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INDEXING/ABSTRACTING

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Empirical anticoagulation for patients in sinus rhythm at high risk of ischaemic stroke: A review of current literature

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Abstract

Ischaemic stroke is one of the commonest causes of morbidity and mortality worldwide and around a fifth of events can be attributed to a cardioembolic source. This is typically due to atrial fibrillation (AF), the most common sustained cardiac arrhythmia. However, AF can, at times, be difficult to detect due to a relative lack of symptoms and the fact that it can be paroxysmal in nature. Studies have shown that diagnosis of AF improves as the length of cardiac monitoring increases. However, prolonged cardiac monitoring is not a cost-effective way of diagnosing AF. Therefore, an alternative approach may be to empirically anticoagulate individuals who are at high risk of stroke. This article summarises current evidence surrounding stroke risk prediction, the use of anticoagulation in the secondary prevention of stroke and its use in the primary prevention of stroke in high risk groups with the aim of determining whether empirical anticoagulation is a safe and effective strategy.

Key words: Anticoagulation; Ischaemic stroke; Atrial fibrillation; CHA2DS2VASc; CHADS-2; Heart failure; Coronary artery disease; Peripheral arterial disease

Core tip: This is a contemporary review exploring issues related to the risk of stroke and use of anticoagulation in patients who are in sinus rhythm (SR). It examines the prediction of stroke in patients without known atrial fibrillation (AF), the identification of AF in patients following stroke and the use of anticoagulation in post-stroke patients seemingly in SR or those at high-risk of stroke. The main findings are: (1) prolonged cardiac monitoring increases the rate of AF diagnosis but is not cost-effective; (2) current risk stratification schemes such as CHA2DS2VASc can identify those in sinus rhythm who are at risk of stroke; and (3) further research is required to determine whether individuals at high-risk of stroke would benefit from anticoagulation.

INTRODUCTION

Ischaemic stroke is a leading cause of morbidity and mortality worldwide[1] and, following a first event, around a quarter of patients will go on to have a recurrent stroke[2,3]. Atrial fibrillation (AF), a common cause of stroke, is the most common sustained cardiac arrhythmia with an estimated prevalence approximately 3% in adults aged 20 years or older[4], a figure that is expected to double over the next 50 years[5]. This arrhythmia carries a five-fold risk of stroke and patients who experience an AF-related stroke often suffer the most severe forms of the condition[6].

Risk scores such as CHADS-2 and, more recently, CHA2DS2VASc have been developed in order to identify those patients with AF and an increased risk of stroke who would potentially benefit from anticoagulation. However, these risk scores are currently used only in patients with a confirmed diagnosis of AF, a condition which is underdiagnosed due to the fact it can be asymptomatic and paroxysmal. Therefore, given that 45% of all AF-related strokes occur in patients with previously undetected AF[7], many more patients could potentially benefit from empirical anticoagulation therapy and there may be a role for using these risk scores in patients without known AF but with risk factors for developing stroke.

In view of the fact that AF can be difficult to detect, a number of studies have attempted to determine whether it is appropriate to give empirical anticoagulation to patients in sinus rhythm (SR) with risk factors for stroke. This article aims to summarise these studies and determine whether there are clinically relevant scenarios where anticoagulating patients in SR may be appropriate to reduce their risk of stroke.

LITERATURE SEARCH AND METHOD

A Medline and Embase search was performed in August 2016 using the following terms: CHADS-2, CHA2DS2VASc, anticoagulation, vitamin K antagonist, warfarin, Coumadin, novel oral anticoagulant, direct oral anticoagulant, apixaban, eliquis, dabigatran, pradaxa, rivaroxaban, xarelto, edoxaban, lixiana, sinus rhythm, non-atrial fibrillation, normal heart rhythm, "without atrial fibrillation", stroke, cerebrovascular accident, cerebrovascular event, transient ischaemic attack (TIA), mini-stroke, heart failure, cardiac failure, left ventricular failure, left ventricular impairment, left ventricular dysfunction, impaired ventricle, coronary artery disease, coronary heart disease, myocardial ischaemia, myocardial infarction, acute coronary syndrome, peripheral arterial disease and peripheral vascular disease.

