

1 **ATRIAL FIBRILLATION AND STROKE: A PRACTICAL GUIDE**

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1 **ABSTRACT**

2 Neurologists and stroke physicians will be familiar with atrial fibrillation as a major cause of ischaemic  
3 stroke, and the role of anticoagulation in preventing cardioembolic stroke. However, making decisions  
4 about anticoagulation for individual patients remains a difficult area of clinical practice, in which the  
5 serious risks of ischaemic stroke and major bleeding, particularly intracranial haemorrhage, must be  
6 carefully balanced. Atrial fibrillation is an interdisciplinary condition, in which collaboration with  
7 colleagues in cardiology and haematology is essential. Recent advances in the field, most notably the  
8 now-widespread availability of direct oral anticoagulants, have brought opportunities to improve  
9 stroke care while posing new challenges. This article gives an overview of the contemporary diagnosis  
10 and management of atrial fibrillation, and the associated evidence base. Where uncertainty exists, we  
11 describe our own approach to these areas, while highlighting ongoing research which is likely to guide  
12 future practice.

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## 1 **1. INTRODUCTION**

2 Atrial fibrillation (AF) affects 2% of the UK population over 45 years old, and 4% of those over 65 [1].  
3 It causes at least one-fifth of ischaemic strokes [2], and is one of the strongest individual stroke risk  
4 factors [3]. Most AF patients presenting to a neurologist will do so following an ischaemic stroke or  
5 TIA, but AF may also be found incidentally. The mainstay of stroke prevention in AF is anticoagulation,  
6 which is highly effective in preventing disabling ischaemic cardioembolic stroke, but can cause serious  
7 complications, most notably intracranial haemorrhage, which is unpredictable and often fatal or  
8 disabling. Treatment decisions in AF are therefore often complex and associated with important risks  
9 that are difficult to quantify. Indeed, balancing treatments to reduce ischaemic (vaso-occlusive) events  
10 while minimising the risk of intracranial bleeding is a central challenge of stroke medicine. Here, we  
11 aim to provide an overview and practical approach to the common issues likely to be encountered by  
12 neurologists in relation to atrial fibrillation, while highlighting some important uncertainties.

## 13 **2. ATRIAL FIBRILLATION AS A RISK FACTOR FOR ISCHAEMIC STROKE**

14 The first description of atrial thromboembolism came, perhaps surprisingly, from a neurologist: in  
15 1875, William Gowers described simultaneous emboli in the brain and retina, spleen and kidneys,  
16 concluding that they had all originated in the left atrial appendage, which contained clots [4]. In the  
17 early 20<sup>th</sup> century autopsy studies linked mitral stenosis, AF and intracardiac thrombus formation, and  
18 so identified the contribution of AF to stroke risk [5]. The connection between “non-valvular” AF and  
19 stroke was then consolidated by Miller Fisher and Adams in 1951 [6]. The risk was quantified by Wolf  
20 and colleagues in 1978, using epidemiological data from the Framingham study: valvular and non-  
21 valvular AF increased ischaemic stroke risk 17-fold and five-fold respectively overall [7]. Much effort  
22 has since aimed to estimate ischaemic stroke risk in individual patients, producing the risk scoring  
23 systems which are the mainstay of current guidelines.

### 24 **Paroxysmal, persistent, and permanent AF**

25 An initial consideration in estimating ischaemic stroke risk is whether all types of AF – paroxysmal,  
26 persistent, and permanent – are equivalent. No current national or international guideline makes a  
27 distinction [8–10], based largely on observational longitudinal data from the Stroke Prevention in  
28 Atrial Fibrillation studies in the 1980s and 90s, which showed no difference in annual ischaemic stroke  
29 rate in aspirin-treated patients in paroxysmal versus persistent or permanent AF (3.2% vs. 3.3%) [11].  
30 Conflictingly, a more recent retrospective analysis of patients enrolled into the ACTIVE-A and  
31 AVERROES studies receiving aspirin monotherapy suggests that persistent and permanent AF might  
32 carry a higher risk than paroxysmal AF (3.0%, 4.2%, and 2.1%/year, respectively) [12]. These results

1 might be more applicable to contemporary practice, given advances in the management of other  
 2 cardiovascular risk factors. However, in practice, a quarter of patients with paroxysmal AF will progress  
 3 to persistent or permanent AF within five years, and a third within ten years [13]. In our view it is  
 4 therefore reasonable to treat paroxysmal, persistent, and permanent AF in the same way.

5 **Risk scores: CHADS2 and CHA2DS2VASc**

6 The first widely-adopted AF stroke risk score was the CHADS2 score (table 1), which included risk  
 7 factors identified by the Atrial Fibrillation Investigators (AFI) [14] and the Stroke Prevention and Atrial  
 8 Fibrillation (SPAF) investigators [15], and was validated in an independent cohort of 1,733 Medicare  
 9 beneficiaries [16]. Limitations included the exclusion of patients under 65, limiting widespread  
 10 applicability, and the inclusion of a low proportion of high-risk (CHADS2 >4) patients, giving rise to  
 11 wide confidence intervals for ischaemic stroke risk in higher-scoring patients (table 2). Importantly,  
 12 around a quarter of patients in the validation cohort had an “intermediate risk” CHADS2 score of 1, a  
 13 proportion that increased to 60% in subsequent studies [17]. This is problematic because in this large  
 14 patient population the treating physician would need to make a judgement between doing nothing,  
 15 giving aspirin (no longer advised under European Society of Cardiology guidelines) or recommending  
 16 anticoagulation.

17 *Table 1: CHADS2 and CHA2DS2VASc risk scores*

CHADS2		CHA2DS2VASc	
Risk factor	Score	Risk factor	Score
Congestive heart failure	1	Congestive heart failure	1
Hypertension	1	Hypertension	1
Age ≥75	1	Age ≥75	2
Diabetes	1	Diabetes	1
Stroke/TIA	2	Stroke/TIA	2
		Vascular (MI, PAD, aortic plaque)	1
		Age ≥65 (<75)	1
		Sex category (female)	1

**Score <1: Low risk; 1: intermediate risk; >1 high risk\***

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\* Note that in ESC 2016 guidelines that female gender alone does not score 1 unless in presence of an additional risk factor

1 *Table 2: CHADS2 data table – adapted from [16]*

Risk score	Number of patients (n=1,733)	Number as percentage of cohort	Number of strokes (n=94)	Adjusted annual stroke rate (95% CI)
0	120	6.9	2	1.9 (1.2-3.0)
1	463	26.7	17	2.8 (2.0-3.8)
2	523	30.2	23	4.0 (3.1-5.1)
3	337	19.4	25	5.9 (4.6-7.3)
4	220	12.7	19	8.5 (6.3-11.1)
5	65	3.8	6	12.5 (8.2-17.5)
6	5	0.3	2	18.2 (10.5-27.4)

10 The CHA2DS2VASc system was developed in response, by including additional risk factors and a lower  
 11 age threshold of 65 years while further weighting ages over 75 years (table 1) [17]. Validated on the  
 12 Euro Heart Survey on AF population in 1,084 patients not taking anticoagulants at baseline, the  
 13 CHA2DS2VASc low-risk category had a very low incidence of thromboembolic events (none in the  
 14 initial validation cohort, table 3), and the number of patients categorised as being at intermediate risk  
 15 (14.9%) was lower than with CHADS2 (table 3). There remain limitations of this revised score: a  
 16 number of important ischaemic stroke risk factors are not included – notably left atrial remodelling  
 17 from any aetiology (detectable on echocardiography), chronic kidney disease (particularly those with  
 18 CKD 3B or greater (eGFR <45ml/min/1.73m<sup>2</sup>)), obstructive sleep apnoea, circulating cardiac  
 19 biomarkers (review [18]), or brain biomarkers of cerebrovascular disease [19]. Scoring systems that  
 20 incorporate one or more of these factors have been developed and are in the process of validation.  
 21 For example, the ABC score combines age, cardiac biomarkers (NT-proBNP and Troponin I), and clinical  
 22 history of stroke or TIA, outperforming CHA2DS2VASc in its derivation and external validation cohorts,  
 23 with c-statistics of 0.68 and 0.66 vs. 0.62 and 0.58 respectively [20]. However, whether such scores  
 24 offer a significant advantage in clinical practice over the simple and cheap CHA2DS2VASc score  
 25 remains to be determined.

