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Novel oral anticoagulants for stroke prevention in atrial fibrillation: results of the European Heart Rhythm Association survey

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The purpose of this European Heart Rhythm Association (EHRA) survey was to assess clinical practice in relation to stroke prevention in atrial fibrillation (AF), particularly into the use of novel oral anticoagulants (NOACs) for stroke prevention, among members of the EHRA electrophysiology (EP) research network. In this EP Wire survey, we have provided some insights into current practice in Europe for the use of NOACs for stroke prevention in AF. There were clear practice differences evident, and also the need for greater adherence to the guidelines, especially since guideline adherent management results in better outcomes in AF.

Keywords Atrial fibrillation • Anticoagulation • Guidelines • Warfarin • New oral anticoagulants • Apixaban • Dabigatran • Rivaroxaban • Stroke • EP wire • EHRA survey

Introduction

Stroke prevention is central to the management of atrial fibrillation (AF). The 2012 focused update of the European Society of Cardiology guidelines on atrial fibrillation[1] and all contemporary guidelines have directed focus on the use of effective stroke prevention, which is oral anticoagulation therapy—whether delivered as well controlled adjusted dose vitamin K antagonists (VKAs) or one of the novel oral anticoagulants (NOACs).

Most guidelines now recommend that where oral anticoagulation is indicated, the NOACs should be considered instead of VKAs, given the greater efficacy, safety, and convenience of NOACs compared with the VKAs.[2,3] Antiplatelet therapy plays a minimal role, in view of its limited efficacy for stroke prevention, and since the risk of bleeding is not different between aspirin and warfarin.[4–6] In the ESC guidelines, antiplatelet therapy is only recommended for stroke prevention, where patients refuse all forms of anticoagulation, and should be given as aspirin–clopidogrel combination therapy, or—less effectively—aspirin.

In Europe, three NOAC drugs are now licensed, which the oral direct thrombin inhibitor, dabigatran (in its 150 and 110 mg twice a day dose regimes), and the oral Factor Xa inhibitors, rivaroxaban and apixaban. Dabigatran was first licensed in Europe in 2011, and has the longest post-marketing clinical experience, with publication of 'real world' post-marketing data. Many questions and issues with regard to the practical use of NOACs have arisen, and these have been addressed in various consensus guidelines or position statements.[7–9] The European Heart Rhythm Association (EHRA) has recently issued a comprehensive practical guide on the management of AF patients taking NOACs.[10]

The purpose of this electrophysiology (EP) wire survey was to assess the European clinical practice in relation to the use of oral anticoagulants for stroke prevention in AF. We were particularly interested in NOACs as a management strategy.

Methods and results

Participating centres

This survey is based on an electronic questionnaire sent out to the EHRA EP research network participating centres. Responses were received from 45 centres and of these, 66.7% were university

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hospitals, 22.2% private hospitals, and 'others' 11.1%. Most respondents (90.9%) were EP centres, with 75% having a dedicated AF and/or arrhythmia clinic.

Risk stratification for stroke and bleeding

For stroke risk scoring in everyday clinical practice, the main score used was CHA_2DS_2-VASc in 93.2% and $CHADS_2$ in 6.6%. No respondents used other scores, 'clinical judgement' or 'no risk assessment'. For bleeding risk assessment, the HAS-BLED score was used in 86.4% and $HEMORR_2HAGES$ in 2.3%, with 6.8% using 'clinical judgement' and 4.6% reporting 'no bleeding assessment made'. No respondents used the ATRIA, Shireman, or ORBI scores.

Availability and use of oral anticoagulants

For AF patients taking VKAs, the main types used were warfarin (43.18%), acenocoumarol (36.4%), and phencoumarol (13.6%). In patients starting VKAs, 90.6% would perform a counselling session with information on the do's and don't's.

Novel oral anticoagulants were available for most respondents, with dabigatran being available in 90.6%, rivaroxaban in 76.1%, and apixaban in 40.6%. Novel oral anticoagulants were not available in 6.3% and 3.1% reported that 'they do not prescribe NOACs'. Of the latter, the reasons cited were 'too expensive' (38.5%), not available (46.2%), and 'someone else does it for me' (15.4%). None reported that they did not know enough about it.

