Review

Risk factors for anticoagulation-related bleeding complications in patients with atrial fibrillation: a systematic review

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Summary

Atrial fibrillation (AF) is associated with an increased stroke risk that may be reduced by therapeutic anticoagulation. However, anticoagulation is associated with an increased risk of bleeding that in some patients may outweigh the benefits in reducing the risk of stroke. We systematically reviewed the literature for risk factors of anticoagulation-related bleeding complications in patients with AF, as part of the formulation of recently published national guidelines for the management of AF. We identified nine studies that reported anticoagulation-related bleeding complications in AF patients. The following patient characteristics were identified as having supporting evidence for being risk factors for anticoagulation-related bleeding complications: advanced age, uncontrolled hypertension, history of myocardial infarction or ischaemic heart disease, cerebrovascular disease, anaemia or a history of bleeding, and the concomitant use of other drugs such as antiplatelet agents. The presence of diabetes mellitus, controlled hypertension and gender were not identified as significant risk factors. Some of the risk factors for anticoagulation-related bleeding are also indications for the use of anticoagulants in AF patients. There is a need for further research in this area to help physicians to balance the risks and benefits of anticoagulation in AF patients.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, with a prevalence of approximately 7.2% in those aged >65 years. It is also a significant risk factor for ischaemic stroke, with AF patients being almost five times more likely to experience a stroke compared to non-AF patients. Numerous clinical trials have demonstrated that this increased stroke risk can be substantially reduced through the use of effective anticoagulation, typically using oral anticoagulants such as warfarin. These should be administered to a target INR of 2.5, with a lower and upper limit of 2.0 and 3.0, as there is a disproportionate increase in ischaemic stroke at INR values <2.0, and a disproportionate increase in bleeding events at values >3.0. Despite this evidence, recent guidelines for the management of AF in the US and Europe have suggested that an INR of >3.0 be considered in patients with a previous...
thromboembolic event, if a patient experiences a stroke while anticoagulated to a lower INR target.\(^5\)

While anticoagulation is clearly effective in reducing the risk of ischaemic stroke in AF patients (typically by around 67% compared to placebo\(^6\)), the risk of stroke is not homogenous, with patients who do not have certain risk factors having an incidence of stroke that may not justify the use of anticoagulation. Various stroke risk assessment models have been devised that can identify such low-risk patients.\(^7\)–\(^20\) These models define low-risk patients as those who are younger or have fewer additional cardiovascular risk factors (heart failure, diabetes, hypertension, previous stroke) than those at higher risk.

The use of risk assessment models can be useful when deciding whether or not to administer anticoagulation in a particular patient with AF. However, just as the risk of ischaemic stroke may be low enough not to justify anticoagulation, in other patients the increased risk of bleeding associated with anticoagulation may also not justify anticoagulation, despite an elevated risk of ischaemic stroke. It is pertinent therefore to examine in which patients the increased risk of bleeding associated with anticoagulation is too great to justify the use of anticoagulation.

Recently published evidence-based national guidelines for the management of AF in the UK\(^22\) have recommended a careful assessment of bleeding risk prior to the administration of anticoagulation. These guidelines, issued by the National Institute for Health and Clinical Excellence (NICE) are different from other expert consensus guidelines issued by learned societies,\(^12\) as the methodology is based on systematic literature reviews following specification of the guideline scope.\(^23\) The guideline recommendations were formulated by a multidisciplinary panel of physicians, patient representatives and health service researchers given the results of the systematic literature reviews and guideline scope.

While the NICE guideline recommendations do not include a formal bleeding risk assessment model, they do list various risk factors that are identified as increasing the risk of bleeding and are recommended to be considered prior to prescribing anticoagulation, as follows: (i) age >75 years; (ii) co-prescription of anti-platelet drugs (such as aspirin or clopidogrel) or non-steroidal anti-inflammatory drugs; (iii) co-prescription of multiple other drugs (i.e. polypharmacy); (iv) uncontrolled hypertension; (v) history of bleeding (for example, peptic ulcer or cerebral haemorrhage); and (vi) history of poorly controlled anticoagulation therapy. The aim of this systematic review is to evaluate and discuss the evidence supporting these risk factors for bleeding, as stated in the NICE guideline, and to identify any other risk factors not included in the above list.

