The Practitioner®

Reducing stroke risk in patients with atrial fibrillation

Briosa e Gala A, Pope MTB, Betts TR. Reducing stroke risk in patients with atrial fibrillation.
Practitioner Nov 2019;263(1831):11-16

Dr Andre Briosa e Gala
MD MRCP
Clinical Research Fellow in Cardiac Electrophysiology

Dr Michael TB Pope
BM MRCP
Clinical Research Fellow in Cardiac Electrophysiology

Dr Timothy R Betts
MD FRCP
Consultant Cardiologist and Electrophysiologist

Department of Cardiology,
Oxford University Hospital NHS Foundation Trust,
Oxford, UK

Practitioner
Medical Publishing Ltd

©Practitioner Medical Publishing Ltd.
Reprint orders to *The Practitioner*, 10 Fernthorpe Road, London SW16 6DR, United Kingdom. Telephone: +44 (0)20 8677 3508
www.thepractitioner.co.uk

Reducing stroke risk in patients with atrial fibrillation

AUTHORS
Dr Andre Briosa e Gala
MD MRCP
Clinical Research Fellow in Cardiac Electrophysiology

Dr Michael TB Pope
BM MRCP
Clinical Research Fellow in Cardiac Electrophysiology

Dr Timothy R Betts
MD FRCP
Consultant Cardiologist and Electrophysiologist

Department of Cardiology, Oxford University Hospital NHS Foundation Trust, Oxford, UK

