**Title:** **The Impact of Atrial Fibrillation Type on the Risks of Thromboembolic Recurrence, Mortality, and Major Haemorrhage in Patients with Previous Stroke: A Systematic Review and Meta-analysis of Observational Studies**

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**Tables:** 1

**Figures:** 4

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**Supplementary Tables:** 4

**Supplementary Figures:** 4

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**ABSTRACT**

**Introduction:** There is conflicting evidence on the impact of atrial fibrillation (AF) type, i.e. non-paroxysmal (NPAF) or paroxysmal (PAF), on thromboembolic recurrence. The consensus of risk equivalence is greatly based on historical evidence, focusing on initial stroke risks. We conducted a systematic review and meta-analysis to describe the impact of AF type on the risk of thromboembolic recurrence, mortality and major haemorrhage in patients with previous stroke.

**Methods:** We systematically searched four multidisciplinary databases from inception to December 2018. We selected observational studies investigating clinical outcomes in patients with ischaemic stroke and AF, stratified by AF type. We assessed all included studies for risk of bias using the 'Risk of Bias In Non-randomised Studies – of Exposures' tool. The Comprehensive Meta-Analysis Software was used to calculate odds ratios (OR) from crude event rates.

**Results:** After reviewing 14,127 citations, we selected 108 studies for full-text screening. We extracted data from 26 studies, 23,054 patients. Overall, risk of bias was moderate. The annual incidence rates of thromboembolism in patients with NPAF and PAF were 7.1% (95%CI: 4.2-11.7)% and 5.2% (95%CI: 3.2-8.2)%, respectively. The OR for thromboembolism in patients with NPAF versus PAF was 1.47 (95%CI: 1.08-1.99, p=0.013). The annual mortality rates in patients with NPAF and PAF were 20.0% (95%CI: 13.2-28.0)% and 10.1% (95%CI: 5.4-17.3)% respectively, OR=1.90 (95% CI: 1.43-2.52, p< 0.001). There was no difference in rates of major haemorrhage, OR=1.01 (95%CI: 0.61-1.69, p=0.966).

**Conclusion:** In patients with prior stroke, NPAF is associated with significantly higher risk of thromboembolic recurrence and mortality than PAF. Although current guidelines make no

distinction between NPAF and PAF for secondary stroke prevention, future guidance and risk stratification tools may need to consider this differential risk. (PROSPERO ID: CRD42019118531)

## INTRODUCTION

Atrial fibrillation (AF) is an atrial arrhythmia characterised by uncontrolled, rapid firing of atrial action potentials. This causes reduced cardiac output and turbulent flow, which can lead to blood coagulation and emboli.[1] Hence, AF is associated with an increased risk of stroke and consequently death.[2] AF is sub-classified into paroxysmal (PAF) and non-paroxysmal (NPAF) forms. PAF refers to short spontaneously terminating episodes, while NPAF is persistent or permanent. PAF, NPAF and sinus rhythm are often difficult to differentiate and are recognised as non-mutually exclusive categories. Diagnoses differentiating PAF and NPAF are limited by the ability of current monitoring detection algorithms and arbitrary cut offs of AF burden. Emerging evidence suggests that even in the absence of clinical AF, atrial cardiopathy may associated with thromboembolism, thus determining cardiac thrombogenicity remains more complex than categorisation of AF burden.[3] Nevertheless, guidelines suggest that categorisation of AF burden remains practical. The risk of stroke in AF patients is considered independent of AF type. Stroke-risk stratification scores that inform prescribing and management, are based on sex, age and comorbidities rather than AF type.[4] This consensus of relative risk equivalence in patients with PAF and NPAF is based on historical evidence evaluating the risk of index stroke.[5] Despite some conflicting evidence [6-8], the European Society of Cardiology (ESC) guidelines do not recommend that AF type should be a major factor in making decisions regarding oral anticoagulation (OAC) therapy.[9] However, due to limited studies, the impact of AF type on outcomes *following* acute stroke remains unclear.