**Methods**

Studies were considered for inclusion if they reported a measurement for the independent risk of anticoagulation-related bleeding in patients with AF for at least one objectively quantifiable patient characteristic. Independent risk was assumed to be measurable only through either: (i) the appropriate use of regression models where the occurrence of a bleeding event is defined as the dependent variable, and multiple clinically plausible risk factors are defined as the set of independent variables; or (ii) the use of a matched case-control study design with cases and controls defined in terms of a single clinically plausible risk factor.

Study designs that were considered for inclusion were prospective or retrospective case-control studies where either: (i) a case was defined as a case of anticoagulation-related bleeding and a control was defined as an absence of anticoagulation-related bleeding; or (ii) a case was defined as the presence of a possible risk factor for anticoagulation-related bleeding, and a control was defined as the absence of the possible risk factor.

Participants with AF receiving long-term administration of an anticoagulant such as warfarin were included. Long term anticoagulation was defined as any period of continuous anticoagulation of at least 4 weeks. Studies were excluded if they comprised a proportion of non-AF patients, or if they involved the administration of subtherapeutic (INR < 2) or no long-term anticoagulation for some or all of the study population. The exclusion of studies involving some or all patients not receiving anticoagulation is an important consideration, since it is possible that bleeding risk factors in anticoagulated patients may not be the same as in control patients. In particular, such risk factors could plausibly involve interactions between warfarin and other drugs or other disease processes such as liver disease. Studies based in clinical trial populations were considered as well as observational studies.

**Types of outcome measure**

**Patient characteristic outcomes**

In those case-control studies where a case was defined as a case of anticoagulation-related bleeding, the following patient characteristics were measured for an independent effect on the risk
of bleeding by at least one included study: patient age, patient gender, history of thromboembolism, myocardial infarction or bleeding, co-morbid diabetes, hypertension or cerebrovascular disease, polypharmacy or the co-administration of other anti-thrombotic agents. In those case-control studies where a case was defined as the presence of a possible risk factor for anticoagulation-related bleeding, the two possible risk factors of patient age and polypharmacy were included.

The independent risk of bleeding attributable to any patient characteristic may be expressed in multiple ways (odds ratio, relative risk, regression coefficient, and so on), which may not always be converted from one form to another based on the information available in the study alone. While meta-analytic methods exist for estimating risk-based outcome measures across multiple studies, this is not a methodologically valid procedure for studies involving multivariate regression models. These studies typically exclude variables based on an absence of any statistically significant univariate association with the outcome variable in the first step, and subsequently exclude non-significant variables during the iterative regression procedure. Moreover, the estimated value of the independent risk as calculated by a multivariate regression model is dependent on the choice of independent variables selected by the study investigators, which varies between studies.

The main outcome of interest in this review was therefore considered to be the statistical significance of the independent risk attributable to the patient characteristic, rather than an estimation of the independent risk parameter, however expressed; specifically, whether \( p < 0.05 \) for each patient characteristic.

**Bleeding outcomes**

Incident cases of anticoagulation-related bleeding were defined by the presence of at least one bleeding event during the study period. Bleeding outcomes considered included the occurrence of any bleeding event (major or minor), of only a major bleeding event, or of only a particular kind of major bleeding event, such as intracranial haemorrhage (ICH). Bleeding outcomes defined as the presence of minor bleeding events only were not considered.