Table 1 shows survey respondents for AF patients in various clinical categories, with the most common proportions reported as being given VKA, NOAC, aspirin, combination aspirin–clopidogrel therapy, or nothing. In patients with AF who were first referred to the cardiologist, most respondents reported that patients were on VKA (48%) or an NOAC (26%), while 6.9% reported that most patients were on aspirin and 64.5% were on aspirin–clopidogrel. *Table 2* shows survey respondents AF patients who are taking an NOAC, and the most common proportions reported as who were given dabigatran, rivaroxaban, or apixaban.

In established AF patients, i.e. attending clinic for >1 year, 84.4% of the respondents would have >50% on VKA, with 9.7% on an NOAC, and 6.7% on aspirin with only 3.6% on aspirin–clopidogrel. In newly diagnosed paroxymal AF patients, 46.9% reported VKA use in >50% of cases, while 16.1% would be on an NOAC and 10% on aspirin. In established paroxysmal AF patients, 71.9% reported use of VKA in >50%, and 16.7% of NOACs. Aspirin (6.7%) and aspirin–clopidogrel (3.6%) were also used.

Drug preference

When asked if the respondent's institution/department had a preference list (first-line treatment) if anticoagulation therapy is indicated in AF patients, 40.6% reported no preference list, while 59.4% did have one. For the latter, dabigatran had the highest priority score, followed by rivaroxaban, then apixaban (*Table 3*).

When asked whether the knowledge and diversity of improved indications had influenced the choice of NOAC for an individual patient, 84.3% answered 'yes'. In patients already on a VKA, 100% would only swop to an NOAC when there were side effects in VKA, inability to attend for monitoring or poor time in therapeutic range. None reported that they would 'never swop'.

Cardioversion and electrophysiology procedures

In patients undergoing cardioversion, 87.5% of centres reported mainly use of VKAs, while 6.7% used an NOAC. In patients undergoing elective cardioversion, VKA is preferred in 46.9%, while an NOAC in 21.9%, with no preference in 32.3%. In patients on an NOAC undergoing cardioversion, 25% of centres asked their patients to sign an agreement, or to use a dosage box or some kind of reminder to be compliant with taking their drugs.

In those undergoing AF ablation, 73.3% of centres reported use of VKAs, while NOACs were used in 3.5%. In patients on an NOAC undergoing ablation, 12.5% would continue NOAC uninterrupted, while 40.6% would stop NOAC 1–2 days before, bridge with heparin, and restart NOAC after haemostasis. Of note, 26.9% would not use an NOAC for patients undergoing ablation.

In AF patients undergoing pacemaker implantation, VKAs were most commonly reported by 43.8%, with NOACs in 0%.

Acute coronary syndrome and stroke

In AF patients presenting with acute coronary syndrome (ACS), many would commonly (>50%) be on VKA (43.8%), aspirin (30%), or aspirin–clopidogrel (26.7%). In patients with AF requiring a percutaneous coronary intervention/stenting, 50% reported that >50% of their patients were on a VKA, while 36.7% reported aspirin–clopidogrel use.

In patients presenting with an acute stroke, VKA use pre-admission would be evident in ~40% and an NOAC in 7.1%.

Monitoring the anticoagulant effect

For AF patients taking VKA, the main monitoring of anticoagulation, in the majority of cases, was the general practitioner in 36.4%, cardiologist in 34.1%, dedicated anticoagulant clinic in 31.6%, and self-monitoring in 2.27%. No specific anticoagulation monitoring services were in place for 4.6%.

When asked about common blood tests available to measure the anticoagulant effect of various NOACs, 81.2% had the activated partial thromboplastin time (aPTT) available, while 68.8% had the prothrombin time (PT), 37.5% had the Haemoclot (dilute thrombin time), 21.9% had the ecarin clotting time (ECT), and 43.8% had the anti-Factor Xa assay; however, 28.1% were 'not sure' what was available.

Protocols for bleeding or urgent surgery

Only 12.5% of the respondents had a specific protocol for emergency bleeding when the patients were taking NOACs, but none had a specific protocol for emergency surgery; 25% had protocols for both. Of note, 62.5% had no protocols in place for emergency bleeding or urgent surgery for a patient on an NOAC.