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1 *Table 3: CHA2DS2VASc data table – adapted from [17]*

Risk score	Number of patients (n=1,084)	Number as percentage of cohort	Number of strokes (n=25)	Annual stroke rate (95% CI)	Annual stroke rate adjusted for aspirin use
0	103	9.5	0	0 (0-0)	0
1	162	14.9	1	0.6 (0.0-3.4)	0.7
2	184	17.0	3	1.6 (0.3-4.7)	1.9
3	203	18.7	8	3.9 (1.7-7.6)	4.7
4	208	19.2	4	1.9 (0.5-4.9)	2.3
5	95	8.8	3	3.2 (0.7-9.0)	3.9
6	57	5.3	2	3.6 (0.4-12.3)	4.5
7	25	2.3	2	8.0 (1.0-26.0)	10.1
8	9	0.8	1	11.1 (0.3-48.3)	14.2
9	1	0.1	1	100 (2.5-100)	100

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3 **Risk scores: more than stroke risk?**

4 An interesting point to note is that the CHADS and CHA2DS2VASc scores are essentially summaries of  
 5 cardiovascular risk factors that portend endothelial and myocardial dysfunction, and so do not only  
 6 predict ischaemic stroke risk. Even in patients without AF, both scores correlate with measures of  
 7 general vascular dysfunction and perform moderately well in predicting ischaemic stroke, myocardial  
 8 infarction and cardiovascular death [21]. Moreover, in patients admitted with an acute coronary  
 9 syndrome, the CHADS2 and CHA2DS2VASc scores also predict ischaemic stroke independently of an  
 10 antecedent diagnosis of AF [22]. Both scores also predict new onset of AF, with c-statistics of 0.72 and  
 11 0.74 respectively [23]. Therefore, in those with cryptogenic stroke, a high CHA2DS2VASc score should  
 12 perhaps prompt a more aggressive rhythm monitoring strategy in those patients in whom initial  
 13 rhythm monitoring has not made an AF diagnosis.

14 **3. DIAGNOSIS OF AF AFTER STROKE**

15 In the UK, 15–20% of acute ischaemic stroke patients have known atrial fibrillation at the time of  
 16 stroke [24,25]. Standard guideline-based investigations for AF in the remainder, if potentially eligible  
 17 for anticoagulation, would comprise a routine ECG on admission, inpatient telemetry lasting 12–24hrs,  
 18 and, in the absence of a definite alternative mechanism, further outpatient monitoring, usually for 1–  
 19 7 days [26–28]. A further ~20% of patients will be diagnosed with AF by this approach [2]. Three major

1 randomised controlled trials have examined what further monitoring should be undertaken in patients  
2 with cryptogenic stroke (i.e. those with no alternative cause found after standard investigations,  
3 including imaging of the extracranial arteries): CRYSTAL-AF, EMBRACE, and FIND AF<sub>RANDOMISED</sub> [29–31].  
4 The results, summarised in *Table 4*, showed significantly higher detection rates with more intensive  
5 rhythm monitoring strategies than with standard care. Higher use of oral anticoagulation resulted,  
6 though these studies were not powered to show reduced recurrent stroke risk. In CRYSTAL-AF, the  
7 detection rate continued to rise past one year, reaching 30% at 3 years [32]. Although this might  
8 partially represent incident AF unrelated to the original stroke, this finding would still generally justify  
9 anticoagulation in an ischaemic stroke patient.

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1 Table 4: Key trials of prolonged ECG monitoring after ischaemic stroke; the results show the rate of AF  
 2 detection in the intervention (I) and control (C) arms of the studies.

		CRYSTAL-AF [29,32]		EMBRACE [30]		FIND AF <sub>RANDOMISED</sub> [31]	
Population		Cryptogenic stroke within 90 days; >40yrs; negative vascular imaging, TOE, thrombophilia screen + >24hrs ECG monitoring; n=441		Cryptogenic stroke within 6 months; >55yrs; negative vascular imaging, echo, >24hrs ECG monitoring		Cryptogenic stroke within 7 days; >60yrs; negative vascular imaging and admission ECG	
Intervention		Implanted cardiac monitor		Non-invasive 30-day event-triggered loop recorder		10-day Holter monitoring at enrolment, three months and six months	
Control		Routine care ( <i>ad hoc</i> ECG and Holter monitoring)		Additional 24hr Holter monitoring		At least 24hrs telemetry (mean 73hrs) +/- 24hrs Holter monitoring	
Outcome		Detection rate AF episode >2mins (I) or >30s (C)		Detection rate AF episode >30s		Detection rate AF episode >30s	
Results	Follow up (months)	I	C	I	C	I	C
	1	3.7%	3.7%	16.1%	3.2%		
	6	8.9%				13.5%	4.5%
	12	12.4%					
	24	21.1%					
	36	30.0%	3%				

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## 1 **Which patients should have prolonged monitoring?**

2 Risk factors and biomarkers of AF could theoretically help select patients for prolonged monitoring.  
3 However, many patient-related risk factors for AF, such as age and hypertension, are poorly-  
4 discriminating, also being risk factors for atherosclerosis [33]. Heart failure and mitral stenosis might  
5 be more specific [34], and the recently-developed HAVOC risk score, which weights congestive heart  
6 failure heavily, has shown potential for triaging cryptogenic stroke patients into low, medium and  
7 high-risk categories for AF detection [35]. ECG biomarkers including PR prolongation and atrial  
8 premature beat count are also being developed [36,37].

9 Clinical and radiological features might also help identify patients likely to have AF. Large cardiac fibrin-  
10 rich thrombi tend to travel in medium calibre high-flow vessels, leading to proximal arterial occlusion  
11 and a large infarct, or fragmentation and distal embolization into terminal cortical branches.  
12 Consequently, the features of cardioembolic stroke include higher clinical severity, more cortical  
13 symptoms and signs, and certain radiological patterns (figure 1), including whole-territory infarction,  
14 wedge-shaped infarcts extending into the cortex, striatocapsular infarction (from transient M1  
15 occlusion), isolated posterior cerebral artery infarction causing hemianopia, scattered distal infarcts  
16 within an arterial territory or external borderzone, and multi-territory bihemispheric or anterior and  
17 posterior circulation infarcts [38]. Haemorrhagic transformation has also been suggested to be  
18 characteristic of cardiac embolism, since cardiac, “red” (fibrin-rich) thrombi are more liable to re-  
19 perfuse and consequently have associated haemorrhage within the infarct. However, none of these  
20 findings are wholly reliable: even small subcortical infarction has been described in the presence of a  
21 definite embolic mechanism [39], and a recent meta-analysis showed that the AF detection rate at  
22 seven days after ischaemic stroke is similar whether the stroke is classified clinico-radiologically as due  
23 to small or large vessel occlusion [40]. Importantly, high detection rates in the prolonged monitoring  
24 trials were obtained in relatively unselected cryptogenic stroke patients. Therefore, until a biomarker-  
25 based approach is validated, we advocate prolonged monitoring in all cryptogenic stroke patients.