Although previous systematic review has examined the role of AF type as a risk factor for initial stroke occurrence and adverse outcomes,[6] no systematic review has investigated the role of AF type following acute ischaemic stroke, i.e. as a risk factor for thromboembolic recurrence, mortality and major haemorrhage. The risk of ischaemic stroke is significantly higher in AF patients who have had a previous stroke than those who have not.[10] Due to higher

event rates, the impact of AF type on secondary prevention outcomes may be more pronounced.

Decisions to start effective AF-related stroke thrombo-prophylaxis following acute ischaemic stroke or intracerebral haemorrhage are rarely clear cut: patients have reluctance and own prejudices, relative contraindications, and are influenced by their individual clinicians' perceptions of risks and benefits. In addition, the current AF risk stratification tools are not perfect. A better understanding of risk factors could improve their prognostic and clinical utility. There are plausible reasons to think that AF type may be an important factor that has hitherto been ignored.

We conducted a systematic literature review and meta-analysis of observational studies to evaluate the impact of atrial fibrillation type on the risk of thromboembolic recurrence (stroke and systemic embolism), major haemorrhage and mortality in patients with prior stroke.

## METHODS

### Inclusion and exclusion criteria

We conducted a systematic literature search of multidisciplinary databases: MEDLINE (OVID), EMBASE (OVID), Web of Science (Thomson Reuters), CINAHL (EBSCO) to identify observational studies in which clinical outcome data were prospectively or retrospectively collected from inception to December 2018. We registered the study protocol on PROSPERO (CRD42019118531).

*Study designs*

We included prospective and retrospective cohort studies and case series that investigated patients with AF post-stroke and distinguished between AF types. We did not include studies on topics other than stroke outcomes in AF patients, unless stroke outcomes were reported. We excluded randomised control trials, as they are not representative of natural population frequencies. We also excluded review articles, commentaries, conference papers and case reports. We placed no restrictions on the basis of language; however, any foreign-language studies identified were only included when they could be translated into English.

*Patients/Participants*

We included studies in which patients had an ischaemic stroke/ transient ischaemic attack (TIA) of any form consistent with the current (ICD-10) World Health Organisation (WHO)[10] definition, diagnosed in a hospital setting. We included mixed population studies (i.e. studies including patients with index and recurrent stroke) if they differentiated between AF types. We contacted the studies' authors of mixed population studies if: 1) the data of interest were not available from the original report, 2) they had been conducted within the last 10 years, and 3) they differentiated between AF types. We allowed one month for the authors to reply, with a follow-up/ reminder email after two weeks. We included studies of authors who provided us with outcome data of interest within the specified time frame.

*Exposures*

We included studies if their definition of AF was compatible with the current International Classification of Disease (ICD-10)[10]. The definitions of AF types in included studies had to be consistent with current American Heart Association (AHA), American College of Cardiology, European Society of Cardiology (ESC) and Heart Rhythm Society (HRS) guideline classifications of AF patterns:

1. Paroxysmal AF (PAF): Self-terminating, typically within 48 hours, but may continue up to 7 days. An AF episode terminated by cardioversion may still be considered paroxysmal if this (i.e. cardioversion) occurs within 7 days.
2. Non-paroxysmal AF (NPAF):
    a. Persistent AF: AF that lasts longer than 7 days, including episodes terminated by cardioversion after 7 or more days.
    b. Long-standing persistent AF: Continuous AF lasting for at least a year until a rhythm control strategy is adopted.
    c. Permanent AF: AF that is accepted by patient and physician, therefore not including patients on rhythm control therapy.[9, 11, 12]

We included studies that failed to use the current terminology of paroxysmal and non-paroxysmal AF if their definitions were considered compatible, as judged by consensus of two authors (AM, AHAR). We grouped the terms 'sustained', 'constant' or 'chronic' AF as NPAF and 'intermittent' or 'recurrent' AF as PAF. We excluded studies failing to differentiate between AF types.