When dealing with emergency bleeding or urgent surgery for a patient on an NOAC, 84.3% had access to use of prothrombin complex concentrates (PCCs), 59.3% to recombinant Factor VIIa (rFVIIa), 25% for Factor VIII inhibitor bypassing activity (FEIBA), 90.6% for haemodialysis, and 40.6% to charcoal filtration. Of note, 6.3% did not have any interventions, and would need to be referred elsewhere.

Table 1 Survey respondents for AF patients in various clinical categories, with the most common proportions (%) reported as being given VKA, NOAC, aspirin, aspirin–clopidogrel, or nothing

	% Used in respondent's practice	VKA (%)	NOACs (%)	Aspirin (%)	Aspirin–clopidogrel (%)	Other type of antithrombotic drugs, e.g. dipyridamole, trifusal (%)	No antithrombotic drugs (%)
Newly diagnosed, i.e. first referral to you for management	1–9	3.2	22.6	34.5	32.3	6.7	35.4
	10–19	3.2	19.4	20.7	3.2	3.3	19.4
	20–29	12.9	6.5	3.5	0	0	9.7
	30–49	29.0	9.7	10.3	0	3.3	3.2
	50+	48.4	16.1	6.9	0	0	0
	0	3.2	25.8	24.1	64.5	86.7	32.3
Established patients, i.e. attending clinic >1 year	1–9	0	41.9	46.7	32.1	6.7	35.5
	10–19	3.1	19.3	13.3	3.6	0	3.5
	20–29	0	9.7	6.7	0	0	3.5
	30–49	12.5	9.7	6.7	0	0	0
	50+	84.4	9.7	6.7	3.6	3.5	3.5
	0	0	9.7	20	60.7	82.8	48.3
Paroxysmal AF patients, newly diagnosed	1–9	6.3	32.3	40	30	13.3	36.7
	10–19	6.3	22.6	10	10	0	10
	20–29	21.9	6.5	10	0	0	6.7
	30–49	15.6	9.7	3.3	0	0	0
	50+	46.9	16.1	10	0	0	3.3
	0	3.1	12.9	26.7	60	86.7	43.3
Paroxysmal AF patients established, i.e. attending your clinic already for >1 year	1–9	3.1	40	43.3	37.9	10.3	37.9
	10–19	0	20	16.7	0	0	13.8
	20–29	3.1	3.3	6.7	0	0	0
	30–49	21.9	10	3.3	0	0	0
	50+	71.9	16.7	6.7	3.6	3.5	3.5
	0	0	10	23.3	58.6	86.2	44.8
Patients with AF undergoing cardioversion	1–9	3.1	35.5	32.1	24.1	10.7	17.2
	10–19	0	16.1	7.1	0	0	0
	20–29	3.1	22.6	0	0	0	0
	30–49	3.1	12.9	0	3.5	0	0
	50+	87.5	6.5	0	0	0	0
	0	3.1	6.5	60.7	72.4	89.3	82.7
Patients for ablation	1–9	6.7	41.4	25.9	29.6	14.8	18.5
	10–19	0	0	3.7	0	0	3.7
	20–29	0	13.8	7.4	0	0	0
	30–49	13.3	10.3	7.4	0	0	0
	50+	73.3	3.5	0	0	0	0
	0	3.1	31.0	55.6	70.4	85.2	77.8
Patients undergoing pacemaker implantation (who also have AF)	1–9	6.3	48.3	42.9	35.7	10.7	32.1
	10–19	3.1	9.7	10.7	0	0	3.6
	20–29	0	6.5	0	3.6	0	0
	30–49	3.1	6.5	7.1	7.1	0	3.6
	50+	84.3	9.7	3.6	0	0	0
	0	6.7	19.4	35.7	53.6	86.2	60.7
Patients with AF presenting with an acute coronary syndrome (drugs on admission)	1–9	12.5	30	26.7	33.3	13.8	27.6
	10–19	0	16.7	16.7	10	0	3.5
	20–29	18.8	3.3	13.3	0	0	0
	30–49	12.5	6.7	0	3.3	0	0
	50+	43.8	0	30	26.7	0	0
	0	12.5	43.3	13.3	26.7	86.2	68.9
Patients with AF presenting with an acute stroke (drugs on admission)	1–9	6.7	39.3	32.1	33.3	18.5	14.3
	10–19	23.3	7.1	14.3	11.1	0	10.7
	20–29	3.3	7.1	14.3	7.4	0	3.6
	30–49	10	3.6	3.6	0	0	7.1
	50+	40	7.1	3.6	0	0	3.6
	0	12.5	35.7	32.1	48.2	81.5	60.7

