Canadian Journal of Cardiology 33 (2017) 211–213

Editorial

Which Patients With Atrial Fibrillation and Chronic Kidney Disease Should Receive Anticoagulation—And With Which Anticoagulant?

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See article by McAlister et al., pages 243–252 of this issue.

Chronic kidney disease (CKD) is prevalent (about 30%) among patients with atrial fibrillation (AF) (Fig. 1 and Table 1).[1-4] AF is strongly associated with CKD,[5] and moderate CKD is an important independent predictor of AF-associated stroke. CKD is also a powerful risk factor for bleeding.[4] In this issue of the *Canadian Journal of Cardiology*, McAlister et al.[6] assessed 7 previously published risk prediction models for stroke and major bleeding in patients with AF and found them to be poorly predictive in patients with AF and CKD.[6]

This retrospective (2002-2013) longitudinal cohort study was based on Alberta Health administrative databases and included 55,451 patients with incident nonvalvular AF who were not treated with anticoagulants and who were followed for a mean of 2.6 years.[6] Patient groups that were not included because of specific inclusion criteria warrant mention: 24,415 patients with AF who were prescribed anticoagulation therapy were not included nor were 25,567 patients with AF in whom kidney function was not measured within 3 months of diagnosis. Patients with AF receiving renal replacement therapy or those who had undergone previous renal transplantation were also excluded. These stipulations contributed to a relatively young AF study cohort (mean age, 66 years, which is 5-10 years younger than typical AF cohorts), with 11% having a history of previous bleeding. Also of note, thromboembolic outcomes included transient ischemic attacks (35%), and the definition of major hemorrhage was "any bleed requiring emergency department visit or hospitalization, intracranial hemorrhage, or gastrointestinal bleeding" (different from and not comparable to the criteria used in recent large randomized trials). CKD defined by reduced (< 60 mL/min/1.73m^2) estimated glomerular filtration rate (eGFR) was present in 24% (and in 31% if additionally considering albuminuria). The observed stroke rate during follow-up of 3.2% per year is relatively high for a cohort with a median $CHADS_2$ (**C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack) score of 1 and a mean CHA_2DS_2-VASc (**C**ongestive Heart Failure, **H**ypertension, **A**ge [≥ 75 years], **D**iabetes, **S**troke/Transient Ischemic Attack, **Va**scular Disease, **A**ge [65-74 years], **S**ex [Female] **sc**ore) of 3 (expected stroke rate of about 2%/y).[7,8] Both the rates of stroke and of major bleeding increased progressively in parallel with the severity of CKD.

Sophisticated statistical analyses were undertaken to assess the predictive value of 7 widely used risk-stratification schemes (4 for prediction of thromboembolism and 3 for major bleeding) in the subgroup of patients with AF and CKD.[6] All schemes performed better in patients with AF without CKD, with poor discrimination in patients with CKD in proportion to CKD severity. The investigators concluded that these risk stratification schemes were inadequate for clinical decision-making in patients with AF and CKD.[6]

The study results support that there are no reliable bleeding risk prediction schemes for anticoagulation in patients with AF, with or without CKD.[9-12] The failure of prediction schemes is particularly important for patients with CKD because of their inherently higher rates of major bleeding.[4] By far the worst complication of warfarin anticoagulation is intracerebral hemorrhage,[13] for which there is no satisfactory acute treatment.[14] Furthermore, extracranial bleeding during anticoagulation is more than just a nuisance; it initiates a series of "consecutively falling dominos" that result in increased mortality.[15,16] Interestingly, the clinical consequences of bleeding during antithrombotic therapies have sometimes been underestimated by regulatory agencies but not by practitioners, who tend to be excessively adverse to bleeding risk when considering antithrombotic drugs for stroke prophylaxis.

In our view, anticoagulation for stroke prevention should be routinely considered for all patients with AF who are ≥ 65 years

Received for publication September 27, 2016. Accepted October 5, 2016.