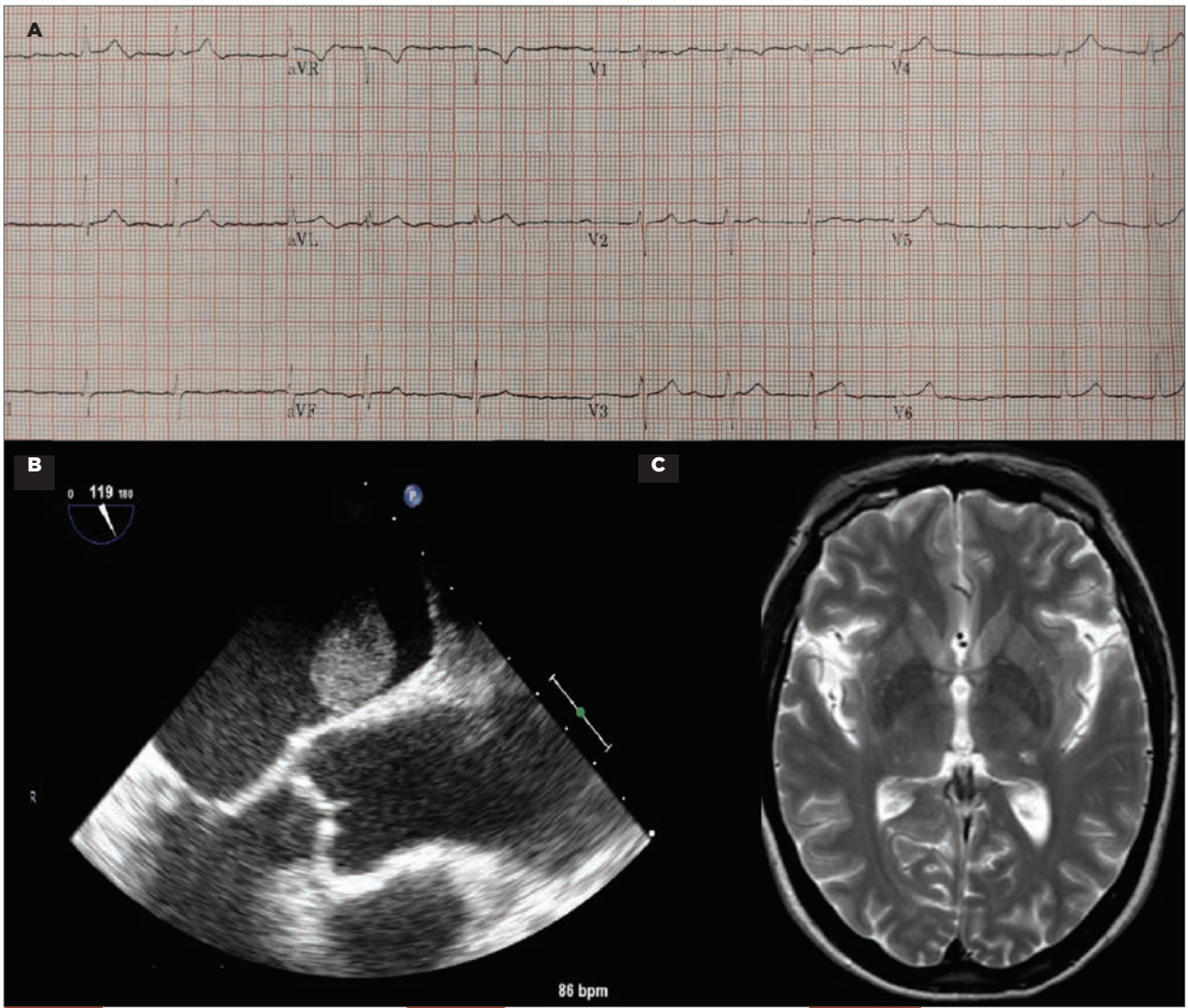


FIGURE 1
A ECG showing atrial fibrillation
B Large left atrial thrombus on transoesophageal echocardiography
C Left thalamic ischaemic stroke seen on MRI

Why are patients with AF at increased risk of stroke?

ATRIAL FIBRILLATION (AF) IS CHARACTERISED BY A CHAOTIC RHYTHM WHICH CAUSES A LACK OF coordination between the atria and ventricles, often at rapid heart rates.

It is the most common sustained arrhythmia affecting millions of people worldwide and is strongly age dependent. In the context of an ageing population its prevalence in Europe is projected to double by 2030.[1]

How should risk be stratified?

Diagnosis relies on electrocardiographic (ECG) documentation of an irregular rhythm with no distinct P-waves. The arbitrary cut-off of 30 seconds of AF on an ECG (which originated as an inclusion criteria for clinical trials) is still used for formal diagnosis.[1]

AF is associated with significant morbidity and mortality, leading to a 1.5-2 fold increase in the risk of death.[2] Stroke is the most debilitating complication. AF-related strokes account for 20-25% of all strokes and are generally more severe and disabling, more likely to recur and associated with higher healthcare costs.[3]

What are the evidence-based treatment options?

Oral anticoagulation (OAC) remains the cornerstone of AF management with a clear prognostic benefit. It reduces stroke risk by two-thirds and mortality by a quarter, at the expense of an increase in bleeding.[4,5] Nonetheless, there is a net clinical benefit in instigating OAC in all but those at a very low stroke risk. »

MECHANISMS OF STROKE IN AF

Although rheumatic heart disease has long been recognised as associated with stroke, it was only in the 1970s that post-mortem studies identified multiple systemic emboli in the context of AF in the absence of rheumatic valve disease.[6] Soon after, this finding was supported by epidemiological evidence from the Framingham heart study that identified a five-fold increased risk of stroke with chronic AF that rose to a 17-fold increase in the presence of rheumatic heart disease.[7] Since then much work has been done to explore the aetiological factors responsible for this association based on the long recognised components of Virchow's triad.

The prevailing view of thrombus formation in AF is one of blood stasis resulting from impaired atrial contraction with the loss of atrial systole. This is particularly evident in the left atrial appendage (LAA) where a large proportion of thrombus formation occurs during both AF and sinus rhythm.[6] Echocardiographic studies have clearly identified abnormalities in LAA flow in relation to thrombus formation.[8,9]

The propensity for atrial stasis is also amplified by progressive atrial dilatation seen in the context of AF and atrial size is independently associated with stroke risk.[10] Stasis is not the only contributory factor and there is increasing evidence of abnormalities in coagulation that contribute to thrombogenesis.[11]

Prothrombotic indices appear to be raised in patients with AF and stroke, and elevated concentrations of von Willebrand factor, suggesting endothelial damage, appear to predict LAA thrombus formation in AF.[9] Furthermore, both endothelial dysfunction and a prothrombotic state may be linked to systemic inflammation.[12]

A number of comorbidities seen alongside AF, such as hypertension, obesity and vascular disease are known to be associated with a chronic inflammatory state. However, there is also evidence of a direct link between AF and inflammation, with increasing levels of C-reactive protein seen alongside AF progression.[13]