**Other methods**

A tailored search expression (available from the corresponding author on request) was used to search for relevant studies in the Medline, Cinahl, EMBASE and Cochrane CENTRAL electronic databases. The results were combined into a single file with duplicates deleted. Further studies were also included following manual cross-referencing and expert consultation. The search encompassed all studies referenced in any of the above databases until 4 July 2005. The systematic literature search covered both English language studies, and those published in other languages whose abstracts were available in English. Non-English language studies were translated if it was agreed (based on the information contained in the abstract) that (i) the same study had not been republished in English, and (ii) it met all of the inclusion criteria.

One reviewer (MH) selected studies for review based on the information published in the study abstract (or full paper where no abstract was available). All of these studies were then evaluated by two reviewers (MH and GYHL) for inclusion based on the criteria for considering studies for this review and the types of outcome measures described above. Studies were evaluated in terms of their methods according to a study appraisal system used by NICE. This system assigns a grade of either ‘++’, ‘+’ or ‘−’ to each study. Studies that were graded as ‘−’ were excluded. There were no cases of disagreement between the reviewers on the exclusion of studies.

Because of the use of the multiple methods of expressing bleeding risk, and the inappropriateness of using any meta-analytic techniques to derive a pooled estimate of bleeding risk, as discussed above, we report the results of our systematic review in a narrative form, considering the results of each study individually.

**Results**

The systematic search of the literature found 2194 published studies that fulfilled the search criteria. Of these, 37 were selected for consideration based on the information contained in the abstract or through recommendation for inclusion following expert consultation. Of the 37, 27 did not meet the criteria for considering studies in this review and were not appraised (Figure 1). The two most common reasons for not appraising these studies were the inclusion of non-AF patients in the study cohort, and not reporting the relative risk of anticoagulation-related bleeding for any clinical or demographic variables. Two studies were excluded because of including a proportion of non-anticoagulated patients in the study population, both were retrospective analyses of clinical trial data.

Ten studies were appraised using the NICE grading scheme. One study comparing the bleeding risk between AF patients with or without mitral
valve disease and with or without a history of previous thromboembolism was excluded because of significant differences in patient characteristics at baseline that could confound the results.

Of the nine studies finally included in this review, four used clinical trial data from warfarin-treated patients involving a total of eight clinical trials. All studies involved patients administered oral anticoagulation with warfarin or other coumarin derivatives. The mean age of patients was >65 years in all included studies. All studies were classified as case-control studies, with most comparing the possible risk factors between those patients with bleeding events and those without. One study compared bleeding risk in elderly versus younger patients, and another measured the effect of polypharmacy defined as at least three prescribed drugs in addition to anticoagulation. The characteristics of the included studies are summarized in Table 1.

From the nine studies included in this systematic review a total of eight possible risk factors were identified and reviewed: increasing age, gender, diabetes, blood pressure, polypharmacy and a history of myocardial infarction, cerebrovascular disease or previous bleeding events. Because the purpose of this review was to identify risk factors for anticoagulation-related bleeding that should be considered prior to the prescription of anticoagulation, the degree of control over anticoagulation measured as, for example, the percentage of time spent outside of a therapeutic range of INR values, was not considered. Nonetheless, there is evidence for poor anticoagulation control being associated with increased risk of bleeding.

A summary of the results for each patient characteristic is shown in Table 2, which indicates for each study whether the patient characteristic(s) considered by the study were found to be (i) an

### Table 1: Characteristics of the studies included in the review

<table>
<thead>
<tr>
<th>Reference</th>
<th>Evidence grade</th>
<th>n</th>
<th>Case definition</th>
<th>Control definition</th>
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<td>Fang et al., 2004&lt;sup&gt;26&lt;/sup&gt;</td>
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<td>1190</td>
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<td>360</td>
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<td>402</td>
<td>Bleeding event</td>
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</tr>
<tr>
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<td>101</td>
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<td>Age 60–69 years</td>
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<tr>
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<td>+</td>
<td>550</td>
<td>Bleeding event</td>
<td>No bleeding event</td>
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<tr>
<td>Sam et al., 2004&lt;sup&gt;31&lt;/sup&gt;</td>
<td>+</td>
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<td>Major bleeding event</td>
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<tr>
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<td>10093</td>
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<tr>
<td>SPAF Investigators, 1996&lt;sup&gt;33&lt;/sup&gt;</td>
<td>+</td>
<td>555</td>
<td>Bleeding event</td>
<td>No bleeding event</td>
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'++' denotes studies with no significant methodological weaknesses and a low risk of bias or confounding of the results; '+' denotes studies with some methodological weaknesses and an acceptable risk of bias or confounding of the results.