*Outcomes*

Our outcomes of interest were the incidence of stroke and systemic embolism, major haemorrhage and mortality:

1. Ischaemic stroke or systemic embolism diagnosed as per definition taken from the original article. This includes stroke recurrence during the treatment period and during follow-up, which was either definitely ischaemic (haemorrhage excluded by brain imaging or autopsy), or of unknown type (no brain imaging or autopsy performed);
2. Death from any cause during the scheduled follow-up period

3. Any intracerebral or major extracranial haemorrhage during the scheduled treatment period:
    a. Intracerebral haemorrhage, including symptomatic haemorrhagic transformation of the cerebral infarct, during the scheduled treatment period and during follow-up. The haemorrhage must have been confirmed by appropriate brain imaging after clinical deterioration or by autopsy
    b. The definition of major haemorrhage was taken from the original article but if none was given it was defined as any fatal bleed, or bleeding severe enough to require transfusion or operation.

We included studies, in which these outcomes for patients with a previous, definitely ischaemic stroke were extractable (i.e. stroke population and mixed population studies).

**Study selection**

The search syntax for MEDLINE was created in cooperation with a research librarian of the University of Glasgow. We adapted this search strategy for the other databases (Supplementary Table 1). All databases were accessed on the 18$^{th}$ of December 2018. We reviewed titles and abstracts using Covidence software (version 1.0, Veritas Health Innovation, Australia). We used the reference lists of retrieved articles for hand searches to identify additional relevant studies. As our emphasis was on published, peer-reviewed articles, we did not search grey literature beyond the scope of the included search engines and hand searches.

**Data extraction and statistical analysis**

*Risk of Bias Assessment*

All included studies underwent risk of bias assessment (Supplementary Table 2). We used the ROBINS-E (Risk of Bias In Non-randomised Studies – of Exposures) tool for non-randomised control trials.[13] We judged all studies, with a particular emphasis on the focus of the paper, selection bias (i.e. recruitment method and exclusion and inclusion criteria), classification of AF and the acknowledgement of confounding factors and co-exposures. Any studies with serious risk of bias were excluded in sensitivity analyses.

*Data extraction*

We extracted the total number of patients with PAF and NPAF who had a previous ischaemic stroke, along with any data on the incidence of recurrent thromboembolic events, mortality and major haemorrhage. We converted Kaplan-Meier curves and risk ratios into crude event numbers to allow data uniformity. We also recorded follow-up period and OAC data. We stored all data on an electronic spreadsheet (Excel, version 2016 Microsoft, USA) after extraction.

*Statistical analysis*

The primary outcome of the meta-analyses was the incidence of recurrent thromboembolic events. The secondary outcomes were incidence of all-cause mortality and major haemorrhage. These analyses were conducted using Comprehensive Meta-Analysis software version 3 (Biostat, USA). As specified in the study protocol, we created a random-effects model to generate a pooled estimate of the summary event rates for both, PAF and NPAF and performed a subgroup analysis accounting for OAC use post-stroke. The a-priori decision to use a random-effects model was made to accommodate the anticipated variation in study design and small sample size of observational studies. We calculated annual event rates by dividing the total number of events by length of follow up (in years). Our analysis assumes that the incidence of events was constant over time. We assessed heterogeneity among studies

by visual inspection of forest plots and $I^2$. We also calculated odds ratios (OR) for the outcomes to compare NPAF and PAF event rates. This analysis only included studies that reported on both AF types. We assessed the strength of the summary data post stroke comparing different AF types using the GRADE criteria[14] (Supplementary Table 3). We visually inspected the funnel plots of outcomes for publication bias.

## RESULTS

We retrieved 14,127 references. Following deduplication, we screened 10,855 references. Finally, we included 108 studies, of which 23 had the data of interest available from the original report. We contacted authors of the remaining 93 studies and received data from 3 further studies. Therefore, we extracted data from a total of 26 studies, reporting outcomes on 23,054 patients.[15-40] Figure 1 shows the process of study selection.

