**Editorial**

**Innovative strategies to improve adherence to non-vitamin K antagonist oral anticoagulants for stroke prevention in atrial fibrillation**

Gregory Y.H. Lip1,2

Deirdre A. Lane1

Tatjana S. Potpara2,3

1Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, UK

2School of Medicine, Belgrade University, Belgrade, Serbia;

3Cardiology Clinic, Clinical Centre of Serbia, Belgrade, Serbia

Correspondence: Prof GYH Lip g.y.h.lip@bham.ac.uk

Key words: atrial fibrillation, stroke prevention, adherence, oral anticoagulation

Stroke prevention is the principal priority in the management of patients with atrial fibrillation (AF), and oral anticoagulation is associated with a significant reduction in stroke/systemic embolism and all cause mortality1. However, central to this is medication adherence and persistence. The vitamin K antagonists (VKAs) have marked inter- and intra-patient variability in the International Normalized Ratio (INR) values, thus requiring regular anticoagulation monitoring to ensure a high time in therapeutic range (TTR). Indeed, poor TTR or anticoagulation cessation has been associated with worse outcomes2, 3, and the need for regular blood tests to check INRs gave an opportunity for healthcare professionals to monitor drug adherence and persistence. Education and counselling can also improve anticoagulation management4, 5, reinforced by smart technology, such as Apps on smartphones.

In a pilot trial (mAFA), the first prospective randomized trial of Mobile Health technology in patients with AF, the mAF App, integrating clinical decision support, education, and patient-involvement strategies, significantly improved knowledge, drug adherence, quality of life, and anticoagulation satisfaction6. However, this approach suited patients in healthcare systems with high smartphone use, and the ability to utilise Apps.

This approach using Apps may not be ideal for everyone. Indeed, Desteghe et al7 have previously reported that only a small proportion of their AF population seemed eligible for the Health Buddies app although the latter was positively rated by its users, but many patients were not willing to participate in this study or to use the app . The main reasons for not participating were general lack of interest in participating in research or in the concept in particular (29%), not feeling comfortable using technology (22%), no interest by the grandchildren or their parents (20%), or too busy a lifestyle (12%).

More recently, the availability of the non-VKA oral anticoagulants (NOACs) have changed the landscape of thromboprophylaxis1. The NOACs do not require anticoagulation monitoring, but given these drugs have a short half-life it became apparent that efforts had to be directed towards improving patient adherence and persistence with treatment8.

The NOACs are generally better tolerated than VKAs, but patient engagement, education and counselling are considered essential aspects of management to ensure optimal uptake, and adherence and different strategies may need to be utilised to suit different patients9.

In this issue of Eur Heart J, Desteghe et al10 report a randomised, single-blind, crossover, controlled trial in 48 AF patients on once or twice daily (OD, BID) NOAC, to evaluate the effect of tele-monitoring on adherence to NOAC. This study used a Medication Event Monitoring System which tracked NOAC intake during three phases of three months each, as follows: (i) daily tele-monitoring, (ii) tele-monitoring with immediate telephone feedback in case of intake errors, and (iii) an observation phase without daily transmissions.

Persistence over the entire study was very high, at 98%. While tele-monitoring-only led to very high taking and regimen adherence, the addition of direct feedback further improved adherence. Observation without daily monitoring resulted in a decline in NOAC adherence, although still high, at 94.3%. Of note, adherence was significantly higher for OD compared to BID NOAC regimes, although unprotected days were similar; nevertheless the small numbers preclude over interpretation of this aspect.

While feedback further optimised adherence, the cost effectiveness analysis suggested that this had an incremental cost of €344,289 to prevent one stroke, which could be as low as €15488 in high-risk patients with low adherence and optimised technology. The authors concluded that tele-monitoring with or without feedback may be a cost-effective approach in high-risk patients deemed poorly adherent.

Nevertheless, some limitations are apparent. There is a very small sample size, without a 'no intervention group' to see what ‘normal’ adherence is like. Also, the very fact that patients are in an adherence trial means they are self-selected (likely to be better adherers and/or to adhere better while being monitored). Finally, patients were not blinded to treatment allocation.

This small study has implications for improving patient-centred approaches to optimise NOAC adherence, notwithstanding that patients could be highly selected, given the unusually high overall adherence rate, at 98%. There is also uncertainty whether all healthcare settings would have the facilities and personnel to undertake such tele-monitoring and feedback, especially an ‘all comers’ approach which could be expensive and not cost-effective. While this strategy could be cost-effective in some high risk patient groups, the small numbers in the present study would need further prospective data in larger and more diverse cohorts to see if appropriate patient groups could be targeted for such interventions.

What are the principles? The approaches to improve patient adherence could be summarised as ‘ADHERE ON’ [Figure]. Assessment of the patient on the appropriateness of tele-monitoring is needed, as this may not be suitable for everyone. The patient would need to be given the appropriate information and help in setting the management strategy. Education and counselling to explain the risks of non-adherence, as well as reinforcement of education is needed. Clearly observation and feedback is part of this, including direct observation or indirect methods including self-reporting, supplemented by family/caregivers, pill counts, mobile technologies, electronic medication monitors, etc.