STROKE RISK PREDICTION IN A GENERAL POPULATION WITHOUT AF

In patients without known AF, risk assessment tools currently focus on overall cardiovascular risk rather than determining their specific risk of stroke. However, could risk scores such as CHADS-2 and CHA2DS2VASc be used within this patient group to determine their cerebrovascular event risk?

An analysis of the Chin-Shan Community Cohort Study tested a number of risk stratification schemes which are currently used to predict thromboembolic risk in AF, including CHADS-2 and CHA2DS2VASc, in a Chinese population without known AF[8]. This showed a modest predictive value of these risk stratification schemes in predicting stroke in non-AF patients with a C-statistic value ranging from 0.658 to 0.728, values which were broadly similar to those seen in an exploratory analysis of patients with AF within the same community.

Similar results were found in a meta-analysis performed by Santos et al who examined the use of the CHADS-2 score at predicting cerebrovascular events[9]. They found that CHADS-2 was able to identify patients at risk of stroke, regardless of whether AF was present or not.

More recently, Saliba *et al*[10] assessed the performance of CHADS-2 and CHA2DS2VASc within a large Israeli population over a three year follow-up period. In individuals without AF, the C-statistic values were 0.718 and 0.714 for CHADS-2 and CHA2DS2VASc respectively and in individuals with AF, the C-statistic values were 0.606 and 0.610 respectively. The authors concluded that these risk tools had a relatively high performance at predicting thromboembolism in patients without AF.

In all of these studies, the results suggest that current risk stratification schemes used in AF patients to predict thromboembolism could also be used in patients without AF as a screening tool to predict their risk of stroke. It remains unclear, however, as to whether anticoagulating these patients is a superior strategy to giving antiplatelet therapy.

SECONDARY PREVENTION OF ISCHAEMIC STROKE/TIA

Around a fifth of ischaemic strokes are cardioembolic in origin[11] and these patients typically receive oral anticoagulants to reduce their risk of future events. However, around a third of ischaemic strokes are termed cryptogenic[12], or without an attributable cause despite extensive work-up. The majority of these cases are likely to have an embolic mechanism and a significant proportion are likely to be related to undiagnosed AF.

Table 1 Randomised control trials which show an increased yield of atrial fibrillation detection with extended cardiac monitoring

Ref.	Design	No. of patients	Inclusion/exclusion criteria	Type of monitoring	Outcome	Comments
Higgins *et al*[14] (2013)	RCT	100	Inclusion: Ischaemic stroke within 7 d; Exclusion: History of AF	7-d event recorder *vs* 24-h ECG (control)	Detection of AF: Sustained (> 20 s) and non-sustained (minimum 6 beats)	Sustained AF detected in 18% (control 2%); Non-sustained AF in 44% (control 4%)
Gladstone *et al*[15] (2014)	RCT	572	Inclusion: Cryptogenic stroke, Age ≥ 55 yr; Exclusion: History of AF	30-d triggered event recorder *vs* 24-h ECG (control)	Detection of AF (> 30 s)	AF detected in 16.1% (control 3.2%)
Sanna *et al*[16] (2014) Brachmann *et al*[17] (2016)	RCT	441	Inclusion: Cryptogenic stroke, Age ≥ 40 yr; Exclusion: History of AF (including 24-h ECG)	Insertable cardiac monitor *vs* Standard care (control)	Detection of AF (> 30 s)	At 6 mo, AF detected in 8.9% (control 1.4%) At 12 mo, AF detected in 12.4% (control 2.0%) At 36 mo, AF detected in 30% (control 3.0%)

AF: Atrial fibrillation; RCT: Randomized controlled trial.

Ziegler *et al*[13] analysed data from patients at risk of thromboembolism (stroke/TIA) who had implantable cardiac devices capable of recording atrial arrhythmias. They identified newly detected episodes of atrial fibrillation/tachycardia in 28% of patients over a 1-year follow-up period.

