Special Report

Underuse of Oral Anticoagulants for Nonvalvular Atrial Fibrillation:

Past, Present, and Future

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Nonvalvular atrial fibrillation (AF) is the most widespread cardiac arrhythmia of clinical significance worldwide, and its prevalence is increasing.[1,2] Atrial fibrillation is a substantial health problem because it significantly increases the risk of thromboembolic events, particularly that of stroke.[3] Moreover, strokes associated with AF are more severe, involve larger vascular territories, and cause more morbidity and death than do strokes from other causes.[4]

Oral anticoagulant (OAC) therapy can substantially reduce the risk of stroke from AF.[5] However, this therapy also carries risk, particularly of bleeding events: intracranial hemorrhage is chief among these. Accordingly, much effort has been devoted to identifying the subset of patients with AF for whom the benefit of stroke prevention outweighs the risk of major bleeding.[6-9] This has led to the development of the $CHADS_2$ and CHA_2DS_2-VASc scores, which have been robustly validated as tools to stratify patients on the basis of their thromboembolic risk.[8,10-15] Guidelines from cardiovascular societies endorse the clinical use of these risk scores to help select those patients who might benefit from anticoagulant therapy. These guidelines include strong recommendations for OAC use in patients whose CHA_2DS_2-VASc score is 2 or higher, and weaker recommendations when that score is 1.[16-19] Despite this, there is evidence that a substantial number of patients for whom OAC therapy is indicated do not receive appropriate treatment. In a systematic review of numerous cohort studies of individuals who had AF and a prior history of stroke (one of the highest-risk groups for recurrent thromboembolism), OAC usage rates were less than 60% in most of the populations studied.[20] Usage rates among patients who had high CHA_2DS_2-VASc scores were similarly poor. Although shared decision-making, patients' preferences, and noncompliance with medical regimens are certainly factors in OAC underuse, clinicians' judgment appears to play the chief role.[21-24] The reasons typically cited for not prescribing OACs are bleeding risk, older age, the risk of falls, and patient noncompliance.[23-25] In fact, two of the strongest risk factors for stroke in AF—prior stroke and increasing age—are actually indicators of withholding appropriate anticoagulant therapy.[26]

Bleeding risk is probably grossly overestimated by clinicians. Several scores have been developed to help estimate the risk of bleeding events in OAC use, analogous to the CHA_2DS_2-VASc score for stroke. However, all of these risk scores have performed relatively poorly in subsequent cohorts, and none is better than physician estimation alone.[27,28] Nonetheless, there is concern that clinicians are using these scores inappropriately, in an attempt to determine a net clinical benefit of OAC therapy in individual circumstances. The bleeding-risk scores have not been validated for this use; rather, they are designed to aid the clinician in identifying potentially modifiable risk factors such as high blood pressure, abnormal renal or liver function, potential medication interactions, and alcohol use. Hypertension, increasing age, and prior stroke—3 of the risk factors included in the most popular risk score, HAS-BLED[29]—are also risk factors for thromboembolism in AF. Indeed, stroke risk and the consequent clinical benefit of anticoagulation increase along with higher HAS-BLED scores within a given CHA_2DS_2-VASc risk category.[6]

Similarly, the contribution of fall risk to bleeding events (while patients are taking OACs) is most likely overestimated. Clinicians might fear increased possibilities of traumatic intracranial hemorrhage and therefore hesitate to prescribe OACs to patients who are perceived to be at high risk of falling; however, the risk of major bleeding events is not significantly higher in this population.[30] In fact, it is estimated that a patient would need to fall approximately 300 times in one year for the risk of increased intracranial hemorrhage to outweigh the benefits of anticoagulation in thromboembolic prevention.[31] In addition, older patients are often thought to be too frail or too high-risk to tolerate anticoagulants, yet again there is strong evidence that patients ≥75 years of age particularly can benefit from OAC therapy.[32]

Previously, vitamin K antagonists such as warfarin were the only OACs approved for chronic stroke prevention in patients who had AF. Clinicians' overestimation of bleeding risk—as well as their concerns about regimen noncompliance, variable pharmacokinetic profiles, and the need for serial monitoring—lessened the appeal of warfarin as a therapeutic option. This has resulted in undertreatment or in the inappropriate substitution of other antithrombotic agents, such as aspirin. Contrary to popular opinion, aspirin has not significantly lowered the risk of stroke from AF in any single randomized trial[5,33] and is especially inferior to OAC therapy in the elderly population, where aspirin is often used.[32,34] However, since approximately 2010, several novel OACs (NOACs) have become available, including the direct thrombin inhibitor dabigatran[35] and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban.[36-38] In randomized clinical trials involving patients who had nonvalvular AF, all the NOACs were not inferior to warfarin in stroke prevention, and most showed a signal for superiority.[39] In addition, NOAC use was associated with a significantly lower rate of intracranial hemorrhage than was warfarin.

