Anticoagulation for Nonvalvular Atrial Fibrillation

Influence of Epidemiologic Trends and Clinical Practice Patterns on Risk Stratification and Net Clinical Benefit

Richard W. Asinger, MD; Gautam R. Shroff, MBBS; Mengistu A. Simegn, MD; Charles A. Herzog, MD

Nonvalvular atrial fibrillation (NVAF), atrial fibrillation (AF) without rheumatic valvular disease, is a strong, independent predictor of stroke[1] presumably from embolization of left atrial appendage thrombus, suggesting that oral anticoagulant (OAC) therapy could provide protection. Randomized placebo, controlled trials (RCTs) of warfarin for clinically detected NVAF reported overwhelming efficacy of warfarin (67% relative reduction in stroke),[1] provided the foundation for contemporary antithrombotic management, and impacted subsequent stroke prevention studies essentially eliminating placebo arms and setting the precedence for warfarin as the comparator.

Guideline recommendations endorsed warfarin for stroke prevention in NVAF[1] and influenced clinical management; warfarin use in US Medicare beneficiaries progressively increased to a plateau between 60% and 70% by the 2000s (Figure).[2] However, it has gone relatively unnoticed that multiple population- and cohort-based studies have reported a steady decline in absolute population ischemic stroke rate (ISR) for NVAF, and clinical practice patterns have changed over the past 3 decades.[2,3]

Epidemiological Trends in the Absolute Population Risk of Stroke With NVAF

A recent analysis of the Framingham cohort reported that the ISR for AF decreased by nearly 75% over the past 50 years.[3] The ISR reported for NVAF patients not prescribed OAC shows wide variation,[4] and any trend in ISR must be evaluated from serial observations of established cohorts or representative populations. Multiple international population studies have reported declines in ISRs or hazard ratios for stroke in nonanticoagulated NVAF patients to values well below previous population studies and reports of placebo-assigned RCT patients.[1] The largest study reporting yearly ISRs and warfarin use in NVAF is a 5% sample of US Medicare beneficiaries where increased warfarin use was associated with a steady decline in ISR between 1992 and 2007.[5] Although the decline in ISR was greater for those prescribed warfarin than those not, the ISR decreased by >50% for both groups, indicating that factors other than anticoagulation contributed to the decline. It therefore bears emphasis that contemporary NVAF patients have ISRs well below those reported several decades ago.

Clinical Practice Patterns for Detection and Management of NVAF

Spurred by heightened awareness of the NVAF stroke risk and efficacy of warfarin for prevention, clinician's practice patterns have changed over the past several decades specifically for NVAF Surveillance and Clinical Management of NVAF.

NVAF Surveillance

Increased surveillance by clinical examination and electrocardiography aids in NVAF detection, particularly paroxysmal AF (PAF), the most common AF category encountered in incident or recently diagnosed NVAF.[6] Although the ISR for NVAF is considered independent of AF category (paroxysmal, persistent, and permanent), a lower rate has been reported for PAF.[7] Sophisticated monitoring techniques also detect PAF in patients without a history of NVAF. Rigidly adjudicated subclinical atrial tachyarrhythmias including PAF are detected in up to half of patients with implanted pacemakers or implanted cardiac defibrillators and, if brief (<15–20 s), have an ISR similar to those without PAF.[8] If lower stroke risk PAF and subclinical PAF patients are included in the broader context of NVAF warranting consideration of OAC, the result may be an even lower ISR for contemporary NVAF patients and potentially lower net clinical benefit.

Clinical Management of NVAF

Increased warfarin use over the last several decades has been associated with a decline in ISR attributed, in part, to therapeutic anticoagulation (Figure). The decline in ISR for those not prescribed warfarin, however, is less easily explained (Figure).[2] Improved treatment of modifiable comorbid risks for stroke with NVAF could contribute to the decline specifically management of atherosclerotic cardiovascular disease, heart failure, and hypertension. Hypertension is the most frequent and modifiable risk factor,[6] and stricter control has been associated with lower ISR. An increase in prevalent NVAF because

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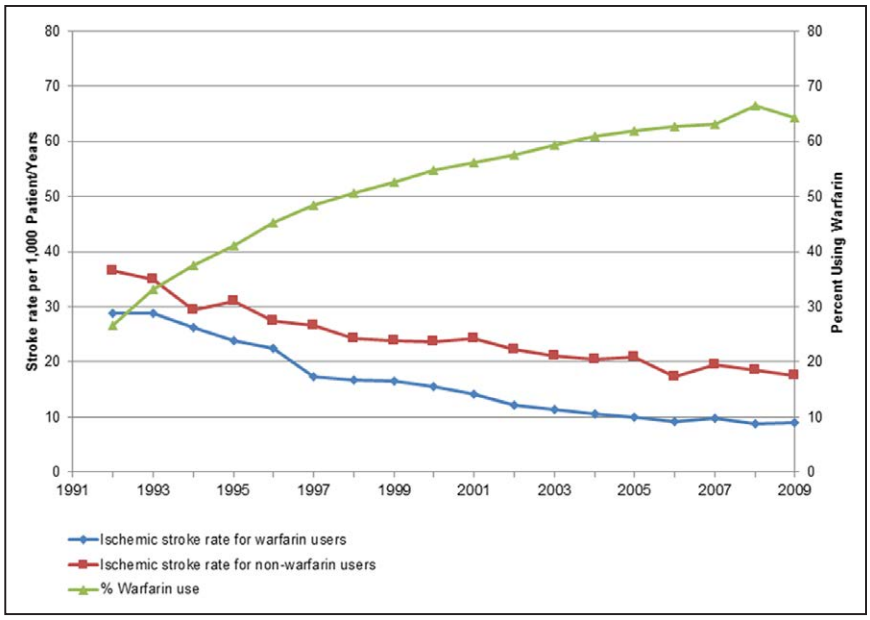