## 26 **Monitoring techniques**

27 The optimal techniques for ECG monitoring are uncertain, with a lack of head-to-head trials and recent  
28 rapid advances in device design. In most departments, first-line non-invasive AF detection remains via  
29 Holter monitoring, developed in 1962 and limited by relatively short recording duration, bulky design,  
30 an inability to use while showering, and delays in reporting. Newer hand-held patient-activated  
31 devices such as Kardia and Zenicor offer portability, cost-effectiveness and speed [41], but do not offer  
32 the continuous monitoring required to detect asymptomatic AF. Our preference is for newer patch-  
33 monitoring devices, such as ZIO, Bardy or e-Patch, or lead monitoring via R-test or Apoplex (table 5,

1 figure 2). These devices allow continuous monitoring for longer durations, a lightweight water-  
2 resistant design, easy application in clinic by a nurse or doctor, and email reporting within 72 hours.

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1 **Table 5: ECG monitoring devices**

	Patch monitors			Standard lead monitors		
	CAM/Bardy	E-patch	ZIO	Apoplex	Holter	R-test
<b>Device characteristics</b>						
Type of device	Lightweight 2 lead patch*	Lightweight 2 lead patch	Lightweight 2 lead patch	3 lead Holter monitor	3-5 Lead monitor	Single lead monitor
Showerproof	Y	Y	Y	Y	N	Y
Device applied in clinic	Y	Y	Y	Y	N	Y
Additional software required to allow upload of data	N	Y	N	Y	N	Y
Recording duration	7 days	5 days	14 days	1-72 hours**	1-7 days	16-32 days
Time to report	<72hrs	<72 hours	48-72hrs	<24hrs	Locally dependent	48hrs
Full report of cardiac rhythm e.g. AF, SVT, VT, ectopics, pauses	Y	Y	Y excludes AF <30 seconds	3 outcomes, 1= AF/PAF, 2= increased risk of AF, 3 = no evidence of AF	Y	Y
What does the patient do with the device?	Device posted by patient to manufacturer for analysis (freepost)	Device returned to clinic and data uploaded for analysis	Device posted by patient to manufacturer for analysis (freepost)	Device returned to clinic and data uploaded for analysis	Device returned to clinic	Device returned to clinic and data uploaded for analysis
How is the data reported?	Computer algorithm with cardiac physiologist review	Computer algorithm with cardiac physiologist review	Computer algorithm with cardiac physiologist review	Computer algorithm	Cardiac physiologist with cardiologist review	Computer algorithm with cardiac physiologist review
Results reporting	Email report	Email report  Option for data to be reviewed locally	Online portal	Email report	Local arrangements for feedback of results	Email report  Option for data to be reviewed locally
Is there patient diary correlation?	Y	N	Y	N	Y	N

2 \*Placement on sternum thought to improve AF detection compared to other patches but no head to head trials

3 \*\* We use the Apoplex device for in clinic monitoring, applied at start of clinic and removed after all tests are complete that day

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1 After non-invasive monitoring, our practice is to proceed to prolonged monitoring via an implanted  
2 cardiac monitor in patients whose ischaemic stroke remains unexplained, with a high suspicion of  
3 cardiac embolism (e.g. non-lacunar, especially if due to cortical branch occlusion, or in multiple  
4 vascular territories, or with other radiological characteristics shown in figure 1), and in whom we  
5 would recommend anticoagulation if AF is found. Traditional catheter-inserted monitors have now  
6 been replaced by subcutaneous devices, inserted via a <1cm incision, which offer up to 3 years of  
7 continuous monitoring, MRI-compatibility, automated arrhythmia detection as well as a patient-  
8 activated event alarm, and wireless data download. The Reveal LINQ monitor (figure 3) has recently  
9 been the subject of a NICE MedTech Innovation briefing [42]. Such systems are generally well-  
10 tolerated, being small and lightweight, with a low rate of complications (in CRYSTAL-AF, the removal  
11 rate due to infection or erosion was 2.4%). Whether their use translates into a reduced risk of stroke  
12 is being addressed by the LOOP trial, expected to report in 2020 [43].

### 13 **Low-burden and implanted device-detected AF**

14 With the greater use of prolonged monitoring, an increasing number of patients will be found who  
15 have short and infrequent paroxysms of AF – that is, a low ‘AF burden’. The patients in the key clinical  
16 trials of anticoagulation and risk score development cohorts will largely have been diagnosed by short  
17 duration monitoring, and are therefore more likely to have had a high AF burden. Therefore, whether  
18 low-burden AF patients diagnosed through prolonged monitoring benefit similarly from  
19 anticoagulation is an important uncertainty. However, current national and international guidelines  
20 do not distinguish by AF burden, and our practice is to consider anticoagulation in any patient with  
21 proven AF of any duration. It is likely that AF burden increases over time, and the haemodynamic  
22 effects of irregular atrial contraction may not be the only mechanism of intracardiac thrombosis in AF  
23 [44]. Most studies correlating AF burden with stroke risk have been performed in patients with  
24 pacemakers or implanted cardioverter-defibrillators able to detect paroxysmal atrial tachycardias  
25 termed ‘atrial high rate episodes’ (AHREs). The results of these studies are inconsistent, finding  
26 ischaemic stroke risk to be increased variously by the presence of an AHRE >5 minutes, 6 minutes or  
27 24hrs, or by a daily burden of 5.5hrs or more on at least one day during the monitoring period [45–  
28 49]. AHREs correlate with AF detection on dedicated rhythm monitoring, but imperfectly; therefore,  
29 these results should not be extrapolated directly to patients with proven AF. Neurologists should  
30 however be aware that interrogation of an implanted cardiac device in a stroke patient may provide  
31 evidence of an increased risk of AF, and that two clinical trials (NOAH AFNET-6 and ARTESIA) are testing  
32 the benefit of anticoagulation in patients with AHREs lasting less than 24hrs [50,51]. In the meantime,  
33 a proposed approach for the management of AHREs, based on European Society of Cardiology  
34 guidance, is to consider anticoagulation for patients with a previous ischaemic stroke, or with an AHRE

1 >24hrs and two or more non-gender risk factors in CHA2DS2VAsC [8,52]. For other patients, an AHRE  
2 should prompt ECG monitoring, and consideration of anticoagulation if AF is then documented.

### 3 **Neurogenic AF**

4 A further complexity concerning AF diagnosed after stroke is that a proportion of this may be caused  
5 by abnormal autonomic drive, possibly related to insular brain injury [53], and inflammation,  
6 especially if detected in the acute phase. This 'neurogenic' AF could be a transient phenomenon and  
7 not require long-term anticoagulation, unlike 'cardiogenic' AF due to structural heart disease [54].  
8 Although there is insufficient supporting evidence to change clinical practice, it has recently been  
9 reported that recurrent ischaemic stroke risk in patients diagnosed with AF after stroke is low  
10 compared to that of patients known to have AF prior to stroke, and similar to that observed in sinus  
11 rhythm [55]. Repeat rhythm monitoring, delayed by several months, might be of value in stratifying  
12 the longer-term risk in these patients.