Although left atrial thrombus is the predominant mechanism of stroke, it does not tell the whole story. AF is also strongly linked with non-cardioembolic stroke as a result of large vessel atherosclerosis, which may also be related to a systemic inflammatory state.[14] Indeed, many of the factors linked to increased risk of stroke in patients with AF, including age, vascular disease, diabetes mellitus and heart failure, are related to stroke in the absence of AF.[15]

RISK STRATIFICATION

Once AF is diagnosed, treatment decisions should be guided by careful assessment of individual stroke and bleeding risks.[1,16] Use of patient decision aids, such as those included in the NICE AF guideline (see Useful information box, p16) is strongly encouraged to help explain the risks and benefits of OAC to patients, promote shared decision making and adherence.[16] Risk assessment tools are available to simplify and standardise decision making but do have inherent limitations. Many were developed using old cohorts which may differ from contemporary cohorts in cardiovascular risk due to modern interventions. Many risk factors are not binary and represent a continuum and risk is not homogeneous.

Clinical scores for stroke

The CHA_2DS_2-VASc score has been extensively validated and is currently the stroke risk assessment tool recommended by the European Society of Cardiology (ESC) and NICE (see table 1, left).[1,16] The current acceptable threshold for OAC is a stroke event rate of 1% per year (see table 2, left). Once the threshold for OAC is met, patients are committed to chronic anticoagulation.

The decision to anticoagulate is taken irrespective of the pattern and duration of AF (paroxysmal, persistent or permanent). This recommendation is based on trials, such as the SPAF I-III trials, completed more than 20 years ago which showed similar stroke rates in different patterns of AF. Recent studies and a large meta-analysis however, suggest the risk may be lower in paroxysmal AF.[17] The episode duration, pattern and burden may refine risk assessment tools in the future.

A large body of evidence supports the benefits of OAC in men with CHA_2DS_2-VASc scores ≥ 2 and women with CHA_2DS_2-VASc scores ≥ 3; hence, in the absence of absolute contraindications, OAC is strongly recommended.[1] The net clinical benefit is less clear in men with a CHA_2DS_2-VASc score of 1 or women with a score of 2. Only a few studies have examined the stroke risk in patients with a single risk factor and found a significant variation in event rates, ranging from 0.1% to 2.1%.[18] Thus, as the benefits are less clear, OAC should be considered using clinical judgment and counselling.[1]

Low-risk patients (CHA_2DS_2VASc score = 0 in men and CHA_2DS_2-VASc score = 1 in women) do not require antithrombotic treatment however they should be reviewed regularly to check whether their risk profile has changed.

Clinical scores for bleeding

The trade-off from using OAC in stroke prevention is an increase in the risk of bleeding, particularly major bleeding.

Table 1

CHA_2DS_2-VASc score and risk criteria

Risk factors	Score
Congestive heart failure	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke /TIA/thromboembolism	2
Vascular disease (previous MI, PAD, aortic plaque)	1
Age 65 to 74 years	1
Sex (female)	1

TIA = transient ischaemic attack
MI = myocardial Infarction
PAD = peripheral artery disease

Table 2

Adjusted stroke risk according to CHA_2DS_2-VASc score

CHA_2DS_2-VASc score	Yearly adjusted stroke risk (%)
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

Table 3

HAS-BLED score and risk criteria

HAS-BLED	Score
Hypertension (SBP ≥ 160 mm Hg)	1
Abnormal renal or liver function	1 or 2
Stroke	1
Bleeding history or predisposition	1
Labile INR (high INR, TTR < 60%)	1
Elderly (age ≥ 65 years)	1
Drug history (aspirin, clopidogrel, NSAIDs) or alcohol ≥ 8 drinks/week)	1 or 2

SBP = systolic blood pressure; TTR = time in therapeutic range

The most dreaded complication is intracranial haemorrhage (ICH) resulting in significant disability and mortality. Fortunately, it is an infrequent event with most studies reporting a rate of approximately 0.4% per year, which is lower than the stroke risk in the majority of patients.