Figure. Trends in warfarin use and incident ischemic stroke for nonvalvular atrial fibrillation in Medicare recipients 1992 to 2009 for both warfarin and nonwarfarin users. Adapted from Shroff et al[2,5] with permission of the publisher. Copyright ©2017, American Medical Association. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

of improved longevity of contemporary patients may also contribute because ISRs are lower with prevalent than incident or newly diagnosed NVAF. All these factors could contribute to a lower ISR for contemporary NVAF than reported in past observational reports and RCTs of stroke prevention.

Another change in clinical management is reflected in the demographic profile of NVAF patients receiving OAC. The average age of NVAF patients reported in RCTs of OAC, population cohorts, and clinical registries has progressively increased over the past 2 to 3 decades suggesting that patients at higher risk not only for stroke but also bleeding are now receiving OAC. Increased comorbidity, frailty, lower body weight, declining cognitive and renal function, polypharmacy and altered pharmacokinetics all contribute to an increase in bleeding risk with advanced age. The average age of patients in the original placebo-controlled RCTs before 1992 was <70 years. Recent registry data report a mean age of 75 to 80 years for those receiving the newer direct OACs (DOACs)[6] even though there have been no DOAC RCTs of those >75 years.[9] This change in demographics for those now receiving OAC may increase bleeding complications and lessen the net clinical benefit.

Impact of Epidemiological Trends and Clinical Practice Patterns on Stroke Risk Stratification for NVAF and Net Clinical Benefit

The primary strategy used to assure high net clinical benefit of OAC in the management of NVAF is risk stratification easily done with widely available risk calculators. Ironically, adherence to traditional thresholds for OAC eligibility based on calculated risk scores may actually decrease the net clinical benefit for selected contemporary NVAF patients because of trends in the absolute population ISR and changes in clinical practice patterns.

Because stroke is such a devastating outcome that patients are willing to accept several OAC-related bleeds to prevent 1 stroke, the focus of risk stratification has shifted toward identification of those at lowest risk where OAC should be avoided. The CHA_2DS_2-VASc (C=history of congestive heart failure, H=history of hypertension, A=Age, D=diabetes, S=previous stroke or transient ischemic attack, VA=vascular disease, and Sc=sex category) risk stratification scheme endorsed by the American College of Cardiology/American Heart Association/Heart Rhythm Society[1] is superior for identifying truly low-risk NVAF (ie, CHA_2DS_2-VASc=0 for men and 1 for women) where there is general agreement that OAC risk outweighs benefit. Controversy continues, however, on antithrombotic therapy for men with CHA_2DS_2-VASc score of 1 and 2 for women. Recommended thresholds for considering OAC remain arbitrary and assume that the ISRs for stratification scores in contemporary NVAF are equivalent to placebo-assigned patients of RCTs. ISRs for contemporary NVAF patients that are not anticoagulated are consistently lower than reported in past observational reports and if recommended thresholds are adhered, potentially lower the net clinical benefit OAC.

Stratification schemes have also been developed for major bleeds for NVAF patients treated with OAC but are limited by inconsistent definitions which preclude confident determination of trends.

Discussion

The efficacy of OAC with warfarin for stroke prevention in NVAF has been established and increased use associated with a steady decline in stroke (Figure).[2] On the basis of single, noninferiority designed RCTs,[1] DOACs have at least equivalent outcomes compared with warfarin, but both efficacy and safety vary by drug and dosage particularly for the elderly.[9,10] DOACs use is rapidly accelerating[6] which will undoubtedly affect the net clinical benefit of OAC for NVAF, and warrants close scrutiny of outcomes.