[insert Figure 1.]

| **Table 1:** Baseline characteristics of all included non-randomised observational studies | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Author name and date** | **Study type** | **Number of patients in study with history of previous stroke** | **Number of patients by AF type** | | **Inclusion criteria** | **Comparators/ Exposure** | **Oral anticoagulation during follow-up (%)** | | **Follow-up (mean or median)** |
| | | | PAF | NPAF | | | PAF | NPAF | |
| Al-Khalili 2016 [15] | Retrospective cohort study | 766 | 61 | 24 | AF patients in Stockholm health centre treated with NOACs | Dabigatran versus Rivaroxaban versus Apixaban | 100% | 100% | 395 days |
| Aronow 1999 [16] | Prospective cohort study | 136 | - | 136 | Chronic AF patients ages 62 years or older | Warfarin versus Aspirin | - | 50%* | 3 years |
| Azoulay 2012 [17] | Retrospective cohort study with case-control analysis | 4643 | - | 4643 | Chronic AF patients in the UK General Practice Research Database† | Warfarin versus Aspirin | - | 23% | 3.9 years |
| Baturova 2017 [18] | Prospective cohort study | 336 | 65 | 44 | AF patients who suffered first-ever ischaemic stroke in the Lund Stroke Register | Effect of heart rhythm and OAC use | 45% | 45%* | 10 years |
| Britton 1984 [19] | Prospective cohort study | 288 | 31 | 61 | AF patients diagnosed with brain | AF versus sinus rhythm | - | - | 10 days |

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|---|---|---|---|---|---|---|---|---|---|
| | | | | | infarction in Stockholm | | | | |
| Christensen 2014 [20] | Prospective cohort study | 85 | 18 | - | Patients with prior cerebrovascular ischaemic event without prior AF diagnosis | Benefits of PAF detection by implantable loop recorder, no direct comparator | 94% | - | 1.5 years |
| Friberg 2010 [21] | Prospective cohort study | 298 | 91 | 207 | Patients with AF treated as inpatients in 2002 in Stockholm | AF type (paroxysmal versus permanent) | 32% | 38% | 3.6 years |
| Grond 2013 [22] | Prospective multicentre cohort study | 1135 | 49 | - | Survivors of stroke or transient ischaemic attack (TIA) without known AF | Detection rates of PAF by 24-hour vs. 72-hour holter ECG monitoring | - | - | Hospital stay |
| Koga 2016 [23] | Prospective multicentre cohort study | 1192 | 434 | 758 | NVAF patients with acute ischaemic stroke or TIA | Type of AF (paroxysmal versus sustained) | - | - | 1.8 years |
| Levy 1999 [24] | Prospective cohort study | 15 | 1 | 14 | Patients diagnosed with AF, none hospitalised | AF type (paroxysmal, chronic or persistent) | 26% | 52% | 8.6 months |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Liantinioti 2017 [25] | Single-centre prospective cohort study | 184 | 23 | - | Cryptogenic stroke patients with no prior history of AF | Duration of PAF | 85% | - | 3 months |
| Marini 2005 [26] | Prospective cohort study | 3530 | 55 | 814 | Patients with index ischaemic stroke | AF versus sinus rhythm | - | - | 3.75 years |
| Ntaios 2013 [27] | Prospective cohort study | 811 | 277 | 534 | AF patients with acute ischaemic stroke | AF types (paroxysmal, persistent and permanent) | 33.9% | 38.8% | 10 years |
| Önundarson 1987 [28] | Prospective cohort study | 6 | - | 6 | Men and women of Reykjavik | Chronic AF versus sinus rhythm | - | - | unclear |
| Paciaroni 2018 [29] | Prospective cohort study | 2040 | 886 | 1154 | Patients with acute ischaemic stroke and AF | PAF versus sustained AF | 87.3% | 80% | 120 days |
| Palomäki 2017 [30] | Retrospective cohort study | 3256 | 1448 | 1808 | AF patients with acute ischaemic stroke or TIA | PAF versus chronic AF | 32.2% | 63.6% | 30 days |
| Petty 1998 [31] | Retrospective cohort study | 1111 | 129 | 138 | All residents of Rochester who have suffered from stroke | Characteristics that could impact survival and recurrence post stroke | - | - | unclear |
| Rietbrock 2008 [32] | Retrospective population-based cohort study | 7628 | - | 7628 | Chronic AF patients over 40 years in the UK General | CHADS2 risk stratification points | - | - | 3.3 years |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Practice Research Database† | | | | |
| Staszewski 2009 [33] | Prospective cohort study | 178 | 70 | 108 | AF patients with acute ischaemic stroke and at least 72-hours of continuous ECG monitoring | AF type (paroxysmal versus permanent) | - | - | 6 months |
| Tanaka 2016 [34] | Retrospective cohort study | 449 | 178 | 271 | Patients with acute ischaemic stroke and AF | Age (aged 80 years or older versus younger than 80) | - | - | 90 days |
| Tsivgoulis 2005 [35] | Prospective cohort study | 207 | 66 | 141 | AF patients with first-ever ischaemic stroke | Oral anticoagulants versus aspirin | - | - | 7.4 years |
| Wolf 1978 [36] | Prospective cohort study | 20 | - | 20 | Men and women of Framingham aged 30 to 62 | Chronic AF versus sinus rhythm | - | - | unclear |
| Yamanouchi 1988 [37] | Retrospective cohort study | 23 | 5 | 18 | NVAF patients with sustained embolic brain infarction on warfarin anticoagulation treatment | Warfarin versus no treatment (autopsy series)‡ | 100% | 100% | 3.8 years |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Yanagisawa 2016 [38] | Prospective cohort study | 64 | 27 | 37 | Elderly patients with AF receiving outpatient treatment in Nagoya | Body mass index | - | - | 1.6 years |
| Yu 2018 [39] | Retrospective cohort study | 69 | - | 69 | NV, persistent AF patients who survived hospital stay | Type of anti-thrombotic treatment | - | 41.1% | 360 days |
| Zolotovskaya 2018 [40] | Prospective cohort study | 661 | 153 | 354 | NVAF patients with history of carotid cardio-embolic stroke without carotid artery stenosis | Type of AF (first diagnosed, paroxysmal, persistent and constant) | - | - | 1 year |