### Table 2: Summary of results

<table>
<thead>
<tr>
<th>Study</th>
<th>Age</th>
<th>Gender</th>
<th>DM</th>
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<th>Bleeding</th>
<th>MI/IHD</th>
<th>CVD/TE</th>
<th>Poly</th>
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<td>Shireman et al., 2004&lt;sup&gt;32&lt;/sup&gt;</td>
<td>0*</td>
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<td>SPAF Investigators, 1996&lt;sup&gt;33&lt;/sup&gt;</td>
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Risk factors: Age, increasing age; Gender, being female; DM, presence of diabetes mellitus; BP, elevated blood pressure or a history of hypertension; Bleeding, a history of bleeding, MI/IHD, history of myocardial infarction or ischaemic heart disease; CVD/TE, history of cerebrovascular disease or thromboembolism; Poly, polypharmacy. Results: 0, the study tested the patient characteristic as a risk factor for one or more bleeding outcomes, but no significant association was found; 0*, the result was of borderline significance; +, a significant association was found between the patient characteristic and at least one bleeding outcome, but it was not an independent risk factor; ++, the patient characteristic was found to be an independent risk factor for at least one bleeding outcome.
independent risk factor; (ii) a marker of increased risk in terms of a statistically significant association between the patient characteristic and at least one bleeding outcome; or (iii) of no, or only borderline, significance.

The following reports the results for each patient characteristic in detail.

Age

In one study, involving approximately 770 patient-years of follow-up, patients aged >75 years were more likely to suffer bleeding complications than those <aged 75 years. The relative risk (RR) was reported as 6.6 (95%CI 1.2–37; \( p = 0.032 \)). A similar result was found in another slightly larger study, involving approximately 1110 patient-years of follow-up, where the estimated odds ratio (OR) of having a bleeding event if aged >75 years was reported as 2.45 (\( p = 0.006 \)). In another study involving approximately 637 patient years of follow-up, being aged >75 years was not found to be a significant risk factor for bleeding complications.

Two smaller studies also failed to find age as a significant risk factor, although each was limited in its ability to discriminate, based on the number of patient-years of follow-up and the choice of age categories considered in the risk model. One involved 101 patient years of follow-up and compared the incidence of bleeding complications between those aged \( \geq 75 \) years compared to those aged 60–69 years. Another, which followed-up

Gender

No study found any significant independent association between gender and bleeding complications. However, one study, involving approximately 2489 patient years of follow-up found female gender to be of borderline significance as an independent risk factor, with OR 1.40 (95%CI 1.00–1.95; \( p = 0.05 \)). Another, smaller study also found a similar borderline result, with OR 3.19 for being female (95% CI 0.98–10.41; \( p = 0.054 \)).

Diabetes mellitus

A history of diabetes was not associated with an increased risk of bleeding complications in three studies. No study reported the incidence of bleeding complications to be higher in those with a history of diabetes than in those without a history of diabetes.