## 13 **4. DECIDING ON ANTICOAGULATION**

14 In AF patients, oral anticoagulation with warfarin reduces the relative risk of ischaemic stroke by  
15 approximately two-thirds, regardless of absolute risk [56,57]; this means that those patients at highest  
16 absolute risk gain the most absolute benefit from anticoagulation. Direct oral anticoagulants (DOACs)  
17 offer similar protection against ischaemic stroke to vitamin K antagonists (warfarin) [58]. This benefit  
18 must be weighed against the risk of anticoagulation-associated haemorrhage, particularly  
19 intracerebral haemorrhage (ICH), which is rare (generally less than 1% per year in clinical trials) but  
20 incurs much higher morbidity and mortality than ischaemic stroke [59]. The trade-off between the  
21 reduced risk of ischaemic stroke and increased risk of ICH, weighted by severity, has been described  
22 as the 'net clinical benefit' of anticoagulation. Overall, using CHADS2 for risk stratification, a positive  
23 net clinical benefit is obtained for patients scoring 2 or more [60]. A subsequent analysis using  
24 CHA2DS2VAsC, which is more accurate than CHADS2 in lower-risk patients, found a small net clinical  
25 benefit for patients with a score of 1 [61]. Female patients with a CHA2DS2VAsC of 1 (that is, with no  
26 other risk factors beyond gender) have a very low risk of ischaemic stroke, comparable to that for men  
27 with CHA2DS2VAsC of 0, and may not benefit from anticoagulation with warfarin [62]. The threshold  
28 for benefit with DOAC use has not been as fully studied, but modelling indicates this is likely to be  
29 lower, due to their substantially reduced risk of ICH [63]. In view of these data, the 2016 European  
30 Society of Cardiology guidelines suggest consideration of anticoagulation for any patient with AF and  
31 a single non-gender CHA2DS2VAsC risk factor [8], as do the 2018 guidelines of the American College  
32 of Chest Physicians (ACCP) [64]. The 2014 American Heart Association guidelines endorse  
33 anticoagulation for CHA2DS2VAsC >1, but suggest no treatment, anticoagulation or aspirin for patients

1 with CHA<sub>2</sub>DS<sub>2</sub>VASc =1, though acknowledge a lack of evidence for aspirin in the prevention of  
2 cardioembolic stroke [65].

3 Having established that a patient has an appreciable ischaemic stroke risk and should be considered  
4 for anticoagulation, the next step is to assess bleeding risk. Ideally, it would be possible to calculate  
5 the net clinical benefit of anticoagulation for an individual. To this end, several bleeding risk scores  
6 have been generated, including HASBLED, HEMORR2HAGES, ATRIA and ORBIT. These scores perform  
7 similarly and modestly, with c-statistics for major bleeding between 0.6 and 0.7 [66]. Limitations of  
8 risk scores include the use of risk factors which are dynamic and difficult to know prospectively or  
9 based on a single assessment (e.g. uncontrolled hypertension, labile INR), the use in some cases of  
10 variables not routinely measured in clinical practice (e.g. genetic data in HEMORR2HAGES), their  
11 derivation largely for warfarin-treated patients, and the use of a composite 'major bleeding' outcome  
12 measure which weights a two-unit transfusion equally to a disabling ICH. Notably, they perform less  
13 well for predicting intracranial haemorrhage specifically, the major bleeding risk relevant to  
14 anticoagulation decisions in atrial fibrillation, with c-statistics close to 0.5 [67]. Given this, a  
15 straightforward comparison of calculated 'major bleeding' and ischaemic stroke risks cannot currently  
16 be recommended. However, bleeding risk scores are useful to inform discussions with patients  
17 considering anticoagulation, and to identify patients requiring closer monitoring and aggressive  
18 treatment of modifiable bleeding risk factors. Patients at particularly high risk of bleeding and stroke  
19 may be considered for non-pharmacological treatment, such as left atrial appendage occlusion.

20 More precise estimation of bleeding risk (including intracranial haemorrhage) might be enabled  
21 through the use of MRI biomarkers including cerebral microbleeds (figure 4) [19]. The CROMIS-2 study  
22 included 1490 participants with recent ischaemic stroke or TIA and AF; the symptomatic intracranial  
23 haemorrhage rate in patients with cerebral microbleeds was 9.8 per 1000 patient-years (95% CI 4.0-  
24 20.3) compared with 2.6 per 1000 patient-years (95% CI 1.1-5.4) in those without cerebral microbleeds  
25 (adjusted hazard ratio 3.67, 95% CI 1.27-10.60). Compared with the HAS-BLED score alone, models  
26 including cerebral microbleeds predicted symptomatic intracranial haemorrhage significantly better  
27 with a c-statistic of 0.74 (95% CI 0.60-0.88). Further data from large international collaborative studies  
28 are awaited to establish the value of cerebral microbleeds in predicting intracranial haemorrhage.

### 29 **Anticoagulation in the elderly**

30 Beyond bleeding risk scores, increasing age is sometimes seen as a contraindication to  
31 anticoagulation, particularly in those over 75 years, with antiplatelets sometimes used instead. Older  
32 patients are at the highest risk of stroke, so have the most to gain from treatment, and to lose if  
33 anticoagulation is needlessly withheld. The BAFTA study [68] showed warfarin to be superior to aspirin

1 in stroke prevention in patients aged seventy-five or older (mean age 81.5 +/- 4.2yrs), with a relative  
2 risk of all-cause stroke of 0.48 in the warfarin arm. The risk of haemorrhagic complications did not vary  
3 significantly between the two groups, and was relatively low overall, with an annual risk of major  
4 haemorrhage of 1.9% with warfarin and 2.0% with aspirin (and 2.9% and 3.7% respectively in those  
5 >85yrs). The relative efficacy of warfarin in ischaemic stroke prevention is maintained despite  
6 increasing age, so a greater absolute benefit is derived in older, and so higher risk, patients,  
7 outweighing a slower increase in ICH risk. Overall, older patients seem to gain a greater net clinical  
8 benefit from anticoagulation [69]. Secondary analyses of three pivotal DOAC trials (ARISTOTOLE,  
9 ROCKET-AF and RE-LY) show that older patients benefit similarly to younger patients from DOACs  
10 [70,71], although the use of dabigatran at the higher dose of 150mg BD is associated with high rates  
11 of extracranial bleeding in those older than 80 years [72]. We therefore do not recommend any upper  
12 age cut-off for considering anticoagulation.

### 13 **Cognitive impairment, frailty, and falls**

14 These are common reasons for withholding anticoagulation, but this might be unjustified. The use of  
15 a DOAC potentially avoids much of the difficulty of warfarin monitoring in cognitively-impaired  
16 patients, but measuring adherence might be challenging unless a relative or carer is available to  
17 supervise use. Frailty, usually defined as a decline in physiological reserve across multiple systems  
18 leading to increased vulnerability to stressors, is independently associated with reduced prescription  
19 of anticoagulants [73], but the limited evidence available does not support this: in the ORBIT-AF  
20 registry of nearly 10,000 patients, of whom over 500 met AGS criteria for frailty, survival was improved  
21 by anticoagulation even in frail patients, and frailty did not independently predict an increased risk of  
22 major bleeding or stroke [74]. Falls are cited as a reason to withhold anticoagulation in over a quarter  
23 of untreated AF patients [75]. This is understandable: anticoagulation with warfarin triples the risk of  
24 subdural haemorrhage [76], thought often due to falls, and frequent falls quadruple the risk of  
25 traumatic ICH [77]. However, ICH after a single fall is rare, even in anticoagulated patients [78], and  
26 the risk of subdural haemorrhage in anticoagulated AF patients is very low compared to the risk of  
27 ischaemic stroke [76]. As a result, it has been estimated that an AF patient with an 6% annual  
28 ischaemic stroke risk would need to fall 295 times per year not to benefit from warfarin [79]. Although  
29 this figure will be lower for patients with a lower ischaemic stroke risk, the average elderly patient  
30 who falls does so only 1.8 times each year, and most patients who fall will have an elevated stroke risk  
31 because of their age and co-morbidities. Pragmatically, it is also not clear that being screened as 'high  
32 falls risk' or having fallen in the last year is associated with an increased risk of haemorrhage in  
33 anticoagulated patients [80,81]. Therefore, we do not recommend withholding anticoagulation in  
34 patients who fall, but do suggest a thorough assessment and modification of falls risk where possible.

