European Heart Journal Supplements (2020) **22** (Supplement I), I38–I42
The Heart of the Matter
doi:10.1093/eurheartj/suaa103

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European Society
of Cardiology

The importance of adherence and persistence in the elderly atrial fibrillation patient

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KEYWORD
Atrial-fibrillation
Anticoagulation Stroke
Elderly

Older adults with atrial fibrillation are at the highest risk of ischaemic stroke yet are the least likely to be prescribed anticoagulant therapy, adhere to this therapy, and maintain long-term persistence with this therapy. The reasons for this under treatment are multifactorial and include patient-driven factors, physician-driven factors, medical system complexities, and current unknowns regarding the biology and natural history of AF. Understanding these challenges to stroke prevention and addressing identified barriers to medication adherence and persistence in this vulnerable age group will improve outcomes related to AF.

Older adults with atrial fibrillation are at the highest risk of ischaemic stroke. Without anticoagulation, the average incidence of ischaemic stroke in this age group is ~8–10% per year.[1,2] The 30-day mortality from an AF-related stroke is ~24% and those who survive often have life-altering neurological disability.[3]

The most convincing early evidence supporting the use of anticoagulant therapy for older adults came from the 2007 Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA) wherein individuals aged 75 years or older were randomized to receive either warfarin or aspirin (75 mg per day).[4] The primary endpoint was fatal or disabling stroke, intracranial haemorrhage, or systemic embolus. The trial enrolled 973 individuals with a mean age of 81.5 years. Among those treated with warfarin, there were 24 primary events (21 strokes, 2 other intracranial haemorrhages, and 1 systemic embolus) and 48 primary events (44 strokes, 1 other intracranial haemorrhage, and 3 systemic emboli) among those participants randomized to aspirin [annual risk 1.8% vs. 3.8%, relative risk 0.48, 95% confidence interval (CI) 0.28–0.80, $P = 0.003$]. The annual risk of extracranial haemorrhage was 1.4% (warfarin) vs. 1.6% (aspirin) (relative risk 0.87, 0.43–1.73). This seminal trial demonstrated the superior efficacy of anticoagulation therapy for stroke prevention compared to aspirin and the underappreciated hazards of aspirin in this older age group. Further validation of these findings ultimately led to changes in clinical practice guidelines which no longer included aspirin as a treatment option for stroke prevention in AF.[5,6]

Despite the heightened risk for stroke, elderly individuals with AF are least likely to receive anticoagulant therapy. Among 429 417 individuals with AF prospectively enrolled in the Practice Innovation and Clinical Excellence Registry (PINNACLE), ~50% received oral anticoagulant therapy including the highest risk patients.[7] Similar findings were reported from the Global Anticoagulant Registry in the FIELD (GARFIELD) study. Among 10 614 patients with newly diagnosed AF, 59% of higher risk patients defined as having a CHA_2DS_2-VASc score of 2 or greater received anticoagulant therapy.[8]

Once initiated, persistence with anticoagulant therapy remains a challenge. A recent study of 66 090 individuals with AF newly starting a non-vitamin K oral anticoagulant (NOAC) and naïve to anticoagulation found that 59% persisted in taking the medication at 6 months and subsequently further declined to 31.6% at 12 months.[9] Rates of adherence and persistence were considerably higher in a Danish study, perhaps in part attributable to different methodologies to assess exposure. Importantly, this study documented wide gaps in drug refills of 7–89 days that were common across treatment groups. Incidence rates for medication-specific gaps per 1000 person-years were 339.1