Multiple studies have shown that the yield of detecting AF increases as the length of ambulatory monitoring increases (Table 1)[14-17]. A systematic review and meta-analysis performed by Dussault et al assessed the relationship between the duration of ECG monitoring and the incidence of AF detection in patients who had suffered a cerebrovascular event, using data from 31 studies[18]. They found that extending monitoring from 24 h to 30 d improved AF detection from 4.38% to 15.2% and if this monitoring was extended out to 180 d, detection rates increased to 29.15%.

Studies have also shown that in patients with implantable electronic devices, asymptomatic episodes of AF can be associated with an increased risk of thromboembolic events[19-25], with a hazard ratio ranging from 2.2 to 9.4[26]. The length of each episode that is required to increase overall stroke risk varies in these studies, from a minimum of 5 min in the Ancillary MOde Selection Trial[19] to a maximum of 24 h in the Italian AT500 Registry[20]. At present, the episode duration and burden of asymptomatic AF that best predict future thromboembolic events are still matters of debate and need to be addressed by future studies.

A more recent systematic review performed by the Canadian Agency for Drugs and Technologies in Health examined not only the clinical effectiveness of cardiac monitoring in patients who had recently experienced a stroke or TIA, but also the cost effectiveness[27]. They showed that there was a substantial increase in the detection of AF when monitoring was performed for more than 24 h. Monitoring beyond 30 d increased this detection further although these improvements were modest. From an economic point of view, they

concluded that in patients who were admitted with a cerebrovascular event and did not receive in-patient continuous cardiac monitoring, 7 d cardiac monitoring was likely to identify significantly more cases of AF compared with current 24 h monitoring, with an acceptable increase in cost [CAN$ 50000-80000/QALY (£ 28000-46000/QALY) gained]. Cost-effectiveness could be improved further by targeting stroke survivors who were relatively healthy and in whom there was a higher suspicion of underlying AF. However, they also concluded that extending monitoring beyond 7 d was unlikely to be cost-effective [> CAN$ 85000/QALY (>£ 49000/QALY) gained].

Current guidance continues to recommend long-term cardiac monitoring in patients who have a stroke with an undiagnosed cause with the AHA/ACC/HRS specifying at least 30 d. In view of the fact that this may not be cost-effective, would it be more appropriate to use current risk stratification schemes to identify those patients who may be at risk of further cerebrovascular events?

A trial by Ntaios *et al*[28] examined whether CHADS-2 and CHA2DS2VASc scores could be used to predict long-term outcomes in non-AF stroke patients. They divided patients into low, intermediate or high risk sub-groups, dependent upon their pre-stroke CHADS-2 and CHA2DS2VASc score. In both the CHADS-2 and CHA2DS2VASc sub-groups, they found that there were significant differences in stroke recurrence, cardiovascular events and 5-year mortality. They also demonstrated that compared with the low-risk sub-group, patients in the high-risk sub-group had a higher risk of stroke recurrence [CHADS-2, hazard ratio (HR): 1.71; CHA2DS2VASc, HR: 2.93]. These results suggest that current clinical risk scores can be used to predict future events in patients who have had a stroke or TIA.

To improve the accuracy of these risks scores in post-stroke patients further, modification of certain variables may be helpful. Thijs *et al*[29] assessed

patients who had suffered a cryptogenic stroke or TIA and had an insertable cardiac monitor to determine whether there were specific factors which could predict the development of AF in this population. Following multivariate analysis, they found that increasing age [HR per decade 1.9 (1.3-2.8), *P* = 0.0009] and PR interval prolongation [HR per 10 ms: 1.3 (1.2-1.4), *P* < 0.0001] were independently associated with an increased incidence of AF. Therefore, in non-AF stroke/TIA patients, the addition of PR interval duration and placing further emphasis on age may help improve the accuracy of current risk scores.

Nevertheless, despite the fact that CHADS-2 and CHA$_2$DS$_2$VASc may help to predict future events in non-AF stroke/TIA patients, more evidence is required to determine whether those within an intermediate or high-risk group should be offered anticoagulation.

