

# Sub-optimal oral anticoagulant treatment in patients with atrial fibrillation and the effect of study setting on clinical event rates: a systematic review

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## Abstract

**Background:** Anticoagulation therapy for stroke prevention in patients with atrial fibrillation (AF) is often suboptimal. This study evaluated the receipt of anticoagulation in eligible high-risk patients. Clinical event rates associated with oral anticoagulant (OAC) therapy from observational studies and randomized clinical trials (RCTs) were also analyzed.

**Methods:** Literature searches identified 98 studies (1997–2008)\* on current treatment practice for stroke prevention in patients with AF, and a further 53 on clinical event rates (stroke, transient ischaemic attack (TIA), embolism, bleeding). Percentages of patients eligible for OAC therapy due to prior stroke/TIA, or a high-risk CHADS<sub>2</sub> score (≥ 2) were compared with those receiving prophylaxis.

**Results:** Of 50 studies that reported both risk level and patients treated, most showed underuse of OAC therapy. Treatment levels ranged from 19% to 81.3% for AF patients with prior stroke/TIA (Table). Subjects with CHADS<sub>2</sub> score of 2 were also suboptimally treated, levels ranged from 39% to 70%, although one study reached 92.3%. Analysis showed higher stroke rates in hospital/general practice settings compared with anticoagulation clinics or RCTs; little difference was seen in major bleeding rates (Table).

**Conclusions:** Low levels of OAC therapy, and variation in event rates across settings, were observed. This indicates the need for improved management of patients with AF to prevent stroke in clinical practice.

### Literature review: OAC treatment levels and adverse events associated with OAC therapy by study setting

OAC therapy use (patients with AF)	# of studies	% patients treated
Stroke/TIA	27	56.3%
Other high-risk criteria	13	36.2%
Other high-risk criteria	7	23.4%
Ischaemic stroke (setting)	19	Rates (per 100 person-years)
General practice and 10		1.2–3.4
Anticoagulation clinic	3	0.5–1.2
RCT	6	0.1–1.63
Major bleeding (setting)	24	Rates (per 100 person-years)
General practice and 9		0.51–7.35
Anticoagulation clinic	6	0.8–2.1
RCT	9	0.4–1

\*Analysis was expanded to included papers from 1997–2008; values have been updated to reflect this

## Introduction

Atrial fibrillation (AF) is associated with substantial mortality and morbidity from stroke and thromboembolism<sup>1</sup>. AF incidence in the general population ranges from 0.85 to 4.1 per 1,000 person-years,<sup>2,4</sup> and increases dramatically with age.<sup>5</sup> Due to the overall ageing of western populations, AF is projected to affect between 5.6 and 15.9 million people in the US by 2050.<sup>3</sup> AF predisposes patients to the development of atrial thrombi and is associated with a 4- to 5-fold increase in the risk of stroke.<sup>6</sup>

According to international treatment guidelines, AF patients at high risk for stroke should receive oral anticoagulation (OAC) therapy.<sup>7-11</sup> However, despite the availability of effective prophylaxis (warfarin), patients with AF who are at high risk for stroke are often under-treated.

This study systematically reviews the literature to evaluate the gap between current practices for stroke prevention in AF and guidelines for prophylaxis.

Secondly, whether the results of randomized clinical trials (RCT) reflect 'real life' clinical practice with regard to anticoagulation for stroke prevention in AF is open to debate.

A systematic review performed 10 years ago examining clinical event rates in RCTs is compared to usual clinical practice found no difference in stroke or bleeding rates.<sup>12</sup> In contrast, a comparison of open label versus double blind RCTs reported a higher stroke rate in the open label trial.<sup>13</sup> To further investigate and update the area, clinical event rates reported in observational studies from hospital or general practice settings were compared with those reported by observational studies set in anticoagulation clinics and those reported during RCTs.