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for apixaban, 306.3 for dabigatran, 199.7 for rivaroxaban, and 424.3 for vitamin K antagonists (VKA). Medication gaps exceeding 90 or more days were 27.6, 37.2, 25.8, and 57.5, respectively.[10] These data attest to the frequent interruptions in therapy that occur in clinical practice that render patients vulnerable to thrombotic events.[11,12] The association of medication nonadherence with stroke outcomes was demonstrated in a study of 64 661 individuals with AF initiating oral anticoagulant therapy identified within a US commercial insurance database. The investigators used the proportion of days covered (PDC) as the metric to determine drug exposure. During a median follow-up of 1.1 years, 47.5% of patients prescribed a NOAC (apixaban, dabigatran, or rivaroxaban) achieved the benchmark of acceptable adherence, a PDC of 80% or greater. For patients taking warfarin, this percentage was even lower, 40.2%. For patients with a CHA_2DS_2-VASc score >3, the risk of stroke increased according to duration of time off therapy: hazard ratio, 1.96 (95% CI 1.48–2.60) for gaps of 1 to 3 months, 2.64 (95% CI 1.93–3.61) for 3–6 months, and 3.66 (95% CI 2.68–5.01) for 6 months or longer compared with not taking oral anticoagulants <1 week.[13] In a study of primary care practices in Germany, adherence and treatment persistence were measured for new users of rivaroxaban, dabigatran, and VKA among 7265 individuals with AF.[14] The mean age of patients included was 74 years. At 6 months, the percentage of patients still taking the drug was 66.0%, 60.3%, and 58.1%, respectively. At 1 year, these proportions further declined to 53.1%, 47.3%, and 25.5%, respectively. Older age, renal dysfunction, and concomitant use of antiplatelet drugs were significantly associated with a lower likelihood of anticoagulant drug persistence of >180 days.

Factors associated with medication adherence and long-term persistence

Adherence and long-term persistence of drug therapy among elderly individuals are challenging for many reasons including patient-driven factors, physician-driven factors, and factors related to the medical system (*Figure 1*).[15-18] From a patient perspective, complex regimens, competing priorities, cost, polypharmacy, and lack of information on drug benefit and side effects often lead to cessation of treatment or omission of doses. Understanding the indication and belief of personal vulnerability are integral to adherence and persistence. Perhaps the most critical step is the initial discussion of AF, the risks related to AF, and the benefits and risks of anticoagulant therapy with a trusted physician. Key messages are revisited and reinforced at each subsequent episode of care. Physician judgement on what constitutes drug candidacy and personal interpretation of 'do no harm' are key components of the initial and refill prescription decisions. As shown in the GARFIELD registry, physician perceptions about bleeding risk, fall risk, ability to adhere to treatment, among others, constituted 48% of the reasons for not prescribing anticoagulant therapy.[8] In addition, the increasingly complex patterns of care and process barriers within complicated medical systems lead to fragmentation and breakdowns in communication. Seamless delivery of care with consistent management is difficult across multiple surgical and medical disciplines and care settings particularly amid changes in a patient's health status. When a hospitalization occurs, medication reconciliation spans four stages of care and needs to account for drug-relevant changes in the patient's health status: home to hospital, medical or surgical discharge to rehabilitation facility, discharge to home, and post-discharge outpatient physicians' follow-up and evaluation. Communication of these changes throughout this continuum and ultimately to the physician responsible for the patient's long-term management is paramount.

Lastly, uncertainties related to the biology and natural history of AF itself constitute a grey area in patient management that inevitably leads to practice variation in long-term prescription persistence. Debates and individual physician beliefs regarding burden of AF and stroke risk, in addition to mechanistic uncertainty regarding the relative contribution of atrial substrate vs. rhythm, create different thresholds for long-term anticoagulation therapy for patients with paroxysmal AF and for those patients after cardioversion or ablation.[19-22] Among patients with a documented history of AF presenting with an acute ischaemic stroke, Aronis *et al.*[23] found that having been diagnosed with paroxysmal AF and being age 80 years or older were the most potent factors associated with not taking an anticoagulant at the time of the stroke. Rigorous studies to define the efficacy and safety of 'triggered' intermittent anticoagulant therapy based on smartphone alerts, patient pulse taking, or other AF detection modalities are also direly needed before these strategies permeate clinical practice. The extent to which the concept of intermittent definable risk affects patients' long-term commitment to anticoagulation therapy also warrants study.