1 **5. STARTING AN ANTICOAGULANT**

2 Most AF patients will be offered a vitamin K antagonist (VKA; generally, warfarin), a direct thrombin  
3 inhibitor (dabigatran), or a factor Xa inhibitor (apixaban, rivaroxaban, edoxaban). The latter classes act  
4 directly on components of the common coagulation pathway, so are termed ‘direct oral  
5 anticoagulants’ (DOACs). Compared to warfarin, they have a rapid onset of action, without an initial  
6 procoagulant effect, a short half-life, few interactions with food and medication, and do not require  
7 dose titration or monitoring blood tests. Their characteristics are summarised in *Table 6*. In phase  
8 three trials, all were at least non-inferior to warfarin for the prevention of stroke and systemic  
9 embolism (SES), with about half the rate of intracranial haemorrhage [82–85]. This clinical trial data is  
10 strongly supported by data from observational studies in ‘real world’ populations [86]. Our practice,  
11 supported by European guidelines [8], is to recommend a DOAC to all patients without a specific  
12 indication for a VKA (e.g. a mechanical prosthetic heart valve or significant mitral stenosis [87]) (*box*  
13 *1*). We also generally prefer a VKA (or low molecular weight heparin) in patients with active  
14 malignancy, in whom fluctuations in renal function and body weight are common during treatment  
15 and disease course. However, a recent analysis of outcomes for patients in ENGAGE-AF-TIMI 48  
16 diagnosed with cancer during the trial found the benefit of edoxaban to be preserved, suggesting that  
17 the use of DOACs in these patients should be investigated further [88].

18



1 **Table 6: Summary of oral anticoagulant properties**

	Apixaban	Edoxaban	Rivaroxaban	Dabigatran	Warfarin
<b>Mechanism</b>	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Direct thrombin inhibitor	Vitamin K antagonist
<b>Indication</b>	Non-valvular AF + 1 of: <ul style="list-style-type: none"> <li>• Ischaemic stroke/TIA</li> <li>• Age &gt;75yrs</li> <li>• Symptomatic/congestive HF</li> <li>• DM</li> <li>• HTN</li> </ul>				Non-valvular AF Valvular AF Metallic valve
<b>Standard dose</b>	5mg BD	60mg OD	20mg OD	150mg BD	Dose-adjusted to INR
<b>Reduced dose</b>	2.5mg BD (at least 2 of: age>80yrs, weight <60kg, Cr >133µmol/L)	30mg OD (any of: CrCL <50ml/min, weight <60kg, concomitant strong P-gp inhibitor use)	15mg OD (CrCl <50ml/min)	110mg BD (>80yrs, verapamil; also consider if 75-80yrs, CrCl 30-50ml/min, gastritis, increased bleeding risk)	N/A
<b>Contraindications</b>	Clinically-significant bleeding or high risk of bleeding complication				
	<ul style="list-style-type: none"> <li>• CrCl &lt;15ml/min</li> <li>• Severe hepatic impairment</li> <li>• Pregnancy</li> <li>• Breast-feeding</li> </ul>	<ul style="list-style-type: none"> <li>• CrCl &lt;15ml/min</li> <li>• Hepatic impairment with coagulopathy</li> <li>• Uncontrolled severe HTN</li> <li>• Pregnancy</li> <li>• Breast feeding</li> </ul>	<ul style="list-style-type: none"> <li>• CrCl &lt;15ml/min</li> <li>• Hepatic impairment with coagulopathy</li> <li>• Pregnancy</li> <li>• Breast feeding</li> </ul>	<ul style="list-style-type: none"> <li>• CrCl &lt;30ml/min</li> <li>• Hepatic impairment expected to affect survival</li> <li>• Pregnancy</li> <li>• Breast feeding</li> </ul>	<ul style="list-style-type: none"> <li>• Pregnancy (1<sup>st</sup> and 3<sup>rd</sup> trimester)</li> </ul>
<b>Pharmacokinetics</b>	T1/2: c. 12hrs 27% renal excretion	T1/2: 10-14hrs 35% renal excretion	T1/2: 5 – 13hrs 65% renal excretion	T1/2: 13–18hrs 80% renal excretion	T1/2: 20 – 60hrs 35% renal excretion
<b>Summary of interactions<sup>1</sup></b>	<u>Avoid:</u> Strong CYP3A4 + P-gp inhibitors <sup>2</sup>  <u>Caution:</u> Other CYP3A4/P-gp inhibitors <sup>3</sup> , CYP3A4 inducers <sup>4</sup>	<u>Reduce dose:</u> Strong P-gp inhibitors <sup>5</sup>  <u>Caution:</u> other P-gp inhibitors <sup>6</sup> , P-gp inducers <sup>7</sup>	<u>Avoid:</u> Strong CYP3A4 + P-gp inhibitors  <u>Caution:</u> Other CYP3A4/P-gp inhibitors, CYP3A4 inducers	<u>Avoid:</u> strong P-gp inhibitors, P-gp inducers  <u>Reduce dose:</u> verapamil  <u>Caution:</u> other P-gp inhibitors	Extensive interactions via CYP3A4 <sup>8</sup>
<b>Common side-effects</b>	Bleeding complications				
	Nausea	Dizziness, headache, abdominal pain, nausea, itch	Itch, headache	Dyspepsia, abdo pain, diarrhoea (tartaric acid excipient)	
<b>Reversal agent</b>	Andexanet alfa (FDA-approved, not currently licenced in UK)			Idarucizumab	Vitamin K PTCC

2

3 <sup>1</sup>Adapted from manufacturers' SPCs and with reference to [89] ; consulting BNF and local guidelines also suggested

4 <sup>2</sup>Strong inhibitors of both CYP3A4 and P-gp: ketoconazole, itraconazole, voriconazole, posaconazole, dronedarone, HIV protease inhibitors (increased anticoagulant effect)

6 <sup>3</sup>Other inhibitors of CYP3A4 and P-gp (i.e. with less potent inhibition of one or both pathways): clarithromycin, erythromycin, fluconazole (increased anticoagulant effect)

8 <sup>4</sup>CYP3A4 inducers: rifampicin, phenytoin, carbamazepine, phenobarbitone, St. John's wort (reduced anticoagulant effect)

9 <sup>5</sup>Strong P-gp inhibitors: as (2), also ciclosporin, tacrolimus and erythromycin (increased anticoagulant effect)

10 <sup>6</sup>Other P-gp inhibitors: verapamil (note dose reduction for dabigatran), amiodarone, quinidine, clarithromycin, ticagrelor (increased anticoagulant effect)

1 <sup>7</sup>P-gp inducers: rifampicin, phenytoin, carbamazepine, phenobarbitone, St. John's wort (reduced anticoagulant effect)

2 <sup>8</sup>Major warfarin interactions: allopurinol, azoles, omeprazole, amiodarone, tamoxifen, statins (esp. fluvastatin), fibrates, erythromycin,  
3 metronidazole (increased effect); phenobarbitone, primidone, carbamazepine, rifampicin, phenytoin, azathioprine, St. John's wort (reduced  
4 effect); steroids, nevirapine, ritonavir (unpredictable effects); liver, broccoli, sprouts, leafy greens (high vitamin K content – reduced effect)

5

### **Box 1: Indications for VKAs over DOACs**

- Absolute
  - Prosthetic (mechanical) heart valve
  - Valvular atrial fibrillation (due to moderate or severe mitral stenosis, usually of rheumatic origin)
  - Severe renal impairment
- Relative
  - Comorbid malignancy
  - Patient choice (e.g. if long-established on warfarin)
  - Extremes of body weight (pharmacokinetics/dosing of DOAC unclear)
  - Likelihood of poor compliance without monitoring blood tests

6

## **7 Choosing between DOACs**

8 Some differences were observed in the performance of the DOACs in their phase three trials against  
9 warfarin. Dabigatran 150mg BD, edoxaban 60mg, and apixaban were superior for the prevention of  
10 stroke and systemic embolism, mainly driven by a reduced risk of intracerebral haemorrhage, whereas  
11 rivaroxaban was non-inferior. Only dabigatran 150mg BD was superior for prevention of ischaemic  
12 stroke. Apixaban, edoxaban and dabigatran 110mg BD were associated with a lower risk of major  
13 bleeding, and edoxaban 30mg with a lower risk of GI bleeding. Dabigatran 150mg BD and rivaroxaban  
14 had higher risks of gastrointestinal bleeding. Given the absence of head-to-head randomised  
15 controlled trials, attempts have been made to infer their relative efficacy through network meta-  
16 analysis; that is, a systematic assessment of their performance against warfarin as a common  
17 comparator. In the largest analysis of this type, the authors concluded that apixaban offered the  
18 optimal balance of safety and efficacy, with dabigatran showing the greatest efficacy but a less  
19 favourable safety profile [90].