*subgroup analysis of OAC versus no OAC treatment available from original report
†Same data-base used, therefore data was not taken from these studies for the same outcomes
‡autopsy series was not included in meta-analysis

**Table 1** presents the baseline characteristics of included studies.

Notably, two studies (Azoulay 2012 and Rietbrock 2008)[17, 32] were based on a single database (UK General Practice Research Database), reporting on thromboembolic recurrence in patients from 1993-2008 and 1987-2007, respectively. Thus, to prevent reporting-bias, we used Rietbrock 2008 for the analysis of thromboembolic recurrence, due to its larger sample size. We extracted major haemorrhage rates from Azoulay 2012, as these data were not available from Rietbrock 2008.[17, 32]

**Quality of Evidence**

The risk of bias was assessed for all included studies (Supplementary Table 2). All studies were from representative AF populations. Confounding factors were common potential sources of bias. Eight studies did not report baseline characteristics stratified by AF types. Three studies had significantly older patients or higher incidences of comorbidities in the NPAF group, particularly coronary artery disease, hypertension, chronic heart failure, and diabetes mellitus. Selection bias was common: 13 studies excluded patients who had died after their index stroke. We classified the risk of bias in Petty 1998 [31] for reporting outcomes as serious, because the relative risk (RR) for all-cause mortality could not be reconciled with crude event rates and must have been misreported. We therefore excluded the all-cause mortality data from Petty 1998 [31] in our analysis. Follow-up duration was adequate for most studies. However, Grond 2013 [22] only followed up patients with PAF for the length of hospital stay post-stroke, potentially leading to an underestimate of outcome incidences in PAF. The funnel plot for the log OR of thromboembolic recurrence indicated potential publication bias (Supplementary Figure 1). The distribution of studies was asymmetrical, smaller studies tended to show lower OR than larger studies. Visual inspection of the other funnel plots

showed greater symmetry. Overall, certainty of evidence, in accordance with the GRADE criteria [14], was low (Supplementary Table 3). However, we were conservative in scoring, downgrading the evidence for being observational.