Continued

Table 1 *Continued*

	% Used in respondent's practice	VKA (%)	NOACs (%)	Aspirin (%)	Aspirin–clopidogrel (%)	Other type of antithrombotic drugs, e.g. dipyridamole, trifusal (%)	No antithrombotic drugs (%)
Patients with AF requiring a percutaneous coronary intervention/ stenting (drugs on admission)	1–9	9.4	43.3	26.7	23.3	10	23.3
	10–19	9.4	10	16.7	3.3	0	3.3
	20–29	6.3	6.7	10	6.7	0	0
	30–49	12.5	3.3	6.7	10	0	3.3
	50+	50	0	16.7	36.7	0	0
	0	12.5	36.7	23.3	20	90	70

Discussion

In this EP Wire survey, we have provided some insights into current practice in Europe for the use of NOACs for stroke prevention in AF, although the low response rate is a limitation. There were clear practice differences evident, and also the need for greater adherence to the guidelines, especially since guideline adherent management results in better outcomes.[11,12]

Risk stratification

For stroke risk scoring in everyday clinical practice, the main score used was CHA_2DS_2-VASc score,[13] with the older $CHADS_2$ score used in 6.6%. No respondents used other scores, many of which are based on complex-weighted formulae derived from multivariate analyses.[14] Furthermore, the 2012 ESC guideline recommended a clinical practice shift so that the initial decision step should be the identification of 'truly low risk patients' (i.e. age <65 and lone AF, or a CHA_2DS_2-VASc score $= 0$), who do not need any antithrombotic therapy.[1] Following this step, effective stroke prevention (which is oral anticoagulation) can be offered to AF patients with ≥ 1 stroke risk factors.

For bleeding risk assessment, the HAS-BLED score[15] was used in the majority (86.4%) and the more complex $HEMORR_2HAGES$ only in 2.3%. The HAS-BLED score has been well validated in multiple independent cohorts, where it has been shown to have better predictive value than other old (and new) scores, and to be predictive of major bleeding on warfarin, non-warfarin oral anticoagulation agents, aspirin, and no-therapy patients, whether AF or non-AF.[14,16] Interestingly, 6.8% of the respondents used 'clinical judgement' and 4.6% reported 'no bleeding assessment made'.

In patients with AF who were first referred to the cardiologist, most respondents reported that patients were on oral anticoagulation, whether a VKA or an NOAC. However, a reasonable minority reported that most patients were on aspirin or aspirin–clopidogrel, which are inferior to oral anticoagulation for stroke prevention, and may not be any safer in terms of major bleeding or intracranial haemorrhage risk. For established AF patients (including paroxysmal AF patients), i.e. attending clinic for >1 year, more respondents would have patients on an oral anticoagulant. It is important to re-emphasize that patients with paroxysmal AF still represent a risk for stroke, especially in the presence of stroke risk factors.

Monitoring of anticoagulation

For AF patients taking VKA, the main monitoring of anticoagulation, in the majority of cases was the general practitioner, cardiologist, or dedicated anticoagulant clinic. Patient self-monitoring was only evident in 2.27%, despite evidence that such patients do as good as (and possibly better) than hospital services.[17] Reassuringly, for patients starting VKAs, most would perform a counselling session with information on the 'do's and don't's', given that educational efforts result in better outcomes in relation to anticoagulation control. The European Heart Rhythm Association has recently established an information website for AF, particularly focused on patients, their carers, and clinicians looking after these patients (www.afibmatters.org).