20 Caution is needed in the interpretation of these results. Although the authors showed a lack of effect  
21 modification by age, gender balance or CHADS2, they could not control for other possible sources of  
22 confounding. For instance, the ROCKET-AF trial of rivaroxaban included a substantially higher-risk  
23 population with more co-morbidities than RE-LY or ARISTOTLE, not all of which are accounted for in  
24 the CHADS2 score. There is therefore still a need for high-quality RCT evidence, though large numbers  
25 would be needed to compare treatments likely to have similar effect sizes. Until such evidence is

1 available, we do not think there is sufficient evidence to make a general recommendation for a  
2 particular DOAC; rather, we suggest balancing the available evidence with patient characteristics and  
3 preferences in choosing an anticoagulant. For some patients, apixaban might be a reasonable default  
4 choice, especially those with impaired renal function. We would consider dabigatran for patients with  
5 high ischaemic stroke risk and low bleeding risk, but avoid it in patients with significant dyspepsia or  
6 previous major GI bleeding. For patients who prefer once-daily dosing, edoxaban and rivaroxaban may  
7 aid compliance. Interactions with other medication should be considered. We recommend the recent  
8 American College of Chest Physicians guidelines for further advice on anticoagulant selection [64].

### 9 **Timing of anticoagulation**

10 The optimal timing to start anticoagulation after a cardioembolic stroke is unclear. Based on studies  
11 of heparin, very early (<48hrs) anticoagulation increases the risk of symptomatic intracranial  
12 haemorrhage without reducing the risk of early recurrence (7-14 days), morbidity or mortality [91].  
13 Current practice is therefore to delay anticoagulation by up to fourteen days. As the risk of recurrence  
14 in this time is around 5%, many clinicians will anticoagulate earlier, according to the size of the infarct  
15 and presence of haemorrhagic transformation. The '1-3-6-12' rule-of-thumb, based only on expert  
16 opinion, suggests anticoagulation on days 1, 3, 6 and 12 respectively after TIA, minor, moderate and  
17 large infarcts [92]. The lower risk of ICH with DOACs may facilitate earlier anticoagulation, and  
18 observational studies do suggest that the risk of symptomatic intracranial haemorrhage in patients  
19 treated with DOACs within the first five days of ischaemic stroke is low, as is the risk of new  
20 asymptomatic haemorrhagic transformation [93,94], at least in patients with small infarcts . Four large  
21 upcoming RCTs, OPTIMAS, TIMING, START and ELAN, will assess the benefit of early anticoagulation  
22 (<4 days) in patients with AF-related stroke, with OPTIMAS due to recruit ~3500 participants  
23 throughout the UK from early 2019 [95].

## 24 **6. COMMON CHALLENGES DURING ANTICOAGULATION**

25 The main challenges encountered in patients established on oral anticoagulation for stroke prevention  
26 in atrial fibrillation comprise treatment failure – recurrent ischaemic stroke – and bleeding  
27 complications - most seriously, intracerebral haemorrhage (ICH).

### 28 **Management of recurrent ischaemic stroke**

29 In this event, the first priority is to determine the patient's eligibility for hyperacute treatment. In  
30 patients taking warfarin, point-of-care INR testing provides an immediate answer: an INR of 1.7 or less  
31 does not contraindicate thrombolysis [96]. With DOACs, this is less straightforward. Although some  
32 standard laboratory clotting indices (particularly the APTT) may be influenced by DOACs, they are not

1 reliable markers of the degree of anticoagulation. More valid assays, such as factor Xa levels (for  
2 apixaban, edoxaban and rivaroxaban) and dilute thrombin time (dabigatran), are not usually available  
3 quickly. In the absence of an assay result excluding a significant DOAC effect, US guidelines advise  
4 against thrombolysis unless it can be clearly established that the patient last took a DOAC more than  
5 48hrs ago and has normal renal function [27]. The European Society of Cardiology recommends also  
6 considering thrombolysis for patients who last took a DOAC between 24 and 48hrs ago, if renal  
7 function is normal and they are otherwise a good candidate [89]. In patients not meeting these criteria,  
8 proceeding directly to mechanical thrombectomy should be considered in patients with thrombus  
9 within the basilar artery or proximal middle cerebral artery. Successful thrombolysis has been  
10 reported after dabigatran reversal. For patients taking FXa inhibitors, a pathway using a rapid anti-Xa  
11 activity assay (RivLev) to guide thrombolysis in patients taking rivaroxaban has been tested  
12 successfully in a single centre [97]. Importantly, over half the patients included who would not have  
13 been eligible for thrombolysis based on last DOAC intake had a RivLev result compatible with  
14 thrombolysis [98]. We are introducing a similar pathway in our centre, and our practice in the absence  
15 of a FXa level reflects European guidelines.

16 Poor compliance is the most obvious cause for treatment failure. In this case, the underlying reasons  
17 should be addressed, which may involve continuing the existing treatment with measures to improve  
18 compliance or choosing a new OAC more acceptable to the patient (for instance, a FXa inhibitor rather  
19 than dabigatran in patients with GI side-effects, a DOAC rather than warfarin in patients reluctant to  
20 undergo blood tests, or a once-daily rather than twice daily DOAC). If compliance is good, drug and  
21 dietary interactions should be considered. A few patients suffer a recurrent ischaemic stroke despite  
22 apparently therapeutic anticoagulation, perhaps due to an alternative mechanism such as  
23 atherosclerosis or small vessel occlusion. There is no accepted evidence-based strategy for such  
24 patients. Seeking any treatable alternative cause of stroke (e.g. carotid stenosis) or stroke “mimic” is  
25 essential. In those on warfarin, a switch to a DOAC might be recommended. Increasing the target INR  
26 instead is associated with a high risk of bleeding. In those on DOACs, an alternative DOAC (with a  
27 different mechanism of action or more frequent dosing) could be used, or a switch to warfarin could  
28 be made if closer monitoring is thought desirable. Adding an antiplatelet is not generally  
29 recommended (at least not long-term), as the concurrent use of aspirin with an anticoagulant was  
30 associated with increased bleeding but not a reduction in the risk of all-cause stroke and systemic  
31 embolism in the RE-LY [99] and SPORTIF [100] trials.