Bleeding and fall risk

Bleeding events are the most common reason for stopping anticoagulant treatment and perception of bleeding risk is pivotal in the decision to start therapy. The most feared complication of anticoagulant therapy is intracranial haemorrhage with resultant morbidity and mortality of 76% among individuals taking warfarin.[24] The incidence of intracranial haemorrhage among patients randomized to warfarin in the AF trials was 0.7–0.8% per year.[25-28] Importantly, the hazard of this complication was reduced on average by ~50% with the use of the factor Xa and direct thrombin inhibitors. To further mitigate, the risk of intracranial haemorrhage in the older age group, concomitant aspirin should be avoided, and blood pressure control maintained. Resumption of anticoagulant therapy following an intracranial bleed is often a therapeutic dilemma given different risks of recurrence depending on location, lobar vs. deep, and aetiology.[29] Few data exist on risks of recurrence with resumption or initiation of NOACs in these settings.

The gastrointestinal tract is the most common site of bleeding in the elderly with peptic ulcer disease the most frequent aetiology followed by diverticular disease.[30] The risk of upper and lower gastrointestinal haemorrhage is substantially increased by antiplatelet therapy and nonsteroidal anti-inflammatory drugs with some gastric

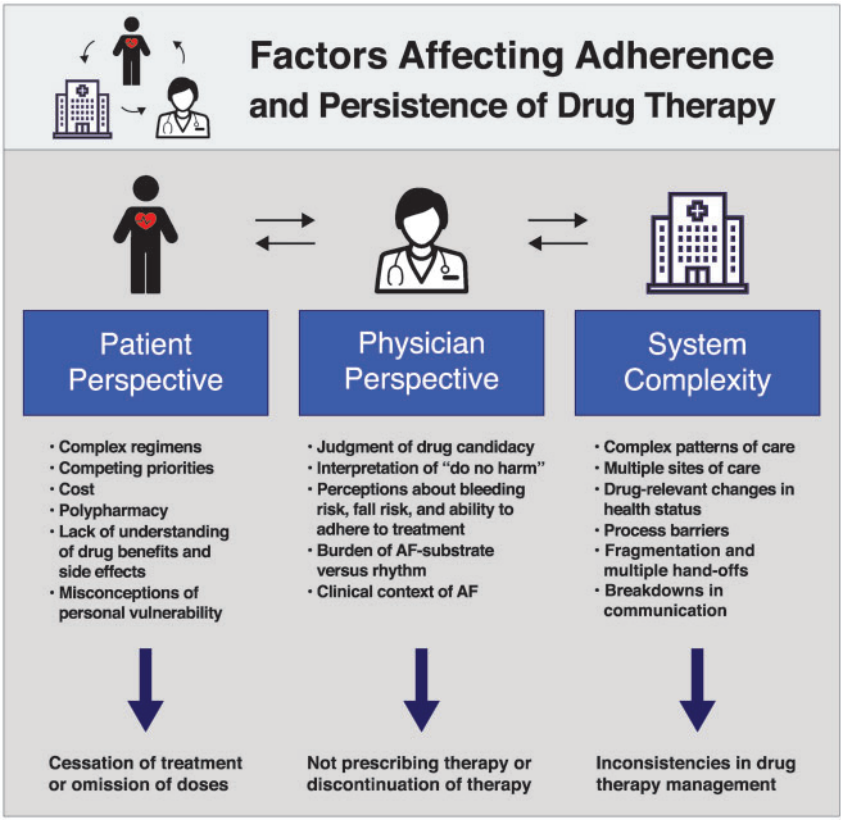

Figure 1 Medication adherence and persistence are driven by patient, physician, and system specific factors, which are all interrelated.

protection provided by proton pump inhibitors.[31,32] Although the NOACs significantly reduced the risk of intracranial bleeding, gastrointestinal bleeding was either increased or comparable to warfarin. In contrast to intracranial hemorrhage, the morbidity and mortality associated with gastrointestinal bleeding was found to be 3% among patients taking warfarin.[24]