Cardioversion and electrophysiology procedures for atrial fibrillation

In patients undergoing cardioversion, most reported use of VKAs, while a minority used an NOAC. The largest published series of cardioversions while on an NOAC is with dabigatran,[18] although smaller series with apixaban and rivaroxaban have been published.[19] In patients on an NOAC undergoing cardioversion, 25% of the respondents asked their patients to sign an agreement, or to use a dosage box or some kind of reminder to be compliant with their drugs. This is an important practice point, given that poor compliance with an NOAC and missed doses may lead to the patient being at risk of stroke and thromboembolism, given the moderate half-life of these drugs.

In those undergoing AF ablation, most reported use of VKAs, while NOACs were used in the minority. In the latter patients on an NOAC undergoing ablation, some would continue NOAC uninterrupted, while most responders would stop NOAC 1–2 days before, bridge with heparin, and restart NOAC after haemostasis. The latter would be consistent with the EHRA practical guide[10] and recent reassuring observational data on ablation while on NOACs.[20,21] Given the initial concerns of increased bleeding, an important proportion of centres (26.9%) would not use an NOAC for patients undergoing ablation. In AF, patients undergoing pacemaker implantation, VKAs were most commonly reported by 43.8%, with NOACs in 0%.

Acute coronary syndrome and atrial fibrillation

In AF patients presenting with an ACS, many would be on a VKA, and the management of such patients is complex, requiring a balance

Table 2 Survey respondents AF patients who are taking an NOAC, and the most common proportions (%) reported as who are given dabigatran, rivaroxaban, or apixaban

	% Used in respondent's practice	Dabigatran, 150 mg bid (%)	Dabigatran, 110 mg bid (%)	Rivaroxaban, 20 mg od (%)	Rivaroxaban, 15 mg od (%)	Apixaban, 5 mg bid (%)	Apixaban, 2.5 mg bid (%)
Overall use	0	16.1	9.7	38.7	43.3	81.3	84.4
	1–9	9.7	25.8	12.9	36.7	9.4	12.5
	10–19	6.5	19.4	6.5	16.7	6.3	3.1
	20–29	12.9	19.4	22.6	3.3	0	0
	30–39	12.9	6.5	3.2	0	0	0
	40–49	16.1	6.5	3.2	0	3.1	0
	50*	25.8	12.9	12.9	0	0	0
Elderly patients, age >80	0	63.3	16.7	65.5	37.9	89.7	82.8
	1–9	20.0	20	10.3	10.3	10.3	10/3
	10–19	6.7	6.7	6.9	10.3	0	3.5
	20–29	0	6.7	6.9	17.2	0	0
	30–39	6.7	6.7	10.3	6.9	0	0
	40–49	3.3	13.3	0	6.9	0	3.5
	50*	0	30	0	10.3	0	0
Patients with moderate renal impairment, e.g. creatinine clearance 30–49 mL/min	0	86.7	30	75.9	37.9	89.3	82.1
	1–9	3.3	16.7	10.3	13.8	3.6	7.1
	10–19	3.3	10	0	10.3	3.6	7.1
	20–29	3.3	6.7	06.9	13.8	3.6	0
	30–39	0	3.3	6.9	6.9	0	0
	40–49	0	3.3	0	0	0	3.6
	50*	3.3	30	0	17.2	0	0
Patients with prior coronary artery disease (e.g. MI, stent etc.)	0	46.7	30	40.4	46.4	78.6	82.1
	1–9	10	20	14.3	25	14.3	14.3
	10–19	6.7	23.3	7.1	10.7	0	3.6
	20–29	6.7	10	7.1	14.3	0	0
	30–39	16.7	3.3	10.7	0	0	0
	40–49	10	0	3.6	0	3.6	0
	50*	3.3	13.3	10.7	10.7	3.6	0
Patients on verapamil	0	70	43.3	57.1	60.7	85.2	85.2
	1–9	16.7	23.3	7.1	25	3.7	3.7
	10–19	6.7	23.3	0	14.3	7.4	3.7
	20–29	3.3	0	10.7	0	0	0
	30–39	3.3	0	7.1	0	0	3.7
	40–49	0	3.3	0	0	3.7	3.7
	50*	0	6.7	17.9	0	0	0
Patients undergoing cardioversion	0	20	20	75.1		82.1	85.7
	1–9	10	23.3	3.6		14.3	14.3
	10–19	6.7	23.3	10.7		3.6	0
	20–29	3.3	10	7.1		0	0
	30–39	13.3	0	10.7		0	0
	40–49	6.7	13.3	0		0	0
	50*	40	10	10.7		0	0

bid, twice a day; od, once daily.