## 32 **Management of OAC-associated ICH**

1 The management of oral anticoagulant-associated ICH entails supportive care, rapid reduction of  
2 systolic blood pressure to <140mmHg [101], and reversal of anticoagulation. For patients taking  
3 warfarin, this is achieved with 5-10mg vitamin K intravenously, and replacement of the vitamin K-  
4 dependent clotting factors (II, VII, IX and X) with four-factor prothrombin complex concentrate (e.g.  
5 Beriplex, Octaplex) in preference to fresh frozen plasma [102]. For patients taking DOACs, there is no  
6 role for vitamin K supplementation, as DOACs act downstream of the vitamin-K dependent portion of  
7 the clotting cascade. Four-factor prothrombin complex concentrate has been used off-label, and is  
8 recommended by European Heart Rhythm Association guidelines [89], but evidence for efficacy is  
9 limited. For dabigatran, a specific monoclonal antibody antidote, idarucizumab, is available, rapidly  
10 and safely normalising laboratory clotting indices and achieving normal intra-operative haemostasis  
11 in patients needing emergency surgery in an uncontrolled phase three study [103]. We recommend  
12 the immediate use of this agent where available in dabigatran-related intracerebral haemorrhage. A  
13 decoy protein reversal agent for FXa inhibitors, andexanet alfa, has been tested in a small clinical study  
14 [104] and has recently been licensed in the United States. It remains expensive and clinically unproven  
15 for FXa inhibitor-related ICH, with a potential procoagulant effect from binding tissue factor, which  
16 could account for an increased rate of thrombosis reported [103]. Thus, if available, adexanet alfa can  
17 be considered for FXa-associated intracerebral haemorrhage, ideally as part of a randomised  
18 controlled trial. Nevertheless, even without the use of a reversal agent, the outcome in patients with  
19 DOAC-related ICH is no worse than that of patients with VKA-ICH in whom anticoagulation is reversed  
20 [105].

21 Because of the early risk of haematoma expansion, anticoagulation is commonly withheld for at least  
22 two weeks after anticoagulant-related ICH even in patients with a strong indication (most often AF).  
23 After this, the decision whether to restart anticoagulation is challenging. A meta-analysis of  
24 observational studies found that resuming anticoagulation reduces the risk of ischaemic stroke  
25 without increasing the risk of haemorrhage [106], with a median time to resumption of 10 – 39 days.  
26 Nationwide observational data from Sweden also suggests benefit from resuming anticoagulation,  
27 estimating the optimal timing to be 7-8 weeks after ICH [107]. Although it is likely that these results  
28 are subject to bias, with lower-risk patients more likely to be selected for resumption of  
29 anticoagulation, this does suggest that at least *some* patients can safely resume anticoagulation.  
30 Several RCTs – including SoSTART, APACHE-AF and PRESTIGE-AF – will provide more definitive  
31 evidence, and an individual patient data meta-analysis is planned through the COCROACH  
32 collaboration. In the interim, we suggest a careful re-evaluation of the bleeding and stroke risks,  
33 including ICH location (as the recurrence risk of lobar haemorrhage is about four times greater than  
34 non-lobar haemorrhage [108]) and MR imaging markers of cerebral amyloid angiopathy [109], careful

1 control of modifiable risk factors, and use of a DOAC in preference to warfarin. We strongly encourage  
2 randomisation of eligible patients into ongoing trials, but left atrial appendage occlusion may  
3 reasonably be considered if the risk of recurrent ICH is judged to be unacceptably high.

#### 4 **7. MANAGEMENT IN SPECIAL CIRCUMSTANCES**

##### 5 **When anticoagulation is contraindicated**

6 In reality, there is no agreement on what constitutes an absolute long-term “contraindication” to oral  
7 anticoagulation but, rather, a spectrum of risk which can change over time. As clinical data indicate  
8 that 90% of all cardiac thrombi in non-rheumatic AF originate from the left atrial appendage (LAA)  
9 [110], exclusion of the left atrial appendage from the circulation offers an alternative strategy for  
10 stroke prevention in patients in whom OAC is thought to be unacceptably high-risk. Surgical excision  
11 of the LAA is undertaken in patients undergoing cardiac surgery (e.g. mitral valve or MAZE procedures)  
12 and is highly unlikely to be offered as an independent intervention purely to reduce stroke risk,  
13 whereas catheter-based left atrial appendage closure devices can achieve minimally invasive LAA  
14 occlusion (LAAO).

15 The Boston Scientific Watchman is FDA approved. In two prospective RCTs comparing the Watchman  
16 to warfarin (PROTECT-AF [111] and PREVAIL [112]), LAAO was not, overall, inferior for the endpoint of  
17 ischaemic stroke and systemic embolism, although there was a higher rate of early, intervention-  
18 related, complications including ischaemic stroke. Ischaemic events after the first 7 days were not  
19 significantly different, but rates of major bleeding and particularly haemorrhagic stroke, were  
20 significantly lower in the LAAO-managed groups. The overall findings persisted over 5-year follow-up,  
21 indicating that the devices are comparable to warfarin in reducing the rate of ischaemic stroke but  
22 with a lower risk of haemorrhage (particularly intracerebral haemorrhage) [113]. The European  
23 Society of Cardiology AF Management guidelines [8] recommend that LAAO be used in high-risk  
24 patients in whom warfarin is contra-indicated (IIb indication, level of evidence B). The recent American  
25 College of Chest Physicians guidelines also suggest LAAO in patients with a strong contraindication to  
26 oral anticoagulation [64].

27 However, these LAAO trials were undertaken in predominantly intermediate risk patients  
28 (CHA<sub>2</sub>DS<sub>2</sub>-VASc 1–2) and excluded patients in whom warfarin was contraindicated. The Watchman  
29 also requires short-term oral anticoagulation, and, based on currently-available data, long-term  
30 antiplatelet therapy. This appears anomalous to the clinical guideline recommendations: it seems  
31 unlikely that many patients with a true contraindication to long-term anticoagulation would tolerate  
32 short-term anticoagulation and long-term antiplatelet therapy [114]. Observational evidence suggests

1 that dual antiplatelet therapy for three to six months in place of anticoagulation may be a safe  
2 alternative, even in patients with previous ICH [115,116]. However, given that long-term single  
3 antiplatelet therapy is still mandated, which arguably has a bleeding risk similar to DOAC therapy  
4 [117], it remains unclear whether LAAO offers a clear benefit over contemporary medical therapy. It  
5 should also be noted that incomplete LAA occlusion may increase thromboembolic risk and so  
6 mandate anticoagulation [114], and that the insertion procedure is not without risk (notably, a roughly  
7 3% risk across PREVAIL and PROTECT-AF of serious pericardial effusion requiring treatment).  
8 Therefore, though LAAO is supported by current international guidelines and is an option that should  
9 be discussed with the cardiologists, the key clinical trials have yet to be performed to demonstrate its  
10 efficacy and safety in moderate- and high-risk patients.

11 There is also interest in whether electrophysiological ablation can reduce ischaemic stroke risk in AF.  
12 We believe this should be viewed as a potential adjunct to anticoagulation, not an alternative, not  
13 least due to the risk of AF recurrence [118]. Although there is observational evidence to suggest  
14 ablation may reduce stroke risk [119], the recent CABANA trial of ablation against medical therapy  
15 (both with anticoagulation) did not meet its primary end-point of a composite of death, disabling  
16 stroke, major bleeding and cardiac arrest in an intention-to-treat analysis [120]. While there was a  
17 high cross-over rate from ablation to medical treatment, and a positive result was obtained in a per  
18 protocol analysis, publication of the detailed results is awaited, and per protocol findings should be  
19 considered hypothesis-generating.