## Aim

This systematic literature review examines the gap between current practices for stroke prevention in AF patients at high risk of stroke and guidelines for prophylaxis.  
 Secondly, clinical event rates reported in observational studies from hospital or general practice settings were compared with those reported during observational studies set in anticoagulation clinics and those reported during RCTs.

## Methods

An extensive search of the recent biomedical literature was performed using PubMed and bibliographies of retrieved articles were also searched. Searches were limited to those published in the last 10 years (since May 1997) and to human subjects.  
 Studies pertaining to current treatment practices for stroke prevention for patients with AF were identified.  
 In addition, studies pertaining to clinical event rates (stroke, TIA, embolism or bleeding) associated with OAC therapy were captured.  
 Analyses were conducted by two independent investigators.

### Analysis of current treatment practices

A first analysis of current treatment practices for stroke prevention in high risk AF patients was performed.  
 The proportion of the study population with prior stroke/TIA, who are all considered to be eligible for OAC treatment according to all published guidelines, was captured.  
 The percentage of patients eligible for OAC treatment according to the relevant risk stratification scheme or treatment guideline used to classify patients in that study was recorded.

Finally, the percentage of patients actually treated with OAC was noted.  
 A treatment level of below 80 percent of the eligible population was chosen for this analysis as the point at which a population was considered undertreated, to allow for the presence of patients with contraindications within these populations.

### Analysis of clinical event rates in different study settings

A second analysis of clinical event rate in different study settings was performed.  
 For the purposes of comparison, events were classified as follows: ischaemic stroke, stroke/TIA, overall embolic event, major bleeding, minor bleeding, and overall bleeding, using the definitions provided in each study.  
 Clinical event rates from different study settings, general practitioner or hospital setting, anticoagulation clinics, or clinical trials, were then compared.

## Results

### Analysis of current treatment practices

Literature searches (1997–2008) identified 98 studies concerning current treatment practices.  
 54 studies contained both stroke risk level and the percentage of eligible patients treated (Figure 1).

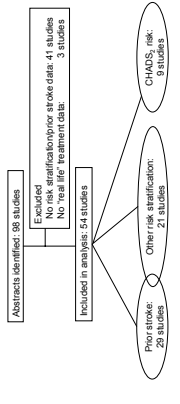


Figure 1. Literature search and study inclusion for OAC treatment levels.

Of these, 29 studies contained treatment data for AF patients with prior stroke or TIA and these were used for the primary analysis.  
 Patients with prior stroke or TIA should all receive OAC therapy according to treatment guidelines.<sup>7-11</sup>  
 However, patients with prior stroke or TIA were under-treated with OAC therapy (a treatment level of < 80% of eligible patients) in all but one of the 29 studies (Figure 2).  
 Indeed, 21 of 29 studies reported OAC treatment levels below 60% (range 19%–81.3%).  
 Only 8 of the 29 studies accounted for AF patients in their population who had contraindications to OAC therapy.  
 Subjects with CHADS<sub>2</sub> score ≥ 2 were also sub-optimally treated; 8 of 9 studies reported treatment levels below 80% (range 39%–92.3%).  
 Studies (21 from 54) that used other stroke risk stratification schemes to designate patients 'high risk' differ in the criteria they use to delineate stroke risk; as such, direct comparison is not possible. In general, patients at a high risk of stroke were under-treated (range 22.8%–81.9%).

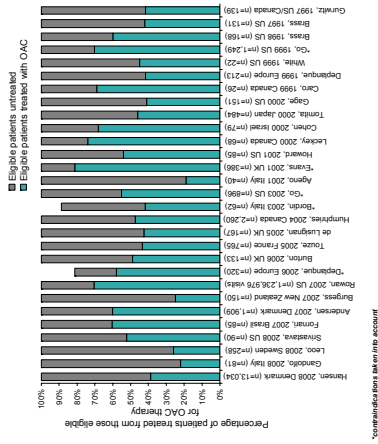


Figure 2. Patients with AF and prior stroke/TIA: OAC treatment levels as a proportion of patients eligible for OAC therapy.