PRIMARY PREVENTION OF ISCHAEMIC STROKE/TIA IN SPECIFIC GROUPS

Heart failure
It has long been established that heart failure (HF) is associated with an increased risk of thromboembolism and in particular, stroke. A systematic review performed by Witt et al analysed stroke rates in heart failure patients and found the risk of stroke to be 1.8% in the first year of HF diagnosis, rising to 4.7% at 5 years[30]. Multiple studies have attempted to clarify whether HF patients in SR would benefit from anticoagulant therapy. Initial trials suffered from poor recruitment and underpowered results and so it is not surprising that they failed to demonstrate an overall benefit of anticoagulation in this population[31-33]. One of these studies, the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial, did however show a significant reduction in non-fatal ischaemic strokes in patients on warfarin compared with aspirin or clopidogrel (*P* < 0.01)[33]. This was at the expense of a higher rate of major bleeding events.

More recently, the Warfarin *vs* Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial compared warfarin and aspirin in patients with HF in SR, using the primary endpoints of ischaemic stroke, intracerebral haemorrhage or death from any cause[34]. Although there was no overall difference in the combined primary endpoints between the two treatments (*P* = 0.4), warfarin was associated with a significant reduction in the rate of ischaemic stroke (2.5% *vs* 4.7%, *P* = 0.005) without a significant difference in the rate of intracerebral or intracranial haemorrhage (*P* = 0.82). Once again, the rate of major bleeding was higher (warfarin 5.8% *vs* aspirin 2.7%, *P* <0.001).

One limitation of the WARCEF study was the time in therapeutic range (TTR) among patients in the warfarin group which was relatively low at 63% (high-quality warfarin treatment is defined as a TTR > 70%[35]). Low TTRs are strongly associated with adverse outcomes

such as major haemorrhage and thromboembolic events[35]. The higher bleeding risk with warfarin may, in part, be related to this low TTR. One solution to this could be use of direct oral anticoagulants (DOACs) which, in the absence of compliance issues, provide a much more consistent level of therapeutic anticoagulation. DOACs have already been shown to be non-inferior, and in some cases, superior to warfarin with respect to stroke and major bleeding risk reduction[36-39]. Further research exploring the use of DOACs in HF patients is needed to determine whether they can reduce thromboembolic risk without significantly increasing bleeding risk.

In terms of estimating stroke risk within HF patients without AF, current clinical risk scores have been assessed. A recent prospective cohort study investigated whether CHA$_2$DS$_2$VASc could be used to predict the risk of ischaemic stroke in HF patients without AF[40]. It performed moderately at predicting ischaemic stroke at 1- and 5-year follow-up (C-statistics 0.67 and 0.69 respectively) and performed well at identifying those at low risk of ischaemic stroke with a negative predictive value of 92%. Additionally, the authors found that those with a CHA$_2$DS$_2$-VASc score of $\geqslant$ 2 had a stroke risk of > 1% per year. To put this into context, patients with AF are typically offered anticoagulation once their annual stroke risk exceeds 1%. This would suggest that the CHA$_2$DS$_2$-VASc score may have a use in identifying those HF patients without AF who at risk of stroke. Whether these patients would gain benefit from anticoagulation remains to be seen and clinical trials are needed to clarify this.

Coronary artery disease
Coronary artery disease (CAD) has been identified as an independent risk factor for stroke[41] and co-existent vascular disease, such as coronary or peripheral artery disease, is present in around 40% of stroke patients[42]. Studies have previously examined the addition of warfarin to antiplatelet therapy in patients with acute coronary syndrome (ACS). These were performed in an era before the widespread use of dual antiplatelet therapy. A meta-analysis of the studies found that the addition of warfarin led to reduction in major adverse cardiovascular events {MACE: death, non-fatal MI, non-fatal ischaemic stroke; [OR = 0.73 (0.63-0.84), *P* < 0.0001]} but this was at the expense of an increased risk of major bleeding [OR 2.32 (1.63-3.29), *P* < 0.00001][43]. As a result, anticoagulation is not routinely given to patients following ACS. However, a proportion of these patients will be at significant risk of thromboembolic events and if a clinical risk score could accurately identify this sub-group, they might well benefit from anticoagulation.