The HAS-BLED score was derived from a large cohort of real-world patients in the EuroHeart AF Survey (see table 3, p12).[19] The ABC score, unlike HAS-BLED, incorporates biomarkers, such as troponin, cystatin C and growth differentiating factor-15, but is only marginally better at predicting bleeding risk than HAS-BLED.[20]

Importantly, there is no specific or perceived bleeding risk at which anticoagulation should be withheld. Physicians should focus on identifying and addressing the modifiable risk factors in order to mitigate the bleeding risk and allow for safe initiation of OAC (see table 4, right).[1]

However, a HAS-BLED score ≥ 3 is associated with an increased risk of ICH and should alert the physician to select anticoagulants with a more favourable bleeding profile.

A common misconception is that elderly patients with falls have a contraindication for anticoagulation. In fact, as age is a strong independent risk factor for stroke, elderly patients derive the greatest benefit from OAC and more than 295 falls in a year are required before the risk outweighs the benefit of OAC.[21,22]

VALVULAR AF

Historically, AF has been divided into valvular and nonvalvular AF. The term valvular AF is frequently a source of confusion. In the latest ESC guidelines, valvular AF pertains specifically to the presence of moderate to severe mitral stenosis or prosthetic mechanical heart valves.[1]

This distinction has important clinical implications; the stroke risk is significantly higher in valvular AF, especially in rheumatic moderate to severe mitral stenosis (17-fold increase).[1,7] Consequently, chronic OAC is indicated regardless of CHA_2DS_2-VASc score.

Moreover, valvular AF was excluded from the landmark direct oral anticoagulants (DOAC) randomised controlled trials (RCTs).[23-26] In fact, only dabigatran has published data from a phase II study in patients with prosthetic heart valves which was prematurely stopped because of increased bleeding and thrombosis (RE-ALIGN).[27] As a result, only warfarin and heparin are licensed in valvular AF.[1]

STROKE PREVENTION

The landscape of stroke prevention has changed significantly with the introduction of DOACs and minimally invasive left atrial appendage occlusion (LAAO) devices.

Antithrombotic therapy

For many decades, warfarin and other vitamin K antagonists (VKA) were the cornerstone of stroke prevention. The role of warfarin in reducing the incidence of ischaemic stroke and systemic thromboembolism is well documented.[1,5]

A large proportion of these trials had an excellent quality of anticoagulation: time in therapeutic range (TTR) above 70%. However, it has proved to be extremely difficult to reproduce these results in clinical practice because of warfarin's narrow therapeutic range, slow onset of action, high susceptibility for food and drug interactions which requires frequent monitoring and dose adjustment. As a result, several observational studies report a poor quality of anticoagulation with TTR below 50%.[28] Nonetheless, warfarin remains in frequent use for non-valvular AF worldwide, particularly in developing countries.

DOACs exert their anticoagulant effect either by inhibiting thrombin directly (dabigatran) or by inhibiting factor X (rivaroxaban, apixaban and edoxaban). Real-world data and the landmark RCTs support the efficacy and safety of DOACs in stroke prevention (see table 5, below, »

Table 4

Modifiable and non-modifiable risk factors for bleeding in anticoagulated patients based on bleeding risk scores (adapted from the ESC 2016 atrial fibrillation guidelines)[1]

Modifiable	Potentially modifiable	Non-modifiable
● Hypertension	● Anaemia	● Age
● Labile INR	● Abnormal renal or liver function	● Cirrhosis or dialysis-dependent kidney disease
● Drugs predisposing to bleeding (aspirin, clopidogrel, NSAIDs)	● Reduced platelet count or function	● History of bleeding
● Alcohol (≥ 8 drinks/week)		● Malignancy
		● Genetic factors

Table 5

Overview of direct oral anticoagulant (DOAC) clinical trials

	Dabigatran	Rivaroxiban	Apixaban	Edoxaban
Trial	RE-LY 2009	ROCKET-AF 2011	ARISTOTLE 2011	ENGAGE AF-TIMI 48 2013
Design	RCT open label	RCT double blind	RCT double blind	RCT double blind
Patients (n)	18,113	14,264	18,201	211,05
Comparator	warfarin	warfarin	warfarin	warfarin
Mean $CHADS_2$	2.1	3.5	2.1	2.8
TTR (%)	65	55	62	65
Follow-up (yr)	2.0	1.9	1.8	2.8
Outcome (risk reduction)*	↓34% stroke/SE ↓7% major bleeding ↓60% ICH	↓12% stroke/SE ↑4% major bleeding ↓33% ICH	↓21% stroke/SE ↓12% major bleeding ↓58% ICH	↓13% stroke/SE ↓20% major bleeding ↓53% ICH
Efficacy	Superior*	Non-inferior	Superior	Non-inferior
Safety	Similar*	Similar	Superior	Superior