A worthy goal is increased utilization of OAC for those at risk. On the basis of epidemiological trends, however, stroke rates currently assigned to stratification scores[1] likely overestimate contemporary risk. This observation combined with increased surveillance to detect subclinical NVAF (where the stroke risk is unclear), improved

treatment of comorbid risks and increased use of OAC in older, higher bleeding risk patients raise concern on the net clinical benefit. This concern supports a cautious approach to OAC eligibility which would include consideration of higher thresholds for use. The threshold for OAC eligibility is unique for each individual, hence the importance of shared decision-making involving the patient, family, and provider. Shared decision-making techniques are well suited to address the many issues in the clinical management of NVAF and are embodied in the societal guidelines.[1] These tools must, however, be based on reliable risk estimates and performed serially. Also, studies of these tools should include safety and efficacy end points to assure high net clinical benefit. Other concerns to assure maintenance of a high net clinical benefit of OAC include demonstration of the clinical effect of OAC for subclinical PAF detected in asymptomatic patients by prolonged monitoring, implanted or handheld devices before this group is included in the broader category of NVAF warranting OAC. RCTs of OAC such as the ongoing LOOP Trial (NCT02036450) are justifiable and should include such variables as method of NVAF detection, frequency, duration, and burden. Also initiation of OAC for stroke prevention potentially leads to lifelong treatment and may be confounded by the competing end point of death. RCTs of OAC versus placebo and of DOAC versus warfarin were all short term, and all-cause death did not confound results. However, for routine clinical management, death may eventually be a competing concern. For patients with NVAF on hemodialysis, the net clinical benefit of warfarin for stroke prevention has been reported to be neutralized by all-cause mortality.[11] Finally, ongoing surveillance of the net clinical effect of stroke prevention strategies for NVAF including OAC should be performed and, in lieu of RCTs, seems best suited with propensity-weighted methods of large inclusive populations or established cohorts.

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References

1. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW; ACC/AHA Task Force Members. 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. *Circulation*. 2014;130:e199–e267. doi: 10.1161/CIR.0000000000000041.
2. Shroff GR, Solid CA, Herzog CA. Atrial fibrillation, stroke, and anticoagulation in Medicare beneficiaries: trends by age, sex, and race, 1992-2010. *J Am Heart Assoc*. 2014;3:e000756. doi: 10.1161/JAHA.113.000756.
3. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, Newton-Cheh C, Lubitz SA, Magnani JW, Ellinor PT, Seshadri S, Wolf PA, Vasan RS, Benjamin EJ, Levy D. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet*. 2015;386:154–162. doi: 10.1016/S0140-6736(14)61774-8.
4. Quinn GR, Severdija ON, Chang Y, Singer DE. Wide variation in reported rates of stroke across cohorts of patients with atrial fibrillation. *Circulation*. 2017;135:208–219. doi: 10.1161/CIRCULATIONAHA.116.024057.
5. Shroff GR, Solid CA, Herzog CA. Temporal trends in ischemic stroke and anticoagulation therapy among Medicare patients with atrial fibrillation: a 15-year perspective (1992-2007). *JAMA Intern Med*. 2013;173:159–160. doi: 10.1001/jamainternmed.2013.1579.
6. Huisman MV, Rothman KJ, Paquette M, Teutsch C, Diener HC, Dubner SJ, Halperin JL, Ma CS, Zint K, Elsaesser A, Bartels DB, Lip GY; GLORIA-AF Investigators. The changing landscape for stroke prevention in AF: findings from the GLORIA-AF Registry Phase 2. *J Am Coll Cardiol*. 2017;69:777–785. doi: 10.1016/j.jacc.2016.11.061.
7. Vanassche T, Lauw MN, Eikelboom JW, Healey JS, Hart RG, Alings M, Avezum A, Díaz R, Hohnloser SH, Lewis BS, Shestakovska O, Wang J, Connolly SJ. Risk of ischaemic stroke according to pattern of atrial fibrillation: analysis of 6563 aspirin-treated patients in ACTIVE-A and AVERROES. *Eur Heart J*. 2015;36:281–287a. doi: 10.1093/eurheartj/ehu307.
8. Swiryn S, Orlov MV, Benditt DG, DiMarco JP, Lloyd-Jones DM, Karst E, Qu F, Slawsky MT, Turkel M, Waldo AL; RATE Registry Investigators. Clinical implications of brief device-detected atrial tachyarrhythmias in a cardiac rhythm management device population: results from the registry of atrial tachycardia and atrial fibrillation episodes. *Circulation*. 2016;134:1130–1140. doi: 10.1161/CIRCULATIONAHA.115.020252.
9. Karamichalakis N, Georgopoulos S, Vlachos K, Liatakis I, Efremidis M, Sideris A, Letsas KP. Efficacy and safety of novel anticoagulants in the elderly. *J Geriatr Cardiol*. 2016;13:718–723. doi: 10.11909/j.issn.1671-5411.2016.08.011.
10. Sharma M, Cornelius VR, Patel JP, Davies JG, Molokhia M. Efficacy and harms of direct oral anticoagulants in the elderly for stroke prevention in atrial fibrillation and secondary prevention of venous thromboembolism: systematic review and meta-analysis. *Circulation*. 2015;132:194–204. doi: 10.1161/CIRCULATIONAHA.114.013267.
11. Shih CJ, Ou SM, Chao PW, Kuo SC, Lee YJ, Yang CY, Tarng DC, Lin CC, Huang PH, Li SY, Chen YT. Risks of death and stroke in patients undergoing hemodialysis with new-onset atrial fibrillation: a competing-risk analysis of a nationwide cohort. *Circulation*. 2016;133:265–272. doi: 10.1161/CIRCULATIONAHA.115.018294.

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