### Analysis of clinical event rates in different study settings

Overall, 39 studies were selected from a possible 53 that contained data pertaining to adverse event rates.  
 Of these, 31 contained embolic event rate data for AF patients treated with OAC therapy and 34 contained bleeding event rate data, most studies reported both types of data (Figure 3).

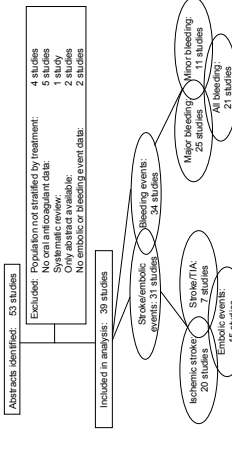


Figure 3. Literature search and study inclusion for clinical event rates in AF patients treated with OAC therapy. Analysis demonstrated higher ischaemic stroke rates in hospital/general practice (GP) (1.2–5.4 per 100 person-years) versus anticoagulation clinics or RCTs (0.3–1.2 and 0.1–1.63 per 100 person-years, respectively) (Figure 4)

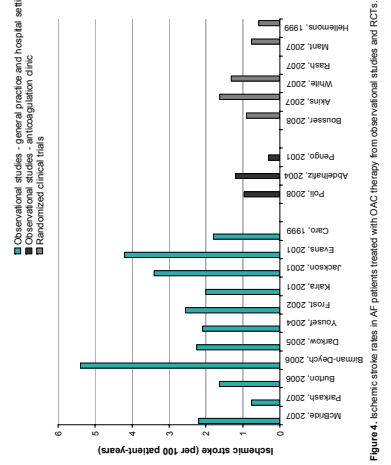


Figure 4. Ischaemic stroke rates in AF patients treated with OAC therapy from observational studies and RCTs.

## Conclusions

This systematic review and analysis of available evidence has highlighted the sub-optimal treatment of high risk AF patients.  
 Patients with AF and prior stroke or TIA were found to be under-treated with OAC therapy in all but one of the studies.  
 Nearly three-quarters of the studies analyzed reported a treatment level of under 60 percent of eligible patients.  
 Similarly, subjects at high risk of stroke, based on the CHADS<sub>2</sub> stroke risk score, were also sub-optimally treated.  
 Secondly, analysis of clinical event rates while on OAC therapy demonstrated higher ischaemic stroke rates in hospital/general practice versus anticoagulation clinics or RCTs.  
 This finding most likely reflects better quality monitoring of patients in anticoagulation clinics and RCTs compared to general practice.  
 Little difference was observed in major bleeding rates between settings; however the definition of major bleeding differed from study to study limiting the validity of the comparison.

Our findings of overall under-treatment of high risk AF patients with warfarin in clinical practice, coupled with increased rates of ischaemic stroke in real life clinical settings when AF patients are treated, reflect the need for improvements in our provision of thromboprophylaxis in AF.  
 There is an evident need for OAC drugs with a wide therapeutic range, as well as a safe bleeding profile.

### Limitations

The current evidence base prevents more detailed comparisons between published studies.  
 Only a small proportion of AF patients (those with prior stroke) were suitable for direct comparison of treatment levels.  
 Evaluating treatment levels for entire study populations is not possible due to lack of risk stratification.  
 Therefore, our first analysis focussed on studies with treatment values for AF patients with prior stroke and those designated 'high risk' using a common risk stratification scheme (CHADS<sub>2</sub>).  
 Reporting of AF patients with contraindications against warfarin therapy in the literature was limited.  
 Contraindications to warfarin were reported in around 15% of AF patients in previous studies,<sup>14,17</sup> hence our threshold for under-treatment was 80% of eligible patients.  
 Treatment with non-warfarin therapies (antiplaetals) may mitigate the strength of a general claim of 'under-treatment'.  
 For the second analysis only 'hard end point' events (ischaemic stroke, stroke/TIA and major bleeding) provided comparable data across studies.

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