TTR = time in therapeutic range SE = systemic embolism ICH = intracranial haemorrhage *high dose

and table 6, below).[23-26] A large meta-analysis showed that DOACs offer an additional 10% reduction in all-cause mortality and a 19% reduction in stroke and systemic embolism.[4] Of note, only apixaban and high-dose dabigatran (150 mg) were superior to warfarin, while the others were non-inferior. The stroke reduction was largely driven by a reduction in haemorrhagic strokes.[4]

Importantly, no difference in efficacy and bleeding rates was observed between different classes (direct thrombin inhibitors vs factor X inhibitors) and different dosing regimens (once daily vs twice daily).[29] Nonetheless, DOACs should be tailored to specific subgroups of patients based on available trial data (see table 7, p15).[30]

The ESC now recommends a DOAC over warfarin as first-line treatment in primary and secondary stroke prevention.[1] The early period following an ischaemic stroke or transient ischaemic attack (TIA) is high risk for recurrences and therefore it is paramount that OAC is initiated. The exact timing of OAC in secondary prevention is unclear and needs to be balanced against the competing risk of haemorrhagic transformation. A pragmatic approach is to start OAC within 1-12 days based on event severity: one day after a TIA, three days after a small ischaemic stroke and 6 to 12 days after a moderate to large ischaemic stroke provided that repeat imaging has excluded any haemorrhagic transformation.[1] If a stroke or TIA occurs while on OAC a different antithrombotic agent should be considered.

DOACs are an attractive option as, unlike warfarin, they have a rapid onset of action, predictable anticoagulant effect and limited number of drug interactions which obviates the need for regular laboratory monitoring. They are expensive, but cost effective.[31] Importantly, antiplatelet therapy is no longer recommended for stroke prevention in AF.[1,16]

Isolation of the left atrial appendage

For those who have contraindications to OAC or have suffered a stroke despite being on OAC, an alternative stroke prevention strategy is mechanical isolation of the LAA.[1] Self-expanding LAA occlusion (LAAO) devices, such as the Watchman or

Table 6

Direct oral anticoagulant (DOAC) prescribing

	Dabigatran	Rivaroxiban	Apixaban	Edoxaban
Dose	150 mg BD	20 mg OD	5 mg BD	60 mg OD
Reduced dose	110 mg BD if any of: - age ≥ 75 years or - CrCl 30-50 ml/min	15 mg OD if: - CrCl 30-49 ml/min	2.5 mg BD if at least 2 of: - age ≥ 80 years - weight ≤ 60 kg - creatinine ≥ 133 µmo/l - CrCl 15-30 ml/min	30 mg OD If any: - CrCl 15-50 ml/min - weight ≤ 60 kg - P-glycoprotein inhibitors
Contraindication	CrCl < 30 ml/min	CrCl < 30 ml/min	CrCl < 15 ml/min	CrCl < 15 ml/min
Food interactions	No interaction (Taken with water)	Taken with food	No interaction	No interaction
Reversal agent	Idarucizumab	Andexanet alfa	Andexanet alfa	Not licensed

Monitoring
- Routine clotting tests are unreliable and cannot inform anticoagulant effect
- Yearly blood test to monitor Hb, liver and renal function
- Assess compliance and adverse effects every 3 months

Switching from warfarin
- if INR < 2: start DOAC
- if INR 2-2.5: start DOAC the next day
- if INR >2.5: recheck INR in 1-3 days

Missed dose
- OD: can be taken up to 12 hr from missed dose
- BD: can be taken up to 6 hr from missed dose

Double dose
- OD: no change to dosing regimen (24 hr interval)
- BD: skip next dose (24 hr interval)

Stopping DOAC before elective surgery
- minimal bleeding risk: uninterrupted
- low bleeding risk: 24 hr
- high bleeding risk: 48-72 hr (depending on thromboembolic vs bleeding risk)

Preoperative bridging with LMWH or heparin is not recommended

Restarting DOAC after elective surgery
- minimal bleeding risk: 6-8 hr
- low bleeding risk: 8-24 hr
- high bleeding risk: 48-72 hr (depending on thromboembolic vs bleeding risk, may require post-operative thromboprophylaxis)