**The impact of AF type on the recurrence of thromboembolism**

Thromboembolic data were recorded by 18 studies, reporting on a total of 17,627 patients (Figure 2). Confounding factors were reported in 10 studies, accounting for 2,535 patients. Patients with NPAF had a higher median NIHSS as well as higher rates of ischaemic heart disease and congestive heart failure than patients with PAF. The mean reported age was 75 in patients with PAF and 77 in patients with NPAF (Supplementary Table 4). Twelve studies compared PAF and NPAF patients and 6 studies reported only on either PAF or NPAF. Three studies (Koga 2016, Paciaroni 2018, Tsivgoulis 2005) [23, 29, 35] reported a composite outcome of systemic embolism and ischaemic stroke recurrence, whilst the others reported ischaemic stroke recurrence alone. The pooled random effects estimates for the risk of recurrent thromboembolism in NPAF and PAF patients were 14.1% (95% confidence interval (CI): 8.2% to 23.1%, Figure 2A) and 9.0% (95% confidence interval: 5.4% to 14.6%, Figure 2B), respectively. The average follow-up times of studies reporting thromboembolic recurrence in NPAF and PAF were 721 days and 577 days, respectively. We conducted a meta-regression to address the assumption of stable risk of thromboembolic recurrence over the follow-up period. This showed a slight reduction of risk with increasing follow-up, but of small magnitude. (Supplementary Figure 2) Considering only the studies that reported follow-up duration, the average annual event rates of thromboembolic recurrence in NPAF and PAF were 7.1% (95%CI: 4.2% to 11.7%) and 5.2% (95%CI: 3.2% to 8.2%), respectively. We performed a sensitivity analysis as Aronow 1999[16] appeared as an outlier. This resulted in a reduction of the estimated NPAF annual event rate, 6.4% (95%CI: 4.2% to 9.5%). Direct comparison of thromboembolic recurrence in NPAF versus PAF showed significant difference, OR was 1.47

(95%CI: 1.08 to 1.99, *p=0.013*), Figure 2C) based on 12 studies (n= 5,680). Heterogeneity as measured with $I^2$ was moderate at 40.1%. The funnel plot indicated potential publication bias (Supplementary Figure 1).

[insert Figure 2.]

*Oral anticoagulation*

Subgroup analysis comparing the incidence of thromboembolism in studies with a low proportion of patients on OAC (i.e. <50%) to studies with a high proportion of patients on OAC (i.e. >50%), showed no significant difference between NPAF and PAF (Supplementary Figure 3). The event rate estimates in NPAF and PAF were non-significantly higher in the studies reporting lower OAC use, by 3.3% (95%CI: -16.8% to 21.2%) and 3.1% (95%CI: -14.3% to 25.7%), respectively.

**The impact of AF type on all-cause mortality post stroke**

All-cause mortality was reported in 18 studies, representing 7,928 patients. Confounding factors were reported in 12 studies, accounting for 5,897 patients. Patients with NPAF had higher median NIHSS and higher rates of ischaemic heart disease and congestive heart failure than patients with PAF. The mean reported age was 75 in patients with PAF and 79 in patients with NPAF (Supplementary Table 4). Fourteen studies compared NPAF and PAF, and 4 studies reported on one AF type (Figure 3). The pooled random effects estimates for all-cause mortality rate in NPAF and PAF were 34.5% (95%CI: 22.7% to 48.4%, Figure 3A) and 16.3% (95%CI: 8.8% to 28.1%, Figure 3B), respectively. The average follow-up times of studies reporting all-cause mortality in NPAF and PAF were 630 days and 584 days, respectively. We conducted a meta-regression to address the assumption of stable risk of mortality over the follow-up period. The risk of mortality in the included studies showed no association to the length of follow-up. Excluding all studies that failed to report follow-up duration, the

estimated annual mortality rates in NPAF and PAF were 20.0% (95%CI: 13.2% to 28.0%) and 10.1% (95%CI: 5.4% to 17.3%), respectively. The OR for all-cause mortality was significant, 1.90 (95%CI: 1.43 to 2.52, *p< 0.001*, Figure 3C). Heterogeneity was moderate ($I^2$=63.0%). [insert Figure 3.]

Baturova 2017 [18] was an outlier. We performed a sensitivity analysis including the 3-year all-cause mortality data of the study (Supplementary Figure 4). Heterogeneity fell to $I^2$=59.8%, with lower event rates and OR (1.75, 95%CI: 1.35 to 2.28). Another outlier, as seen in Figure 3C, was Levy 1999 [24]. We performed a sensitivity analysis, however due to the small weight of the study (n=15), it had little impact on the OR and did not improve the measure of heterogeneity ($I^2$=62.4%).