Major bleeds often result in permanent discontinuation of treatment. Physician and patient thresholds to resume treatment following a major or minor bleed often diverge. Multiple studies have demonstrated that patients most value avoidance of a disabling stroke and would trade-off multiple major bleeds to avoid one ischaemic stroke.[33–36] Resumption of anticoagulant therapy following gastrointestinal haemorrhage has been shown to lower mortality and reduce thromboembolic events without a significant increase in recurrent haemorrhage.[37] Selection bias was a considered limitation of this nonrandomized study in that healthier patients may have been chosen to resume treatment. These findings were subsequently confirmed in a large meta-analysis that showed resumption of warfarin therapy was associated with a reduction in thromboembolic events and mortality without a statistically significant increase in recurrent gastrointestinal bleeding.[38] The risk of recurrence depends on aetiology and success of remedial intervention. Optimal timing of resumption across the spectrum of patient stroke risk and underlying cause is largely unstudied. Given the documented risk of increased thromboembolic events with larger gaps in treatment, the interval off therapy is best kept to a minimum of a few days, if possible, especially for those at highest risk of stroke.

Older adults at risk for falls constitute a particularly vulnerable group as the risk for both stroke and bleeding are significantly increased compared to peers without this risk. For most patients, the net clinical benefit still weighs in favour of anticoagulation because of the morbidity and mortality associated with ischaemic stroke.[39] However, more data are needed on the effectiveness of NOACs in routine clinical practice outside of randomized trials.[40,41] Measures to reduce fall risk should be vigorously sought at the time of initiation and throughout the course of anticoagulant therapy. Balance training, core strengthening, removal of environmental hazards, improved lighting, and avoidance of medications that induce or exacerbate orthostasis and autonomic dysfunction are a few strategies to mitigate the risk of serious falls.

Summary

Anticoagulant therapy is highly effective in preventing stroke in AF. For elderly individuals, this is a particularly germane issue given their heightened risk of ischaemic stroke. The weight of current evidence favours anticoagulation in this age group while actively seeking interventions to reduce risk of harm.[42–49] Clinicians and patients need further and continuing education regarding the relative

risks of morbidity from ischaemic events and that of minor and major haemorrhagic complications related to therapy. Identifying the barriers to adherence and implementation of strategies to promote medication persistence will lead to more effective therapy.

Acknowledgement

J.R. Hylek for creation of the Figure.

Conflict of interest: E.M.H. has received research funding from Abbott, Bristol Myers Squibb, and Janssen, and honoraria from Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Janssen, Medtronic, Pfizer, and Roche. This paper was published as part of a supplement financially supported by an unrestricted educational grant from Daiichi Sankyo Europe GmbH.