Direct current cardioversion
- DOACs are safe (similar thromboembolic risk as warfarin)

Coronary artery disease
- Combination of DOAC and antiplatelets is safer than vitamin K antagonists and antiplatelets
- After 1 year of PCI (elective or acute coronary syndrome) DOAC monotherapy is recommended

CrCl = creatinine clearance LMWH = low molecular weight heparin
PCI = percutaneous coronary intervention

key points

SELECTED BY

Dr Peter Savill
Former GP, Community Cardiology Specialist, Southampton and Mid Hants, UK

Stroke is the most debilitating complication of atrial fibrillation (AF). AF-related strokes account for 20-25% of all strokes and are generally more severe and disabling and more likely to recur. Oral anticoagulation (OAC) remains the cornerstone of AF management with a clear prognostic benefit. It reduces stroke risk by two-thirds and mortality by a quarter.

The CHA_2DS_2-VASc score is the stroke risk assessment tool recommended by the European Society of Cardiology (ESC) and NICE. The acceptable threshold for OAC is a stroke event rate of 1% per year. The decision to anticoagulate is taken irrespective of the pattern and duration of AF (paroxysmal, persistent or permanent). A large evidence base supports the use of OAC in men with a CHA_2DS_2-VASc score ≥ 2 and women with a score ≥ 3. Hence, in the absence of absolute contraindications, OAC is strongly recommended. The net clinical benefit is less clear in men with a CHA_2DS_2-VASc score of 1 or women with a score of 2.

There is no specific or perceived bleeding risk at which anticoagulation should be withheld. Physicians should focus on identifying and addressing modifiable risk factors in order to mitigate the bleeding risk and allow for safe initiation of OAC. A common misconception is that elderly patients with falls have a contraindication for anticoagulation. In fact, as age is a strong independent risk factor for stroke, elderly patients derive the greatest benefit from OAC and more than 295 falls in a year are required before the risk outweighs the benefit of OAC. Only warfarin and heparin are licensed in valvular AF.

A large meta-analysis showed that direct oral anticoagulants (DOACs) offer an additional 10% reduction in all-cause mortality and a 19% reduction in stroke and systemic embolism. The stroke reduction was largely driven by a reduction in haemorrhagic strokes. No difference in efficacy and bleeding rates was observed between different classes (direct thrombin inhibitors vs factor X inhibitors) and different dosing regimens (once vs twice daily). The ESC now recommends a DOAC over warfarin as first-line treatment in primary and secondary stroke prevention. They are expensive but cost effective. Antiplatelet therapy is no longer recommended for stroke prevention in AF. For those who have contraindications to OAC or have had a stroke despite being on OAC, mechanical isolation of the left atrial appendage is an alternative stroke prevention strategy.

As many patients are asymptomatic, screening to detect AF is vital to facilitate early detection and instigation of treatment. Current guidelines recommend an opportunistic combination of pulse palpation and single lead ECG in those ≥ 65. The emergence of extended ECG monitoring technologies and especially wearable technology within commercially available devices such as smart watches has great potential.

Amplatzer Amulet, are deployed using a minimally invasive percutaneous technique. Only a brief period of dual antiplatelet treatment (6-12 weeks) is needed post procedure to reduce risk of thrombosis at the surface of the device while it becomes endothelialised.

Safety and efficacy data for LAAO devices are derived largely through multicentre global registries. The exception is the Watchman, which has been shown to be non-inferior to warfarin in two RCTs (PROTECT AF and PREVAIL).[32,33] Moreover, a recent meta-analysis of Watchman registries and RCTs reported an 80% reduction in the risk of haemorrhagic stroke and a 50% reduction in the risk of cardiovascular/unexplained death when compared with VKA.[34] At present, there is insufficient good quality data comparing LAAO devices with DOACs. LAAO has now been approved and funded by NHS England at a limited number of specialist centres.

IMPROVING OUTCOMES

As outlined above, the mainstay of stroke prevention in AF is therapeutic anticoagulation. Between 2000 and 2016 anticoagulant prescribing in UK general practice increased from 35.4% to 75.5% and 32.8% to 47.1% in high- and moderate-risk patients respectively.[35] Although this suggests significant improvements in practice have been made, stark variations in prescribing exist between practices and more needs to be done to ensure patients are appropriately treated. Reassuringly, rates of lone antiplatelet prescribing, which is now contraindicated, have fallen in parallel.[1]

Of course, guideline-directed thromboprophylaxis in the context of AF can only be instigated following a diagnosis of the arrhythmia. Unfortunately, stroke is still often the first presentation of AF at which point significant disability has already been suffered. Bearing in mind many patients are asymptomatic, screening to detect AF is vital to facilitate early detection and instigation of treatment.