The NOACs are promising therapeutic alternatives to warfarin for the prevention of thromboembolism in AF; however, they present new challenges and considerations. One perceived major advantage of the NOACs is their more predictable pharmacokinetic profile and therefore obviation of the need for serial therapeutic-drug monitoring. This benefit would make NOAC therapy more convenient for patients but might hinder evaluation of patient compliance. The lower rate of intracranial hemorrhage in NOAC use might appeal to clinicians who have concerns about bleeding or fall risk; however, the current lack of reversal agents for most NOACs might mitigate that potential advantage. The higher cost of these novel agents and their various dosing schedules also might influence therapeutic decisions. Finally, research continues into whether NOACs are effective for specific indications in AF, such as short-term anticoagulation around the time of cardioversion.[40,41]

The NOACs expand the therapeutic arsenal for thromboembolic prophylaxis in AF. However, many data currently available about the rates of OAC use in real-world AF cohorts come from the pre-NOAC years. Little is known about how the introduction of NOACs has changed the prescribing patterns of OACs for AF.[42] A recent analysis of visit-level data from a nationally representative outpatient survey suggested that trends toward increased adoption of NOACs are associated with an overall increase in rates of OAC use[43]; however, no contemporary patient-level data include all the currently available NOACs. Moreover, after the U.S. Food and Drug Administration's recent approval of idarucizumab —the first reversal agent for dabigatran[44]—it remains to be seen how OAC prescription patterns might further evolve. Future investigators should continue to evaluate patterns of OAC prescription and use for AF, identifying areas of noncompliance with well-established, guideline-directed management recommendations as targets for improvement in patient safety and quality of care.

References

1. Naccarelli GV, Varker H, Lin J, Schulman KL. Increasing prevalence of atrial fibrillation and flutter in the United States. Am J Cardiol 2009;104(11):1534-9.
2. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation 2014;129(8):837-47.
3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22(8):983-8.
4. Marini C, De Santis F, Sacco S, Russo T, Olivieri L, Totaro R, Carolei A. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. Stroke 2005;36(6):1115-9.
5. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146(12):857-67.
6. Friberg L, Rosenqvist M, Lip GY. Net clinical benefit of warfarin in patients with atrial fibrillation: a report from the Swedish atrial fibrillation cohort study. Circulation 2012;125 (19):2298-307.
7. Banerjee A, Lane DA, Torp-Pedersen C, Lip GY. Net clinical benefit of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus no treatment in a 'real world' atrial fibrillation population: a modelling analysis based on a nationwide cohort study. Thromb Haemost 2012;107(3):584-9.
8. Singer DE, Chang Y, Fang MC, Borowsky LH, Pomernacki NK, Udaltsova N, Go AS. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. Ann Intern Med 2009; 151(5):297-305.
9. Azoulay L, Dell'Aniello S, Simon TA, Langleben D, Renoux C, Suissa S. A net clinical benefit analysis of warfarin and aspirin on stroke in patients with atrial fibrillation: a nested case-control study. BMC Cardiovasc Disord 2012;12:49.
10. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285(22):2864-70.

11. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010;137(2):263-72.
12. Mason PK, Lake DE, DiMarco JP, Ferguson JD, Mangrum JM, Bilchick K, et al. Impact of the CHA2DS2-VASc score on anticoagulation recommendations for atrial fibrillation. Am J Med 2012;125(6):603.e1-6.
13. Lane DA, Lip GY. Use of the CHA(2)DS(2)-VASc and HAS-BLED scores to aid decision making for thromboprophylaxis in nonvalvular atrial fibrillation. Circulation 2012; 126(7):860-5.
14. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ 2011;342: d124.
15. Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. Neurology 2007;69(6):546-54.
16. European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, Camm AJ, Kirchhof P, Lip GY, Schotten U, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC) [published erratum appears in Eur Heart J 2011;32(9):1172]. Eur Heart J 2010;31(19):2369-429.
17. You JJ, Singer DE, Howard PA, Lane DA, Eckman MH, Fang MC, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2 Suppl):e531S-75S.
18. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association [published errata appear in Eur Heart J 2013;34(10):790 and Eur Heart J 2013;34(36):2850-1]. Eur Heart J 2012;33(21):2719-47.
19. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, et al. 2014 AHA/ACC/HRS guideline 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 Heart Rhythm Society [published erratum appears in J Am Coll Cardiol 2014; 64(21):2305-7]. J Am Coll Cardiol 2014;64(21):e1-76.
20. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. Am J Med 2010;123(7):638-645.e4.
21. Ingelgard A, Hollowell J, Reddy P, Gold K, Tran K, Fitzmaurice D. What are the barriers to warfarin use in atrial fibrillation? Development of a questionnaire. J Thromb Thrombolysis 2006;21(3):257-65.
22. Gage BF, Boechler M, Doggette AL, Fortune G, Flaker GC, Rich MW, Radford MJ. Adverse outcomes and predictors of underuse of antithrombotic therapy in Medicare beneficiaries with chronic atrial fibrillation. Stroke 2000;31(4):822-7.
23. Waldo AL, Becker RC, Tapson VF, Colgan KJ; NABOR Steering Committee. Hospitalized patients with atrial fibrillation and a high risk of stroke are not being provided with adequate anticoagulation. J Am Coll Cardiol 2005;46(9): 1729-36.
24. Gattellari M, Worthington J, Zwar N, Middleton S. Barriers to the use of anticoagulation for nonvalvular atrial fibrillation: a representative survey of Australian family physicians [published errata appear in Stroke 2010;41(4):e398 and Stroke 2008;39(4):e77]. Stroke 2008;39(1):227-30.
25. Pugh D, Pugh J, Mead GE. Attitudes of physicians regarding anticoagulation for atrial fibrillation: a systematic review. Age Ageing 2011;40(6):675-83.
26. Arts DL, Visscher S, Opstelten W, Korevaar JC, Abu-Hanna A, van Weert HC. Frequency and risk factors for under- and over-treatment in stroke prevention for patients with non-valvular atrial fibrillation in general practice. PLoS One 2013;8 (7):e67806.
27. Apostolakis S, Lane DA, Guo Y, Buller H, Lip GY. Performance of the HEMORR(2)HAGES, ATRIA, and HAS-BLED bleeding risk-prediction scores in patients with atrial fibrillation undergoing anticoagulation: the AMADEUS (evaluating the use of SR34006 compared to warfarin or acenocoumarol in patients with atrial fibrillation) study. J Am Coll Cardiol 2012;60(9):861-7.
28. Donze J, Rodondi N, Waeber G, Monney P, Cornuz J, Aujesky D. Scores to predict major bleeding risk during oral anticoagulation therapy: a prospective validation study. Am J Med 2012;125(11):1095-102.
29. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138(5):1093-100.
30. Donze J, Clair C, Hug B, Rodondi N, Waeber G, Cornuz J, Aujesky D. Risk of falls and major bleeds in patients on oral anticoagulation therapy. Am J Med 2012;125(8):773-8.
31. Man-Son-Hing M, Nichol G, Lau A, Laupacis A. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. Arch Intern Med 1999;159(7): 677-85.
32. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet 2007;370 (9586):493-503.
33. Sjalander S, Sjalander A, Svensson PJ, Friberg L. Atrial fibrillation patients do not benefit from acetylsalicylic acid. Europace 2014;16(5):631-8.
34. van Walraven C, Hart RG, Connolly S, Austin PC, Mant J, Hobbs FD, et al. Effect of age on stroke prevention therapy in patients with atrial fibrillation: the atrial fibrillation investigators. Stroke 2009;40(4):1410-6.
35. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation [published erratum appears in N Engl J Med 2010;363(19):1877]. N Engl J Med 2009;361(12):1139-51.
36. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365(11):981-92.
37. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365(10):883-91.
38. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369(22):2093-104.
39. Dentali F, Riva N, Crowther M, Turpie AG, Lip GY, Ageno W. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. Circulation 2012;126(20):2381-91.
40. Yadlapati A, Groh C, Passman R. Safety of short-term use of dabigatran or rivaroxaban for direct-current cardioversion in patients with atrial fibrillation and atrial flutter. Am J Cardiol 2014;113(8):1362-3.

41. Cappato R, Ezekowitz MD, Klein AL, Camm AJ, Ma CS, Le Heuzey JY, et al. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. Eur Heart J 2014;35(47):3346-55.
42. Weitz JI, Semchuk W, Turpie AG, Fisher WD, Kong C, Ciaccia A, Cairns JA. Trends in prescribing oral anticoagulants in Canada, 2008-2014. Clin Ther 2015;37(11):2506-14.e4.
43. Barnes GD, Lucas E, Alexander GC, Goldberger ZD. National trends in ambulatory oral anticoagulant use. Am J Med 2015;128(12):1300-5.e2.
44. Pollack CV Jr, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, et al. Idarucizumab for dabigatran reversal. N Engl J Med 2015;373(6):511-20.