In short, patient engagement could ultimately improve drug adherence and persistence. This is essential with the NOACs, given their short half-life, as even missing a couple of doses would leave patients unprotected from stroke.

What else can we do? Health care professionals have a key role. Collaboration between primary and secondary care can improve awareness and detection of AF, as well as streamlining stroke prevention pathways in a simple approach that leads to higher anticoagulation rates, translating to more strokes prevented and savings on healthcare costs11.

Ultimately, adherence to OAC for stroke prevention is only one part of the integrated care of AF patients that involves a holistic approach to AF management. This has been proposed as a Atrial fibrillation Better Care (ABC) pathway12, that involves **A**voiding stroke (with anticoagulation), **B**etter symptom management (and patient centred, symptom directed decisions on rate or rhythm control) and **C**ardiovascular and other risk factor management, including lifestyle and patient-centred approaches (Figure). Such a holistic and integrated simple approach to AF management would streamline decision-making and ultimately improve patient outcomes.

**DISCLOSURES**

GYHL: Consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally.

DAL has received investigator-initiated educational grants from Bristol Myers Squibb and Boehringer Ingelheim, and has been a speaker and consultant for Boehringer Ingelheim, Bayer, and Bristol Myers Squibb/Pfizer. TSP: Speaker for Bayer.

REFERENCES

1. Lip GYH, Freedman B, De Caterina R, Potpara TS. Stroke prevention in atrial fibrillation: Past, present and future. Comparing the guidelines and practical decision-making. Thromb Haemost 2017;**117**(7):1230-1239.

2. Rivera-Caravaca JM, Roldan V, Esteve-Pastor MA, Valdes M, Vicente V, Lip GYH, Marin F. Cessation of oral anticoagulation is an important risk factor for stroke and mortality in atrial fibrillation patients. Thromb Haemost 2017;**117**(7):1448-1454.

3. Zoppellaro G, Granziera S, Bertozzo G, Denas G, Marigo L, Petruzzellis F, Padayattil Jose S, Rossi K, Nante G, Pengo V. Consequences of warfarin suspension after major bleeding in very elderly patients with non valvular atrial fibrillation. Thromb Haemost 2017;**117**(9).

4. Clarkesmith DE, Pattison HM, Lip GY, Lane DA. Educational intervention improves anticoagulation control in atrial fibrillation patients: the TREAT randomised trial. PLoS One 2013;**8**(9):e74037.

5. Clarkesmith DE, Pattison HM, Khaing PH, Lane DA. Educational and behavioural interventions for anticoagulant therapy in patients with atrial fibrillation. Cochrane Database Syst Rev 2017;**4**:Cd008600.

6. Guo Y, Chen Y, Lane DA, Liu L, Wang Y, Lip GYH. Mobile Health Technology for Atrial Fibrillation Management Integrating Decision Support, Education, and Patient Involvement: mAF App Trial. Am J Med 2017.

7. Desteghe L, Kluts K, Vijgen J, Koopman P, Dilling-Boer D, Schurmans J, Dendale P, Heidbuchel H. The Health Buddies App as a Novel Tool to Improve Adherence and Knowledge in Atrial Fibrillation Patients: A Pilot Study. JMIR Mhealth Uhealth 2017;**5**(7):e98.

8. Raparelli V, Proietti M, Cangemi R, Lip GY, Lane DA, Basili S. Adherence to oral anticoagulant therapy in patients with atrial fibrillation. Focus on non-vitamin K antagonist oral anticoagulants. Thromb Haemost 2017;**117**(2):209-218.

9. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener H-C, Hacke W, Oldgren J, Sinnaeve P, Camm AJ, Kirchhof P, Ahmad A, Heinrich-Nols J, Hess S, Müller M, Münzel F, Schwertfeger M, Van Eickels M, Richard-Lordereau I, Lip GYH, Chiang C-E, Piccini J, Potpara T, Fauchier L, Lane D, Avezum A, Larsen TB, Boriani G, Roldan-Schilling V, Gorenek B, Savelieva I. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace 2015;**17**(10):1467-1507.

10. Desteghe L, Vijgen J, Koopman P, Dilling-Vier D, Schurmans J, Dendale P, Heidbuchel H. Telemonitoring based feedback improves adherence to non-vitamin K antagonist oral anticoagulants intake in patients with atrial fibrillation. Eur Heart J 2018.

11. Lip G, Lane D, Sarwar S. Streamlining primary and secondary care management pathways for stroke prevention in atrial fibrillation. . Eur Heart J 2017:doi:10.1093/eurheartj/ehx554

12. Lip GYH. The ABC pathway: an integrated approach to improve AF management. Nat Rev Cardiol 2017.

Figure. Integrated approach to AF management.



mHSM: mobile Health Services Management; VDOT: Video Directly Observed Therapy; MEMS: Medical Event Monitoring System; OAC: Oral Anticoagulants.