Current guidelines recommend an opportunistic combination of pulse palpation and single lead ECG in those ≥ 65 years of age. While this appears a cost-effective strategy, several limitations exist, particularly the exclusion of many at risk populations aged < 65 and the limited sensitivity for paroxysmal forms of the arrhythmia.

The emergence of extended ECG monitoring technologies and especially wearable technology within commercially available devices such as smart watches has great potential. »

Table 7

Tailoring direct oral anticoagulant (DOAC) choice to individual patient profiles

Patient characteristics	Choice of DOAC
High risk for gastrointestinal bleeding	apixaban 5 mg BD dabigatran 110 mg BD
HAS-BLED ≥ 3	dabigatran 110 mg BD apixaban 5 mg BD edoxaban 60 mg OD
Dyspepsia/gastric symptoms	apixaban 5 mg BD rivaroxiban 20 mg OD
Once daily dosing	rivaroxiban 20 mg OD edoxaban 60 mg OD
Recurrent stroke/TIA	dabigatran 150 mg BD
Moderate renal impairment (CrCl 30-49 ml/min)	apixaban 5 mg BD rivaroxiban 15 mg OD dabigatran 110 mg BD edoxaban 30 mg OD
Severe renal impairment (CrCl 15-29 ml/min)	edoxaban 30 mg OD apixaban 2.5 mg OD

TIA = transient ischaemic attack; CrCl = creatinine clearance

However, some of these commercially available devices may not yet be fully validated. Their widespread use will pose new challenges to GPs with patients requesting advice and seeking further clinical investigation.

CONCLUSION

The majority of strokes related to AF are cardioembolic secondary to thrombus formation within the LAA. For this reason, OAC for stroke prevention is a highly cost-effective treatment. Early detection of the arrhythmia through opportunistic screening in general practice is crucial to allow thromboembolic risk assessment to be completed and decisions regarding treatment to be taken.

Improvements in practice are still required. Outcomes can be improved by early detection of AF, accurate risk estimation, tailored anticoagulation to mitigate side effects and patient education to promote adherence to treatment.

Competing interests

Dr Timothy Betts has received honoraria for speaking at meetings from Pfizer, Boston Scientific and Abbott Medical. The other authors have no competing interests.