**The impact of AF type on the risk of major haemorrhage post stroke**

Major haemorrhage data were reported in 8 studies, based on 2,072 patients (Figure 4). Three studies (Azoulay 2012, Grond 2013 and Staszewski 2009) [17, 22, 33] only reported intracranial haemorrhages as major haemorrhage events. The estimated rates of major haemorrhage in NPAF and PAF were 6.3% (95%CI: 2.9%-13.1%, Figure 4A) and 4.4% (95%CI: 3.0% to 6.3%, Figure 4B), respectively. There was no difference in major haemorrhage risk, OR was 1.01 (95%CI: 0.61 to 1.69, *p=0.966*, Figure 4C). Heterogeneity was negligible ($I^2$=0.00). [insert Figure 4.]

## DISCUSSION

**The impact of AF type on the risk of the thromboembolic recurrence**

Our analysis suggests that, in patients with prior stroke, NPAF is associated with a significantly higher risk of thromboembolic recurrence than PAF. Our analysis is distinct from

previously conducted studies evaluating the impact of AF type on clinical outcomes,[5-8] as the vast majority of patients evaluated in these had no prior stroke. Our analysis adds to the findings of a recent meta-analysis, suggesting that NPAF is associated with a significant increase of thromboembolic risk in patients without prior stroke.[6]

AF is associated with a six-fold increase in stroke.[1] Patients with previous ischaemic stroke have an even higher risk. There are several stroke risk-stratification scores for AF patients that determine whether OAC therapy is suitable. However, none account for AF type, and current guidelines recommend that AF type should not influence decisions regarding OAC therapy.[9] Our analysis challenges this, and indicates that the current belief in the equivalence of thromboembolic risk in NPAF and PAF needs to be re-evaluated.

The potential causes for an increased observed thromboembolic recurrence risk in NPAF than PAF patients may be burden of AF, inherent differences in pathophysiology and development of AF or confounding factors. Even though confounding factors stratified by AF type and history of stroke were only reported in 10 studies, these suggest higher rates of comorbidities in patients with NPAF and are likely to have contributed to the perceived higher thromboembolic risks. Exploring the burden of AF among PAF patients may provide further insight into the causes of the differential risk.

Furthermore, AF is a progressive disease. Up to 15% of new-onset PAF patients may progress to NPAF within 1 year.[41] A previous observational study reported that the progression from PAF to NPAF was associated with increased adverse events.[42] Even though we did not specifically look at patients who had progressed, the higher thromboembolic risk for NPAF in our analysis suggests that there may be clinical need to monitor or even prevent the

progression of PAF to NPAF. The potential of catheter ablation and risk factor modification, which slow disease progression,[43, 44] needs further investigation.

We found potential publication bias on inspection of the funnel plot of log OR of thromboembolic recurrence, which could have led to an overestimation of the increased risk associated with NPAF compared to PAF.

The subgroup analysis adjusting for OAC did not suggest any significant difference in thromboembolic recurrence rates in patients with NPAF and PAF. Unfortunately, due to small sample size and incomplete reporting of OAC use post-stroke, we were unable to analyse the efficacy and risks of OAC in NPAF and PAF appropriately. Our findings do not suggest that the effectiveness of OAC in reducing thromboembolic recurrence is dependent on AF type. In fact, given the smaller bleeding risk profile of direct OAC and the emerging evidence for thromboembolic risks in atrial cardiopathies in the absence of AF, more patients may benefit from OAC than are currently treated.[3] Future studies investigating the effects appropriately could provide further guidance for the initiation of thrombo-prophylaxis post-stroke. Moreover, according to ESC guidelines,[9] all patients included in the study should have received OAC unless contraindicated, as $CHA_2DS_2$-$VAS_C$ recommends OAC in patients with previous stroke or TIA. OAC prescription was much lower than anticipated, as several studies reported that less than 50% of their patient population were receiving OAC.