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See page 213 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2016.10.007

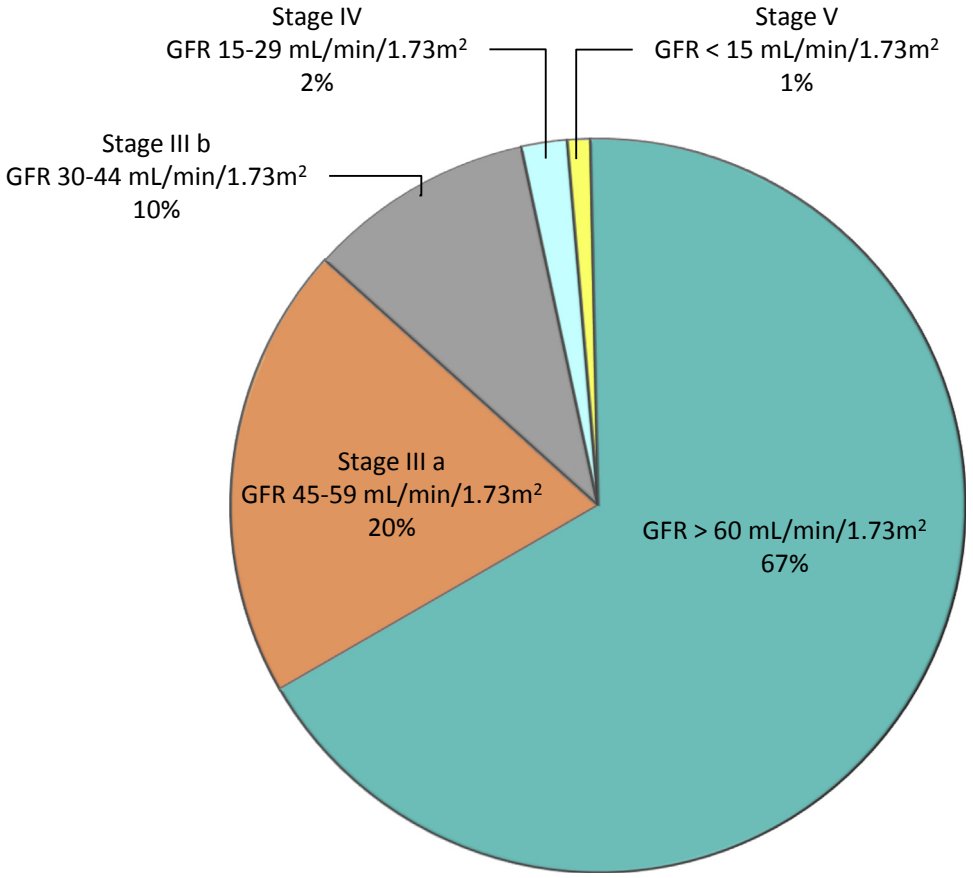

Figure 1. Frequency of chronic kidney disease in patients with atrial fibrillation. Modified from Hart et al.[1] with permission from Elsevier.

of age with moderate CKD (ie, eGFR 30-59 mL/min). The recently introduced direct-acting oral anticoagulants (DOACs) are preferred over warfarin for prevention of stroke in patients with AF, including those with moderate CKD.[17] DOACs are associated with half the risk of intracerebral hemorrhage compared with warfarin.[18] Based on currently available data, we favor apixaban as the anticoagulant of choice for patients with AF and CKD because it is less dependent on renal clearance than are other DOACs.[17,19,20]

Table 1. Stages of chronic kidney disease*

Stage	Description	GFR (mL/min/1.73m^2)
I	Kidney damage with normal or increased GFR	> 90
II	Mild	60-89
III	Moderate	30-59
IV	Severe	15-29
V	End-stage renal failure	< 15

GFR, glomerular filtration rate.