Blood pressure

In one study, involving approximately 637 patient-years of follow-up, the prevalence of a history of hypertension was higher in those with a bleeding complication compared to those with no bleeding complication (45% vs. 23%, respectively; \( p < 0.006 \)). When considering only the development of ICH as an outcome, another study involving 1190 patients found no significant difference in the prevalence of a history of hypertension between those with and those without ICH. This apparent inconsistency may be explained by the less frequent occurrence of ICH compared to any kind of bleeding complication, and the fact that patients with hypertension may nonetheless have blood pressure readings within normal limits. Another study involving 1225 trial participants reported differences in blood pressure defined as a quantitative measure, rather than as a history of hypertension, and found that both mean systolic and mean diastolic blood pressure was higher in those with ICH than in those without (169/93 vs. 141/83 mmHg; \( p = 0.001/0.016 \)).
History of bleeding

In one study, involving approximately 2489 patient-years of follow-up, a history of bleeding was a significant risk factor for future bleeding complications (RR 2.40, 95%CI 1.71–3.38). This result is consistent with another result reported by the same study that a history of anaemia was also a risk factor for bleeding complications (OR 2.52, 95%CI 1.64–3.88).

History of myocardial infarction

In one study, involving approximately 637 patient-years of follow-up, a history of MI was significantly associated with bleeding complications, defined as either a minor or major bleed. Of those with MI, 19% experienced bleeding complications, vs. 12% of those without ($p=0.05$). The same study found a similar result in terms of the association between ischaemic heart disease (IHD) and bleeding complications (49% of those with bleeding complications had IHD, vs. 34% of those without; $p=0.004$). However, when considering only major bleeding complications, no significant association was found for either MI or IHD.

Cerebrovascular disease

One study involving 550 patients failed to find a history of stroke or thromboembolism to be a significant independent risk factor for bleeding complications. Similarly, another study involving approximately 637 patient-years of follow-up did not find any significant association between cerebrovascular disease and incidence of bleeding complications. However, for the specific outcome of ICH, another study involving 1190 patients found cerebrovascular disease to be a significant independent predictor of intracranial haemorrhage (OR 2.2, 95%CI 1.4–3.4).

Polypharmacy

In one study, involving approximately 2489 patient-years of follow-up, the concomitant use of anti-platelet drugs in anticoagulated patients was a significant independent risk factor for bleeding complications (OR 1.53, 95%CI 1.05–2.22). However, the same study did not find an increased number of additional medications (including non-steroidal anti-inflammatory drugs, NSAIDs) to be a significant independent risk factor for bleeding complications (OR 1.33, 95%CI 0.96–1.86) when risk was measured against an increase of one additional drug. In another study, based in a clinical trial population and involving approximately 1110 patient-years of follow-up, patients taking more than three medications in addition to anti-coagulants were at an increased risk of bleeding complications (estimated OR 2.45; $p=0.007$). A similar result was also reported in another study, involving approximately 384 patient-years of follow-up, comparing the incidence of bleeding complications between those patients taking at least three additional medications and those taking fewer than three. The study found a significant difference between the two groups in the incidence of major bleeding complications (11.8% vs. 1.4%; $p=0.0356$) and in the total incidence of bleeding complications (22.2% vs. 3.4%, respectively; $p=0.0073$), although the difference in the incidence of minor bleeding complications was not significant.

Discussion

The aim of this systematic review was to appraise and summarize the evidence from studies attempting to identify risk factors for anticoagulation-related bleeding complications. Consideration of these risk factors should assist in the assessment of bleeding risk prior to anticoagulation.

Bleeding remains a problem for anticoagulated patients, although the quoted risk is variable, depending on study type and clinical setting. One prospective study reported the incidence of ischaemic stroke and major bleeding events to be comparable in an unselected cohort of anticoagulated patients with AF, with a stroke incidence of 2% and major bleeding incidence of 1.7% per year, which was broadly similar to clinical trial populations of AF patients. In the pooled analysis of five primary prevention trials in AF, the annual rate of major bleeding (defined as an intracranial haemorrhage, a haemorrhage requiring at least two units of blood, or an event requiring hospital admission) was 1% in control patients and 1.3% in warfarin-treated patients. The annual risks of intracranial haemorrhage increased from 0.1% in control to 0.3% in warfarin groups. The risk of death from a major bleed ranged from 13% to 33%, and the risk of morbidity in those who survive a major bleed is as high as 15%. One large study based on an elderly cohort of over 10 000 anticoagulated AF patients, reported a yearly incidence of 1.5% major bleeding events, of which 0.3% were intracranial haemorrhage. In another study, based on a population of 6777 AF patients receiving both anticoagulation and anti-platelet therapy, the yearly incidence of major bleeding events was 1.1%, of which 0.6% were
intracranial haemorrhages. The study reported a yearly incidence of 11.8% minor bleeding events.