A prospective registry study by Mitchell *et al*[44] assessed the accuracy of CHADS-2 and CHA$_2$DS$_2$VASc at predicting cerebrovascular events in non-AF patients who had suffered an ACS. They found that the incidence of stroke increased with increases in each risk score and

that a CHADS-2 score $\geq$ 3 or a CHA₂DS₂VASc score $\geq$ 4 was associated with an annual stroke incidence of $\geq$ 1%. Both CHADS-2 and CHA₂DS₂VASc performed moderately at predicting ischaemic stroke [C-Statistics (0.68 and 0.71 respectively)].

Similar results were found in a prospective cohort study which assessed the accuracy of CHADS-2 at predicting cerebrovascular events in non-AF patients who had stable CAD[45]. Those with a CHADS-2 score of 2-3 had a 2.7 times higher rate of stroke and those with a CHADS-2 score of 4-6 had a 4.6 times higher rate of stroke. They concluded that stable CAD patients with a CHADS-2 score of 5-6 had a comparable stroke rate to AF patients with a CHADS-2 score of 2-3, the level at which anticoagulation is felt to be beneficial.

In both of these studies, cerebrovascular events occurred despite antiplatelet therapy. They indicate that in patients with CAD, high CHADS-2 or CHA₂DS₂VASc scores can predict those at risk of stroke or TIA. These patients may therefore benefit from the addition of anticoagulation and further studies are required to clarify this.

Peripheral arterial disease

The presence of peripheral arterial disease (PAD) is a significant predictor of stroke and in one study was found to be present in 14.4% of major ischaemic strokes and 8.9% of minor ischaemic strokes[46]. Warfarin has also been evaluated for the use in this patient group. A meta-analysis which assessed the use of anticoagulation in PAD patients provided inconclusive results[47] and led to the development of the Warfarin Antiplatelet Vascular Evaluation (WAVE) Trial[48]. This compared oral anticoagulation plus antiplatelet therapy *vs* antiplatelet therapy alone. They found no significant difference in MACE events (relative risk: 0.92; 95%CI: 0.73-1.16; *P* = 0.48). However, those receiving combination therapy had a significantly higher rate of major bleeding rate (4.0%), compared with in those receiving antiplatelet monotherapy (1.2%). There is some evidence that patients undergoing vein graft bypass surgery gain benefit from warfarin monotherapy[49] and this is the only sub-group of PAD patients in which anticoagulation is currently indicated.

To date, there is only one trial which has examined the use of clinical risk scores to predict thromboembolic events in patients with PAD. Yang *et al*[50] assessed the accuracy of CHADS-2 and CHA₂DS₂VASc in predicting 5-year cumulative ischaemic stroke risk in PAD patients. They found that each increase in the risk scores led to an increased stroke risk, and both scores performed well at predicting 5-year cerebrovascular events (C-statistics 0.92 for CHADS-2, 0.862 for CHA₂DS₂VASc). In multivariate analysis, each increment of the CHADS-2 or CHA₂DS₂VASc score was associated with around a three-fold increase in stroke risk.

As with CAD, current risk scores appear to be able to identify those PAD patients who are at high-risk of cerebrovascular events and this sub-group may also

benefit from anticoagulation therapy. More clinical evidence is required to confirm this.

CONCLUSION

Cerebrovascular disease remains one of the leading causes of death throughout the world. Those that survive are commonly left with serious long-term disability and are at an increased risk of recurrent events. AF is a common cause of stroke/TIA but because the arrhythmia can be paroxysmal and asymptomatic, it remains a challenge to detect. Long-term ambulatory monitoring has not been shown to be a cost-effective way of diagnosing the arrhythmia. Additionally, the duration of AF which represents an increased risk of thromboembolism is still to be determined.

An alternative strategy is to use current risk stratification schemes such as CHADS-2 or CHA₂DS₂VASc. There is evidence to suggest that these scores can identify those at significant risk of thromboembolic events, not only in the general population but more specifically in those that have suffered a cerebrovascular event or have co-existent HF, CAD or PAD.

At present, it remains unclear as to the most appropriate way of treating these high-risk patients once they have been identified. With the dawn of DOACs, which can provide a more steady-state of anticoagulation and potentially have a better bleeding profile, there are now therapeutic options which may benefit high-risk groups. Future trials should use risk scores to identify high-risk groups in a variety of clinical settings to determine whether anticoagulation therapy can reduce the burden of cerebrovascular disease.

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