References

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;**22**: 983–988.
2. Hylek EM, Go AS, Chang Y, Jensvold NG, Henault LE, Selby JV, Singer DE. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med* 2003;**349**:1019–1026.
3. 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**:263–272.
4. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, Murray E; BAFTA Investigators; Midland Research Practices Network (MidReC). 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**:493–503.
5. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener H-C, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GYH, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K; ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–2962.
6. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, Heidenreich PA, Murray KT, Shea JB, Tracy CM, Yancy CW. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. *Circulation* 2019;**140**: e125–e151.
7. Hsu JC, Maddox TM, Kennedy KF, Katz DF, Marzec LN, Lubitz SA, Gehi AK, Turakhia MP, Marcus GM. Oral anticoagulant therapy prescription in patients with atrial fibrillation across the spectrum of stroke risk: insights from the NCDR PINNACLE registry. *JAMA Cardiol* 2016;**1**: 55–62.
8. Kakkar AK, Mueller I, Bassand J-P, Fitzmaurice DA, Goldhaber SZ, Goto S, Haas S, Hacke W, Lip GYH, Mantovani LG, Turpie AGG, van Eickels M, Misselwitz F, Rushton-Smith S, Kayani G, Wilkinson P, Verheugt FWA; for the GARFIELD Registry Investigators. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the International, Observational, Prospective GARFIELD Registry. *PLoS One* 2013;**8**:e63479.
9. Manzoor BS, Lee TA, Sharp LK, Walton SM, Galanter W, Nutescu EA. Real-world adherence and persistence with direct oral anticoagulants in adults with atrial fibrillation. *Pharmacotherapy* 2017;**37**:1221–1230.
10. Sorensen R, Jamie Nielsen B, Langtved Pallisgaard J, Ji-Young Lee C, Torp-Pedersen C. Adherence with oral anticoagulation in non-valvular atrial fibrillation: a comparison of vitamin K antagonists and non-vitamin K antagonists. *Eur Heart J Cardiovasc Pharmacother* 2017;**3**:151–156.
11. Granger CB, Lopes RD, Hanna M, Ansell J, Hylek EM, Alexander JH, Thomas L, Wang J, Bahit MC, Verheugt F, Lawrence J, Xavier D, Wallentin L. Clinical events after transitioning from apixaban versus warfarin to warfarin at the end of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. *Am Heart J* 2015;**169**:25–30.
12. Patel MR, Hellkamp AS, Lokhnygina Y, Piccini JP, Zhang Z, Mohanty S, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Becker RC, Nessel CC, Berkowitz SD, Califf RM, Fox KAA, Mahaffey KW. Outcomes of discontinuing rivaroxaban compared with warfarin in patients with nonvalvular atrial fibrillation: analysis from the ROCKET AF trial (rivaroxaban once-daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). *J Am Coll Cardiol* 2013;**61**: 651–658.
13. Yao X, Abraham NS, Caleb Alexander G, Crown W, Montori VM, Sangaralingham LR, Gersh BJ, Shah ND, Noseworthy PA. Effect of adherence to oral anticoagulants on risk of stroke and major bleeding among patients with atrial fibrillation. *J Am Heart Assoc* 2016;**5**: e003074.
14. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;**353**:487–497.
15. Kronish IM, Ye S. Adherence to cardiovascular medications: lessons learned and future directions. *Prog Cardiovasc Dis* 2013;**55**:590–600.
16. Cramer J. Identifying and improving compliance patterns. In: JA Cramer, B Spilker, eds. *Patient Compliance in Medical Practice and Clinical Trials*. New York: Raven Press; 1991. p387–392.
17. Elliott WJ, Maddy R, Toto R, Bakris G. Hypertension in patients with diabetes: overcoming barriers to effective control. *Postgrad Med* 2000;**107**:29–32.
18. Beyer-Westendorf J, Ehlken B, Evers T. Real-world persistence and adherence to oral anticoagulation for stroke risk reduction in patients with atrial fibrillation. *Europace* 2016;**18**:1150–1157.
19. Romero J, Avendano R, Diaz JC, Taveras J, Lupercio F, Di Biase L. Is it safe to stop oral anticoagulation after catheter ablation for atrial fibrillation? *Expert Rev Cardiovasc Ther* 2019;**17**:31–41.
20. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD; Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;**347**: 1825–1833.
21. Perez MV, Mahaffey KW, Hedlin H, Rumsfeld JS, Garcia A, Ferris T, Balasubramanian V, Russo AM, Rajmane A, Cheung L, Hung G, Lee J, Kowey P, Talati N, Nag D, Gummidipundi SE, Beatty A, True Hills M, Desai S, Granger CB, Desai M, Turakhia MP; Apple Heart Study Investigators. Large-scale assessment of a smartwatch to identify atrial fibrillation. *N Engl J Med* 2019;**381**:1909–1917.
22. Daccarett M, Badger TJ, Akoum N, Burgon NS, Mahnkopf C, Vergara G, Kholmovski E, McGann CJ, Parker D, Brachmann J, Macleod RS, Marrouche NF. Association of left atrial fibrosis detected by delayed-enhancement magnetic resonance imaging and the risk of stroke in patients with atrial fibrillation. *J Am Coll Cardiol* 2011;**57**:831–838.
23. Aronis KN, Thigpen JL, Tripodis Y, Dillon C, Forster K, Henault L, Quinn E, Berger PB, Limdi NA, Hylek EM. Paroxysmal atrial fibrillation and the hazards of under-treatment. *Int J Cardiol* 2016;**202**: 214–220.
24. Fang MC, Go AS, Chang Y, Hylek EM, Henault LE, Jensvold NG, Singer DE. Death and disability from warfarin-associated intracranial and extracranial hemorrhages. *Am J Med* 2007;**120**:700–705.
25. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;**369**:2093–2104.

26. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener H-C, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–1151.
27. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KAA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**:883–891.
28. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SJ, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FWA, Zhu J, Wallentin L; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**:981–992.
29. Goldstein JN, Greenberg SM. Should anticoagulation be resumed after intracerebral hemorrhage? *Cleve Clin J Med* 2010;**77**: 791–799.
30. Yachimski PS, Friedman LS. Gastrointestinal bleeding in the elderly. *Nat Clin Pract Gastroenterol Hepatol* 2008;**5**:80–93.
31. Hylek EM, Held C, Alexander JH, Lopes RD, De Caterina R, Wojdyla DM, Huber K, Jansky P, Steg PG, Hanna M, Thomas L, Wallentin L, Granger CB. Major bleeding in patients with atrial fibrillation receiving apixaban or warfarin: the ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): predictors, characteristics, and clinical outcomes. *J Am Coll Cardiol* 2014;**63**:2141–2147.
32. Pilotto A, Franceschi M, Leandro G, Paris F, Niro V, Longo MG, D'Ambrosio LP, Andriulli A, Di Mario F. The risk of upper gastrointestinal bleeding in elderly users of aspirin and other non-steroidal anti-inflammatory drugs: the role of gastroprotective drugs. *Aging Clin Exp Res* 2003;**15**:494–499.
33. Alonso-Coello P, Montori VM, Solà I, Schünemann HJ, Devereaux P, Charles C, Roura M, Díaz MG, Souto JC, Alonso R, Oliver S, Ruiz R, Coll-Vinent B, Diez AI, Gich I, Guyatt G. Values and preferences in oral anticoagulation in patients with atrial fibrillation, physicians' and patients' perspectives: protocol for a two-phase study. *BMC Health Serv Res* 2008;**8**:21.
34. Devereaux PJ, Anderson DR, Gardner MJ, Putnam W, Flowerdew GJ, Brownell BF, Nagpal S, Cox JL, Fahey T. Differences between perspectives of physicians and patients on anticoagulation in patients with atrial fibrillation: observational study. *BMJ* 2001;**323**: 1218–1222.
35. MacLean S, Mulla S, Akl EA, Jankowski M, Vandvik PO, Ebrahim S, McLeod S, Bhatnagar N, Guyatt GH. Patient values and preferences in decision making for antithrombotic therapy: a systematic review: antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines Chest. 2012;**141**:e1S–e23S.
36. Lane DA, Meyerhoff J, Rohner U, Lip G. Patients' perceptions of atrial fibrillation, stroke risk, and oral anticoagulation treatment: an international survey. *TH Open* 2018;**2**:e233–e241.
37. Witt DM, Delate T, Garcia DA, Clark NP, Hylek EM, Ageno W, Dentali F, Crowther MA. Risk of thromboembolism, recurrent hemorrhage, and death after warfarin therapy interruption for gastrointestinal tract bleeding. *Arch Intern Med* 2012;**172**: 1484–1491.
38. Chai-Adisaksopha C, Hillis C, Monreal M, Witt DM, Crowther M. Thromboembolic events, recurrent bleeding and mortality after resuming anticoagulant following gastrointestinal bleeding. a meta-analysis. *Thromb Haemost* 2015;**114**:819–825.
39. Gage BF, Birman-Deych E, Kerzner R, Radford MJ, Nilasena DS, Rich MW. Incidence of intracranial hemorrhage in patients with atrial fibrillation who are prone to fall. *Am J Med* 2005;**118**:612–617.