While we found good evidence from two studies, that being older than 75 years is a significant risk factor, five other studies failed to find increasing age a significant risk factor. Nor was any conclusive evidence found to suggest that gender or the presence of diabetes has any affect on the risk of bleeding. No evidence was found to suggest that treated hypertension increases the risk of bleeding, although blood pressure was higher in those with bleeding events than in those without. This result supports the common clinical practice of achieving blood pressure control prior to administering anticoagulation, although based on the result of only one study and only for the specific outcome of ICH.

One study concluded that a history of bleeding was a risk factor for future bleeding. The same study also reported a history of anaemia as a risk factor, but did not indicate whether the anaemia was caused by an internal bleed or some other condition. However, the results of another study which included non-anticoagulated AF patients, and thus was not included in this review, also support anaemia as a risk factor insofar as they identify co-morbid hepatic and renal disease as risk factors for bleeding.

A history of myocardial infarction and ischaemic heart disease were both associated with an increased risk of anticoagulation-related bleeding in one study. While the is no obvious biological mechanism to support this result, which is based on a single study that considered both minor and major bleeding events as the primary outcome, it is supported by another study involving clinical trial participants with AF, some of whom were administered aspirin and some of whom were anticoagulated. Another study which included non-anticoagulated AF patients, while not reporting MI or ischaemic heart disease as risk factors for bleeding, did report co-morbid heart failure as a risk factor.

The results for cerebrovascular disease were inconsistent between studies. In part, this may be partly explained by the definition of ‘cerebrovascular disease’, as it was not made clear in many studies whether this excluded a history of ICH or only considered non-haemorrhagic cerebrovascular disease. Two studies found no association between bleeding complications and the presence of either previous stroke or thromboembolism specifically, or cerebrovascular disease generally. However, one study which considered the more specific outcome of ICH did find an association with cerebrovascular disease.

The evidence for polypharmacy supports the common perception that the combined use of anticoagulants and anti-platelets increases the risk of bleeding beyond that of either drug class alone. This conclusion is further supported by another study which included a proportion of non-anticoagulated patients. Regarding the issue of polypharmacy generally, the evidence does suggest that increasing the number of drugs does increase the risk of bleeding, although there is no reason to assume this is due to the number of drugs per se, rather than the drugs themselves and possible interactions with anticoagulants such as warfarin.

In this systematic review, studies considering the following patient characteristics have been identified and appraised: increasing age, elevated blood pressure, diabetes, history of myocardial infarction, ischaemic heart disease, cerebrovascular disease or thromboembolism, anaemia or a history of bleeding, and polypharmacy, including the concomitant use of other drugs such as anti-platelet agents. While there is some degree of evidence for increasing age, female gender, uncontrolled hypertension and a history of cerebrovascular disease or thromboembolism to be considered as risk factors for anticoagulation-related bleeding, the evidence is inconclusive. Regarding polypharmacy, a history of bleeding, myocardial infarction or ischaemic heart disease, the evidence is consistent, although only polypharmacy has support from multiple studies. No study found diabetes mellitus to be an independent risk factor.

Advanced age and hypertension are recognized to be significant independent risk factors for ischaemic stroke in AF patients, and advanced age is a risk factor for bleeding irrespective of anticoagulation status. This raises the difficult task therefore of attempting to balance the risk of bleeding associated with anticoagulation with the demonstrated benefits in stroke prevention for many patients. More research is clearly needed in this area, to support the use of risk assessment models that combine not only the benefits of anticoagulation, but also its risks, into a single tool that can be used by practicing physicians.

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References