REFERENCES

1 Kirchhof P, Benussi S, Kotecha D et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;37(38):2893-962
2 Stewart S, Hart CL, Hole DJ et al. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med* 2002;113(5):359-64
3 Lin H-J, Wolf PA, Kelly-Hayes M et al. Stroke severity in atrial fibrillation: the Framingham Study. *Stroke* 1996;27(10):1760-64
4 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 randomised trials. *Lancet* 2014;383(9921):955-62
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 Hinton RC, Kistler JP, Fallon JT et al. Influence of etiology of atrial fibrillation on incidence of systemic embolism. *Am J Cardiol* 1977;40(4):509-13
7 Wolf PA, Dawber TR, Thomas HE Jr et al. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. *Neurology* 1978;28(10):973-77
8 Handke M, Harloff A, Hetzel A et al. Left atrial appendage flow velocity as a quantitative surrogate parameter for thromboembolic risk: determinants and relationship to spontaneous echocontrast and thrombus formation: a transesophageal echocardiographic study in 500 patients with cerebral ischemia. *J Am Soc Echocardiogr* 2005;18(12):1366-72
9 Pollick C, Taylor D. Assessment of left atrial appendage function by transesophageal echocardiography. Implications for the development of thrombus. *Circulation* 1991;84(1):223-31
10 Di Tullio MR, Sacco RL, Sciacca RR et al. Left atrial size and the risk of ischemic stroke in an ethnically mixed population. *Stroke* 1999;30(10):2019-24
11 Watson T, Shantsila E, Lip GY. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet* 2009;373(9658):155-66
12 Boos CJ, Anderson RA, Lip GY. Is atrial fibrillation an inflammatory disorder? *Eur Heart J* 2006;27(2):136-49
13 Chung MK, Martin DO, Sprecher D et al. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. *Circulation* 2001;104(24):2886-91
14 Kamel H, Okin PM, Elkind MS et al. Atrial fibrillation and mechanisms of stroke: Time for a new model. *Stroke* 2016;47(3):895-900
15 Parsons C, Patel SI, Cha S et al. CHA_2DS_2-VASc Score: A predictor of thromboembolic events and mortality in patients with an implantable monitoring device without atrial fibrillation. *Mayo Clin Proc* 2017;92(3):360-69
16 National Institute for Health and Care Excellence. CG180. Atrial fibrillation: management. NICE. London. 2014
17 Ganesan AN, Chew DP, Hartshorne T et al. The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. *Eur Heart J* 2016;37(20):1591-1602
18 Joundi RA, Cipriano LE, Sposato LA et al. Ischemic stroke risk in patients with atrial fibrillation and CHA_2DS_2-VASc Score of 1: Systematic review and meta-analysis. *Stroke* 2016;47(5):1364-67
19 Pisters R, Lane DA, Nieuwlaat R et al. 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):1093-1100
20 Hijazi Z, Oldgren J, Lindback J et al. The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study. *Lancet* 2016;387(10035):2302-11
21 Man-Son-Hing M, Nichol G, Lau A et al. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. *Arch Intern Med* 1999;159(7):677-85.
22 Lip GY, Clementy N, Pericart L et al. Stroke and major bleeding risk in elderly patients aged ≥75 years with atrial fibrillation: the Loire Valley atrial fibrillation project. *Stroke* 2015;46(1):143-50
23 Connolly SJ, Ezekowitz MD, Yusuf S et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361(12):1139-51
24 Granger CB, Alexander JH, McMurray JJV et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365(11):981-92
25 Patel MR, Mahaffey KW, Garg J et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365(10):883-91
26 Giugliano RP, Ruff CT, Braunwald E et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369(22):2093-104
27 Eikelboom JW, Brueckmann M, Van de Werf F. Dabigatran in patients with mechanical heart valves. *N Engl J Med* 2014;370(4):383-84
28 Yao X, Abraham NS, Alexander GC et al. Effect of adherence to oral anticoagulants on risk of stroke and major bleeding among patients with atrial fibrillation. *J Am Heart Assoc* 2016;5(2).
29 Providencia R, Grove EL, Husted S et al. A meta-analysis of phase III randomized controlled trials with novel oral anticoagulants in atrial fibrillation: comparisons between direct thrombin inhibitors vs. factor Xa inhibitors and different dosing regimens. *Thromb Res* 2014;134(6):1253-64
30 Freedman B, Potpara TS, Lip GY. Stroke prevention in atrial fibrillation. *Lancet* 2016;388(10046):806-17
31 Marrouche NF, Brachmann J, Andresen D et al. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med* 2018;378(5):417-27
32 Reddy VY, Doshi SK, Sievert H et al. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-year follow-up of the PROTECT AF (Watchman left atrial appendage system for embolic protection in patients with atrial fibrillation) trial. *Circulation* 2013;127(6):720-29
33 Holmes DR Jr, Kar S, Price MJ et al. Prospective randomized evaluation of the Watchman left atrial appendage closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. *J Am Coll Cardiol* 2014;64(1):1-12
34 Holmes DR Jr, Doshi SK, Kar S et al. Left atrial appendage closure as an alternative to warfarin for stroke prevention in atrial fibrillation: A patient-level meta-analysis. *J Am Coll Cardiol* 2015;65(24):2614-23
35 Adderley NJ, Ryan R, Nirantharakumar K et al. Prevalence and treatment of atrial fibrillation in UK general practice from 2000 to 2016. *Heart* 2019;105(1):27-33

Useful information

Atrial Fibrillation Association
www.atrialfibrillation.org.uk

NICE decision aid for patients with atrial fibrillation
http://guidance.nice.org.uk/CG180/PatientDecisionAid/pdf/English

Arrhythmia Alliance
www.arrhythmiaalliance.org.uk

British Heart Foundation
www.bhf.org.uk/informationsupport/conditions/atrial-fibrillation

We welcome your feedback

If you wish to comment on this article or have a question for the authors, write to:
editor@thepractitioner.co.uk