Table 3 Priority ranking on departmental preference list for use of NOACs and VKAs in Europe

	Rivaroxaban (%)	Dabigatran (%)	Apixaban (%)	Warfarin (%)
1 (highest)	7.7	21.4	0	73.3
2	15.4	71.4	8.3	6.7
3	69.2	7.1	16.7	6.7
4 (lowest)	7.7	0	75	13.3

between stroke prevention, recurrent cardiac ischaemic, prevention of stent thrombosis, and the potential risk of major bleeding.[22,23] When antiplatelet therapy is added to any oral anticoagulant, the risk of bleeding is increased. However, it is possible that antiplatelet therapy in combination with a lower dose NOAC may have less major bleeding, with no loss of efficacy.[24,25] Recent studies even suggest that aspirin may not be mandatory and such patients could potentially be managed with oral anticoagulation plus clopidogrel.[26,27] Concerns with the numerical difference in myocardial infarctions has resulted in a small preference to non-use of dabigatran in AF patients with an ACS but reassuring data from real-world post-marketing data,[28] as well as a careful analysis of the RE-LY (Randomized Evaluation of Long-term anticoagulant therapY) dataset shows how the magnitude of gain from stroke prevention reduced serious bleeding, and cardiovascular mortality far outweighs the non-significant numerical difference in myocardial infarction rates with dabigatran compared with warfarin.[29]

Acute stroke and atrial fibrillation

In AF patients presenting with an acute stroke, VKA use pre-admission was probably suboptimal, with many patients on antiplatelet therapy. Such patients represent a loss opportunity for stroke prevention, and are consistent with numerous studies where even high-risk AF patients are suboptimally treated.[30]

Availability and costs of novel oral anticoagulants

It was reassuring to note that NOACs were available for most respondents, with dabigatran being the most commonly available in 90.6%, with rivaroxaban in 76.1%, and apixaban in 40.6%. Of the reasons cited why NOACs were not prescribed, it was because they were 'too expensive' or not available. The cost-effectiveness of the NOACs have been well-established in multiple studies.[31,32] When asked if the respondent's institution/department had a preference list (first-line treatment) if anticoagulation therapy is indicated in AF patients, 40.6% reported no preference list. Of note, greater knowledge and diversity of improved indications with an agent influences the choice of NOAC for an individual patient, in most (84.3%) cases. In patients already on a VKA, 100% would only swop to an NOAC when there were side effects in VKA, inability to attend for monitoring, or poor time in therapeutic range, consistent with the 2012 ESC guidelines. One challenge is perhaps how to identify those patients who could potentially do well on warfarin, with a high percentage time in therapeutic range. The SAMe-TT_2R_2 score could help here, by predicting those who could do well on warfarin (SAMe-TT_2R_2 score 0–1) or those who are likely to have poor anticoagulation control if warfarin is used (SAMe-TT_2R_2 score $\geq$2), where an NOAC could be a better option.[33]

Measurement of the anticoagulant effect and bleeding management of novel oral anticoagulants

When asked about common blood tests available to measure the anticoagulant effect of various NOACs, most had the aPTT or PT available, which could be used to assess a patient on dabigatran or rivaroxaban, respectively.[8,9] Smaller proportions reported the availability of the Haemoclot, ECT, or anti-Factor Xa assay, and these tests may not provide a rapid immediate result in an urgent situation, when we are keen to know whether or not a patient is systematically anticoagulated. Of concern, the majority of respondents (62.5%) had no protocols in place for emergency bleeding or urgent surgery for a patient on an NOAC. However, most centres had access to use of non-specific reversal agents, such as PCCs (84.3%), rFVIIa, or for FEIBA.[34] For dabigatran patients, most centres had access to facilities for haemodialysis (90.6%) or charcoal filtration.

Conclusions

This EP Wire survey reaffirms some aspects of the ESC guidelines being considered in centres responding to this survey. Reassuring information on current practice in Europe for the use of NOACs for stroke prevention in AF is evident, although VKA use still remains dominant in some clinical scenarios.

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