancet* 367: 1903–1912, 2006
- Hylek EM, Singer DE: Risk factors for intracranial hemorrhage in outpatients taking warfarin. *Ann Intern Med* 120: 897–902, 1994
- Guidelines for the management of patients with atrial fibrillation. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). *J Am Coll Cardiol* 48: 854–906, 2006
- Torn M, Cannegieter SC, Bollen WLE, van der Meer FJM, van der Wall EE, Frits R, Rosendaal FR: Optimal level of oral anticoagulant therapy

- for the prevention of arterial thrombosis in patients with mechanical heart valve prostheses, atrial fibrillation, or myocardial infarction. *Arch Intern Med* 169: 1203–1209, 2009
8. Morgagni GB: *Opera Omnia*, Ex Typographia Remondiniana, Venice, Italy, 1764
 9. Sohal AS, Gangji AS, Crowther MA, Treleaven D: Uremic bleeding: pathophysiology and clinical risk factors. *Thromb Res* 118: 417–422, 2006
 10. Chan KE, Lazarus JM, Thadhani R, Hakim RM: Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation. *J Am Soc Nephrol* 20: 2223–2233, 2009
 11. Reinecke H, Brand E, Mesters R, Schabitz WR, Fisher M, Pavenstadt H, Breithardt G: Dilemmas in the management of atrial fibrillation in chronic kidney disease. *J Am Soc Nephrol* 20: 705–711, 2009
 12. Seliger SL, Gillen DL, Tirschwell D, Wasse H, Kestenbaum BR, Stehman-Breen COI: Risk factors for incident stroke among patients with end-stage renal disease. *J Am Soc Nephrol* 14: 2623–2631, 2003
 13. Seliger SL, Gillen DL, Longstreth WT, Kestenbaum B, Stehman-Breen O: Elevated risk of stroke among patients with end-stage renal disease. *Kidney Int* 64: 603–609, 2003
 14. Ezeowitz MD, Connolly S, Parekh A, Reilly PA, Varrone J, Wang S, Oldgren J, Themeles E, Wallentin L, Yusuf S: Rationale and design of RE-LY: Randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. *Am Heart J* 157: 805–810, 2009
 15. Turpie AGG: New oral anticoagulants in atrial fibrillation. *Eur Heart J* 29: 155–165, 2007
-
- See related article, “Warfarin Use Associates with Increased Risk for Stroke in Hemodialysis Patients with Atrial Fibrillation,” on pages 2223–2233.