40. Steffel J, Giugliano RP, Braunwald E, Murphy SA, Mercuri M, Youngsook C, Aylward P, White H, Zamorano JL, White H, Antman EM, Ruff CT. Edoxaban versus warfarin in atrial fibrillation patients at risk of falling: ENGAGE AF–TIMI 48 analysis. *J Am Coll Cardiol* 2016;**68**:1169–1178.
41. Rao MP, Vinereanu D, Wojdyla DM, Alexander JH, Atar D, Hylek EM, Hanna M, Wallentin L, Lopes RD, Gersh BJ, Granger CB; ARISTOTLE Investigators. Clinical outcomes and history of fall in patients with atrial fibrillation treated with oral anticoagulation: insights from the ARISTOTLE trial. *Am J Med* 2018;**131**:269–275.
42. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J, Yang S, Alings M, Kaatz S, Hohnloser SH, Diener H-C, Franzosi MG, Huber K, Reilly P, Varrone J, Yusuf S. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation an analysis of the randomized evaluation of long-term anticoagulant therapy (RELY) trial. *Circulation* 2011;**123**:2363–2372.
43. Halperin JL, Hankey GJ, Wojdyla DM, Piccini JP, Lokhnygina Y, Patel MR, Breithardt G, Singer DE, Becker RC, Hacke W, Paolini JF, Nessel CC, Mahaffey KW, Califf RM, Fox K. Efficacy and safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in the rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF). *Circulation* 2014;**130**:138–146.
44. Halvorsen S, Atar D, Yang H, De Caterina R, Erol C, Garcia D, Granger CB, Hanna M, Held C, Husted S, Hylek EM, Jansky P, Lopes RD, Ruzyllo W, Thomas L, Wallentin L. Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial. *Eur Heart J* 2014;**35**:1864–1872.
45. Kato ET, Giugliano RP, Ruff CT, Koretsune Y, Yamashita T, Kiss RG, Nordio F, Murphy SA, Kimura T, Jin J, Lanz H, Mercuri M, Braunwald E, Antman EM. Efficacy and safety of edoxaban in elderly patients with atrial fibrillation in the ENGAGE-TIMI 48 trial. *J Am Heart Assoc* 2016;**5**:e003432.
46. Patti G, Pecen L, Lucerna M, Huber K, Rohla M, Renda G, Siller-Matula J, Ricci F, Kirchhof P, De Caterina R. Net clinical benefit of non-vitamin K antagonist vs vitamin K antagonist anticoagulants in elderly patients with atrial fibrillation. *Am J Med* 2019;**132**:749–757.
47. Andreotti F, Rocca B, Husted S, Ajjan RA, ten Berg J, Cattaneo M, Collet JP, De Caterina R, Fox KAA, Halvorsen S, Huber K, Hylek EM, Lip GYH, Montalescot G, Morais J, Patrono C, Verheugt FWA, Wallentin L, Weiss TW, Storey RF; on behalf of the ESC Thrombosis Working Group. Antithrombotic therapy in the elderly: expert position paper of the European Society of Cardiology Working Group on Thrombosis. *Eur Heart J* 2015;**36**:3238–3249.
48. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, Haeusler KG, Oldgren J, Reinecke H, Roldan-Schilling V, Rowell N, Sinnaeve P, Collins R, Camm AJ, Heidbüchel H, Lip GYH, Weitz J, Fauchier L, Lane D, Boriani G, Goette A, Keegan R, MacFadyen R, Chiang C-E, Joung B, Shimizu W; ESC Scientific Document Group. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J* 2018;**39**:1330–1393.
49. Ramos Ramirez MJ, Young B, Harjai K, Mascarenhas V, Vijayaraman P. Left atrial appendage occlusion: 2016 in review. *J Interven Cardiol* 2017;**30**:448–456.