## 20 **Embolic Stroke of Undetermined Source**

21 20–25% of ischaemic strokes remain cryptogenic despite routine investigations, including non-  
22 invasive monitoring. Many of these may be embolic, for instance from low-risk cardiac sources, aortic  
23 arch or non-occlusive carotid plaque, or covert paroxysmal AF [121]. It has been argued that  
24 anticoagulation in these patients might be more effective in reducing stroke risk than an antiplatelet.  
25 The concept of “embolic stroke of undetermined source” (ESUS) as a target for anticoagulation has  
26 been tested in three clinical trials. NAVIGATE ESUS was recently stopped early on the basis of a  
27 planned interim analysis showing an excess of bleeding with rivaroxaban 15mg OD compared to  
28 aspirin, and a low probability of a reduction in stroke risk [122]. RE-SPECT ESUS, with a similar design  
29 using dabigatran, is yet to finally report [123]; however, data presented in abstract form at the World  
30 Stroke Conference in October 2018 reported the rate of recurrent stroke (primary outcome) was 4.1%  
31 per year with dabigatran and 4.8% per year with aspirin (HR 0.85; P = 0.1). The rate of major bleeding  
32 was similar in both arms - 1.7% per year with dabigatran and 1.4% per year with aspirin. ATTICUS will

1 test apixaban in a population enriched for probable cardioembolism, with radiological re-infarction at  
2 12 months as the primary end point [124].

3 As well as the echocardiographic markers (left atrial dilation, spontaneous LAA echo contrast, reduced  
4 LAA flow velocity) used for patient selection in ATTICUS, ECG markers of left atrial function may have  
5 a role in identifying ESUS patients more likely to benefit from anticoagulation. For example, increased  
6 p-wave terminal force, defined as the amplitude of the terminal negative deflection of the p-wave in  
7 lead V1 multiplied by its duration, is a risk factor for cryptogenic or cardioembolic stroke, even in  
8 patients without AF [125]. This lends support to the concept of “left atrial cardiopathy” as an  
9 independent cause of cardioembolic stroke and a potential target for future anticoagulation trials  
10 [44]. However, in the absence of positive trial results, we recommend usual antiplatelet treatment  
11 combined with intensive investigation for established high-risk cardiac sources in patients with  
12 suspected but unproven cardioembolic stroke.

### 13 **Patients with Cardiovascular Comorbidities**

14 Whereas cardio-embolism is most effectively prevented by anticoagulation, atherosclerotic disease  
15 affecting the coronary, cervical or peripheral arteries is usually treated with an antiplatelet, based on  
16 the pathophysiological concept of the ‘red’, fibrin-rich thrombus forming under slow-flow conditions  
17 and the ‘white’, platelet-rich thrombus forming on ulcerated plaque. Arterial disease is common in AF  
18 patients, sometimes prompting dual therapy. Large registry studies indicate that combining warfarin  
19 and an antiplatelet clearly increases bleeding risk [126] without improving cardiovascular outcomes  
20 in patients with coronary or peripheral arterial disease [127,128]. Post-hoc analyses of ROCKET-AF  
21 suggest a similar pattern with rivaroxaban [129]. The distinction between anticoagulation- and  
22 antiplatelet-responsive thrombi is unlikely to be absolute – for instance, both warfarin and  
23 rivaroxaban have shown efficacy in place of an antiplatelet in treating coronary artery disease  
24 [130,131]. Reflecting European Heart Rhythm Association guidelines, in anticoagulated AF patients,  
25 we do not add an antiplatelet for secondary prevention in atherosclerotic disease. In patients with AF  
26 undergoing PCI, triple therapy with dual antiplatelets and a DOAC is generally recommended for 1 to  
27 6 months (based on an assessment of atherothrombotic and bleeding risk), then dual therapy to  
28 complete 12 months, then anticoagulation monotherapy. In patients with severe or symptomatic  
29 carotid stenosis, endarterectomy should be performed in preference to stenting, with the addition of  
30 aspirin immediately before surgery, and for ten days afterwards [89].

31 The findings of the COMPASS trial [131] raise a possible alternative approach to stroke prevention in  
32 AF patients with atherosclerotic comorbidities. The combination of rivaroxaban 2.5mg BD and aspirin  
33 improved cardiovascular outcomes, including ischaemic stroke risk, in a population with stable



1 atherosclerotic cardiovascular disease compared to aspirin alone, whereas rivaroxaban 5mg BD alone  
2 did not. These results may also have implications for AF patients who suffer a recurrent ischaemic  
3 stroke despite therapeutic anticoagulation. However, both rivaroxaban doses used were low  
4 compared to that used for stroke prevention in AF, and very few patients with AF were included  
5 (392/27395). RCT evaluation of such an approach in AF patients with atherosclerotic comorbidities  
6 might be of interest.

## 7 **8. CONCLUSION**

8 As the commonest cardiac arrhythmia and main cause of cardioembolic stroke, a working knowledge  
9 of atrial fibrillation is essential for most practising neurologists and all stroke physicians. The diagnosis  
10 of AF offers an opportunity to greatly reduce the risk of ischaemic stroke through prompt  
11 anticoagulation. The now widely-available DOACs facilitate this, offering fewer practical difficulties  
12 and a lower risk of complications than warfarin. Many apparent contraindications to anticoagulation  
13 do not outweigh its benefits, but left atrial appendage occlusion might be a reasonable alternative in  
14 carefully-selected patient at unacceptably high risk of bleeding on long-term oral anticoagulation. In  
15 patients with cryptogenic stroke, intensive investigation for AF with prolonged ECG monitoring will  
16 diagnose a significant minority with AF, but the stroke risk associated with low-burden paroxysmal AF  
17 is uncertain. In the remainder of patients with suspected but unproven cardioembolism, there is  
18 currently no role for empirical anticoagulation, although further trials are ongoing. Advances in  
19 monitoring technology, the use of biomarkers to refine stroke and bleeding risk assessment, and the  
20 greater availability of DOAC reversal agents, are exciting prospects for improving the care of AF  
21 patients in the near future.

22

### **Box 2: Key Points**

- Atrial fibrillation increases ischaemic stroke risk five-fold and justifies anticoagulation in the vast majority of patients, even those who are old, frail or have had falls.
- DOACs are at least as effective as warfarin and offer a much lower risk of intracranial haemorrhage, so should be preferred for most patients.
- The yield of investigation for AF after stroke is high, and will increase as advanced non-invasive and implanted monitors become more widely available.
- When anticoagulation fails and recurrent ischaemic stroke occurs, thrombolysis may be possible even in patients using DOACs.
- Even after anticoagulant-related ICH, restarting anticoagulation might be beneficial, though LAAO can be considered in patients at very high risk of ICH recurrence.

23

1 **AUTHORSHIP STATEMENT**

2 DW had the idea for the article and developed the outline with JB. JB, RB, MH, AC and DW wrote the  
3 manuscript and are responsible for its content.

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9 **FIGURE LEGENDS**

10 **Figure 1:**

11 MR imaging showing patterns of acute infarction associated with cardioembolism.

12 Top row, from left: diffusion-weighted imaging showing isolated cortical infarct, small wedge-shaped  
13 predominantly cortical infarct, and medium-sized cortico-subcortical infarct; T2 weighted imaging  
14 showing large wedge-shaped infarct with T2 hypointensity indicating haemorrhagic transformation.

15 Bottom row, left to right: PCA territory infarction, scattered cortical and subcortical infarcts within  
16 right MCA territory, striatocapsular infarction with additional small right MCA territory infarcts  
17 (suggesting transient M1 occlusion then fragmentation and distal embolization of thrombus),  
18 scattered bihemispheric lesions.

19 **Figure 2:**

20 Patch and lead monitoring devices (left to right): e-Patch, Zio, CAM, R-test, Apoplex

21 **Figure 3:**

22 The Reveal-LINQ is a small implanted cardiac monitor, inserted subcutaneously in the precordium via  
23 a <1cm incision.

24 **Figure 4:**

25 Cerebral microhaemorrhages and intracerebral haemorrhage. Left to right: small left frontal cortical  
26 infarct demonstrated on DWI in a patient with atrial fibrillation; susceptibility-weighted imaging shows  
27 multiple lobar microhaemorrhages (arrowed); lobar ICH two years after initiation of anticoagulation.

28

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