*Kidney Disease Outcomes Quality Initiative (KDOQI) criteria.[1] Renal function is sometimes expressed as estimated creatinine clearance using the Cockcroft-Gault equation that usually exceeds the estimated GFR, particularly at an estimated GFR about 30 mL/min/1.73m^2. Because many clinical laboratories automatically provide an estimated GFR that accompanies measurement of serum creatinine levels, use of the antiquated estimated creatinine clearance should be abandoned.[2] The Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines additionally incorporate albuminuria into classification of renal function.[3] Albuminuria is an independent predictor of major bleeding.[4]

The benefits vs risks of anticoagulation for stroke prevention in patients with AF with a eGFR < 30 mL/min/1.73m^2 or with end-stage CKD are less clear and are controversial.[21-26] Patients with AF undergoing hemodialysis are at substantially increased risk both of ischemic stroke and of serious bleeding (including intracranial bleeding). Both the US Food and Drug Administration (FDA) and the European Medicines Agency have approved the use of apixaban and rivaroxaban in patients with an eGFR 15-30 mL/min; the FDA also approved dabigatran for these patients. In 2014, the FDA extended the approval of apixaban to patients with AF undergoing hemodialysis based on limited pharmacokinetic data,[27] and very limited subsequent clinical outcome data are as yet available.[28] Routine use of apixaban in patients with AF undergoing hemodialysis remains premature in our view.[27,29] The value of warfarin anticoagulation is unclear even for secondary stroke prevention (ie, the highest risk for recurrent stroke) in patients with AF undergoing hemodialysis based on the most recent meta-analysis of observational studies,[26] and the net clinical benefit of anticoagulation for primary prevention of stroke remains dubious for patients undergoing hemodialysis because of excessive bleeding risk.[26] We lament the absence of randomized trials to address this important issue. CKD clinical investigators seem addicted to large observational "big data" studies with contradictory results that are inevitably prone to confounding.

The study by McAlister et al.[6] contributes valuable data relevant to stroke prevention in patients with AF and CKD.[6] In the absence of reliable risk prediction schemes for stroke or

bleeding in these patients, we favour anticoagulation with a DOAC for patients with AF who are $\geq$ 65 years old and have moderate or severe CKD (Table 1) (we also recommend the use of the Canadian Cardiovascular Society 2016 Guideline algorithm for younger patients).[30] Optimal antithrombotic treatment to prevent stroke in patients with AF and end-stage CKD is much less clear. At present, we restrict anticoagulation to those at highest risk (previous cardioembolic stroke) and treat with carefully monitored warfarin, pending more data about DOAC safety in these patients.

Disclosures

Dr Hart receives research support and research stipends from Bayer Healthcare and Bristol Myers-Squibb. Dr Ingram reports no conflicts of interest. Dr Eikelboom has received honoraria and research support from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers-Squibb, Daiichi-Sankyo, Janssen, and Pfizer.

References

1. Hart RG, Eikelboom JW, Brimble KS, McMurty MS, Ingram AJ. Stroke prevention in atrial fibrillation patients with chronic kidney disease. Can J Cardiol 2013;29(7 suppl):S71-8.
2. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39(suppl 1):S1-266.
3. Stevens PE, Levin A. Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Working Group Members. Evaluation and management of chronic kidney disease: synopsis of the KDIGO 2012 clinical practice guidelines. Ann Intern Med 2013;158:825-30.
4. Molnar AO, Bota SE, Garg AX, et al. The risk of major hemorrhage with CKD. J Am Soc Nephrol 2016;27:2825-32.
5. Odutayo A, Wong CX, Hsiao AJ, et al. Atrial fibrillation and risk of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. BMJ 2016;354:i4482.
6. McAlister FA, Wiebe N, Jun M, et al. Are existing risk scores for nonvalvular atrial fibrillation useful for prediction or risk adjustment in patients with chronic kidney disease? Can J Cardiol 2017;33:243-52.
7. Hart RG, Pearce LA. Current status of stroke risk stratification in patients with atrial fibrillation. Stroke 2009;40:2607-10.
8. Coppens M, Eikelboom JW, Hart RG, et al. The CHA_2DS_2-VASc score identifies those patients with atrial fibrillation and a $CHADS_2$ score of 1 who are unlikely to benefit from oral anticoagulant therapy. Eur Heart J 2013;34:170-6.
9. Donze J, Rodondi N, Waeber G, et al. Scores to predict major bleeding risk during oral anticoagulation therapy: a prospective validation study. Am J Med 2012;125:1095-102.
10. Jaspers Focks J, van Vugt SP, Albers-Akkers MT, et al. Low performance of bleeding risk models in the very elderly with atrial fibrillation using vitamin K antagonists. J Thromb Haemost 2016;14:1715-24.
11. Apostolakis S, Lane DA, Guo Y, Buller H, Lip GY. Performance of the $HEMORR_2HAGES$, ATRIA, and HAS-BLED bleeding risk-predictions scores in patients with atrial fibrillation undergoing anticoagulation. J Am Coll Cardiol 2012;60:861-7.
12. Senoo K, Proietti M, Lane DA, et al. Evaluation of the HAS-BLED, ATRIA and ORBIT bleeding risk scores in atrial fibrillation patients on warfarin. Am J Med 2016;129:600-7.
13. Fang MC, Go AS, Chang Y, et al. Death and disability form warfarin-associated intracranial and extracranial hemorrhages. Am J Med 2007;120:700-5.
14. Eikelboom JW, Bosch J, Hart RG. Rapid reversal of haematoma expansion associated with vitamin K antagonists. Lancet Neurol 2016;15:535-6.
15. Eikelboom JW, Mehta SR, Anand SS, et al. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation 2006;114:774-82.
16. Budaj A, Eikelboom JW, Mehta SR, et al. Improving clinical outcomes by reducing bleeding in patients with non-ST-elevation acute coronary syndromes. Eur Heart J 2009;30:655-61.
17. Del-Carpio Munoz F, Gharacholou SM, Munger TM, et al. Meta-analysis of renal function on the safety and efficacy of novel oral anticoagulants for atrial fibrillation. Am J Cardiol 2016;117:69-75.
18. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomized trials. Lancet 2014;383:955-62.
19. Eikelboom JW, Connolly SJ, Gao P, et al. Stroke risk and efficacy of apixaban in atrial fibrillation patients with moderate chronic kidney disease. J Stroke Cerebrovas Dis 2012;21:429-35.
20. Hijazi Z, Hohnloser SH, Andersson U, et al. Efficacy and safety of apixaban compared with warfarin in patients with atrial fibrillation in relation to renal function over time. Insights from the ARISTOTLE randomized clinical trial. JAMA Cardiol 2016;1:451-60.
21. Herzog CA, Asinger RW, Berger AK, et al. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2011;80:572-86.
22. Shah M, Avgil Tsakok M, Jackevicius CA. Warfarin use and the risk for stroke and bleeding in patients with atrial fibrillation undergoing dialysis. Circulation 2014;129:1196-203.
23. Bonde AN, Lip GY, Kamper AL, et al. Net clinical benefit of antithrombotic therapy in patients with atrial fibrillation and chronic kidney disease: a nationwide observational cohort study. J Am Coll Cardiol 2014;64:2471-82.
24. Friberg L, Benson L, Lip GYH. Balancing stroke and bleeding risks in patients with atrial fibrillation and renal failure: the Swedish Atrial Fibrillation Cohort study. Eur Heart J 2015;36:297-306.
25. Zimmerman D, Sood MM, Rigatto C, et al. Systematic review and meta-analysis of incidence, prevalence, and outcomes of atrial fibrillation patients on dialysis. Nephrol Dial Transplant 2012;27:3816-22.
26. Dahal K, Kunwar S, Rijal J, Schulman P, Lee J. Stroke, major bleeding, and mortality outcomes in warfarin users with atrial fibrillation and chronic kidney disease. Chest 2016;149:951-9.
27. Deal EN, Pope H, Ross W. Apixaban use among patients with severe renal impairment. Ann Pharmacother 2014;48:1667.
28. Reed D, Palkimis S, Le T, et al. Safety and efficacy of apixaban in end stage renal disease patients maintained on dialysis. Available at: http://thsna.org/online/core_routines/view_abstract_no.php?show_close_window=yes&abstractno=163. Accessed November 23, 2016.
29. Chan KE, Giugliano RP, Patel MR, et al. Nonvitamin K anticoagulant agents in patients with advanced chronic kidney disease or on dialysis with AF. J Am Coll Cardiol 2016;67:2888-99.
30. Macle L, Cairns J, Leblanc K, et al. for the CCS Atrial Fibrillation Guidelines Committee. 2016 focused update of the Canadian Cardiovascular Society guidelines for the management of atrial fibrillation. Can J Cardiol 2016;32:1170-85.