**The impact of AF type on the risk of mortality post stroke**

Our study implies that, in patients with prior stroke, NPAF is associated with an increased risk of all-cause death compared to PAF. The higher risk-profile and comorbidities of NPAF patients, in particular higher rates of ischaemic heart disease and congestive heart failure, may have contributed to a higher mortality rate. The difference in mortality rate in NPAF versus

PAF exceeded the difference of thromboembolic recurrence in our study. As the increased mortality in AF is primarily attributed to cerebrovascular events,[1] the higher mortality rate may have masked thromboembolic recurrence in NPAF patients.

**Strengths and Limitations**

One major limitation of the current study was the restricted sample size, a result of the small number of included studies, poor reporting and missing stratification of data in mixed population studies. This led to wide confidence intervals, particularly for estimated event rates. Unfortunately, we were unable to account for the limitations of included studies. The data available did not allow the analysis of the impact of patients' risk profiles (i.e. $CHA_2DS_2$-$VAS_C$) on the difference in thromboembolic risks. Further studies are needed to explore the impact of AF type on the risk of thromboembolic recurrence at different stroke-risk profiles.

We only included observational studies, only determining association not causation. While they are non-randomised and result in a higher risk of confounding bias, they represent normal population frequencies and are more suitable for meta-analyses in epidemiology than randomised control trials. Our study may also be subject to recording bias and error, as retrospective studies rely on the adequacy of registry data.

We analysed both retrospective and prospective studies together. Previous analyses have demonstrated differences in outcomes between retrospectively and prospectively identified patients with AF.[45] These differences may have increased heterogeneity of results and decreased reliability of the data. Heterogeneity between studies, evaluated by $I^2$ and visual inspection of funnel plots, was moderate for the analysis of thromboembolic recurrence and mortality. We used a random-effects model to adjust for this, maintaining the robustness of results.

We used crude event rates, allowing data uniformity. However, reporting on confounding was poor; thus, we did not adjust for significant confounders. Nevertheless, $CHA_2DS_2$-$VAS_C$, HAS-BLED, NIHSS scores and risk factors for stroke were recorded when possible (Supplementary Table 4). Not adjusting for confounders, such as age, comorbidities and structural heart disease may have led to overestimation of event rates in patients with NPAF. A secondary analysis using adjusted risk ratios, where available, could reduce confounding bias. We did not conduct such an analysis as adjusted risk ratios were only reported in 3 of the 26 studies.

Selection bias, in particular survivor bias, was common in the included studies, which may have diluted true event rates. We included studies that investigated patient outcomes immediately after stroke and others who examined stroke survivors. Thus, our data do not provide insight into whether the time since index stroke influences the risk of recurrence and death. A sensitivity analysis evaluating outcomes in studies with and without survivor bias independently could determine if it has an impact on risks of thromboembolic recurrence or mortality. However, this analysis would have limited our sample size further. Furthermore, due to large variation in follow-up time and missing longitudinal data, we would still be unable to investigate temporal trends of event rates. High mortality rates could have masked thromboembolic recurrence in both PAF and NPAF, therefore underestimating the risk of stroke recurrence. We were unable to adjust for these competing risks in the study-level meta-analysis.

All included studies evaluated AF at baseline without re-evaluating exposure status during follow-up. As PAF can progress into NPAF over time, some patients with PAF may have

unknowingly progressed to NPAF. This could have led to an underestimate of the effect of NPAF.

## CONCLUSIONS

In patients with prior stroke, NPAF is associated with significantly higher risks of thromboembolic recurrence and mortality, compared to PAF. This suggests potential clinical need to monitor or even prevent the progression of AF. Future stratification scores may need to include this parameter to better estimate stroke recurrence risks. Nevertheless, atrial thrombogenicity remains more complex than the categorisation of AF burden. All Patients with previous stroke should receive OAC therapy, and AF burden should not determine whether patients would benefit from OAC.

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**Declaration of conflicting interests**

We report no conflicts of interest relevant to the study reported.

**Informed consent**

Not applicable.

**Ethical approval**

Not applicable.

**Guarantor**

Not applicable.

**Contributorship:** AHAR supervised the project. AM and AHAR developed the protocol, appraised the literature and performed the statistical analysis. AM drafted the initial article. AM and AHAR were involved in reviewing and reporting of the work. All authors provided critical revision of the article for important intellectual content and approved the final version.

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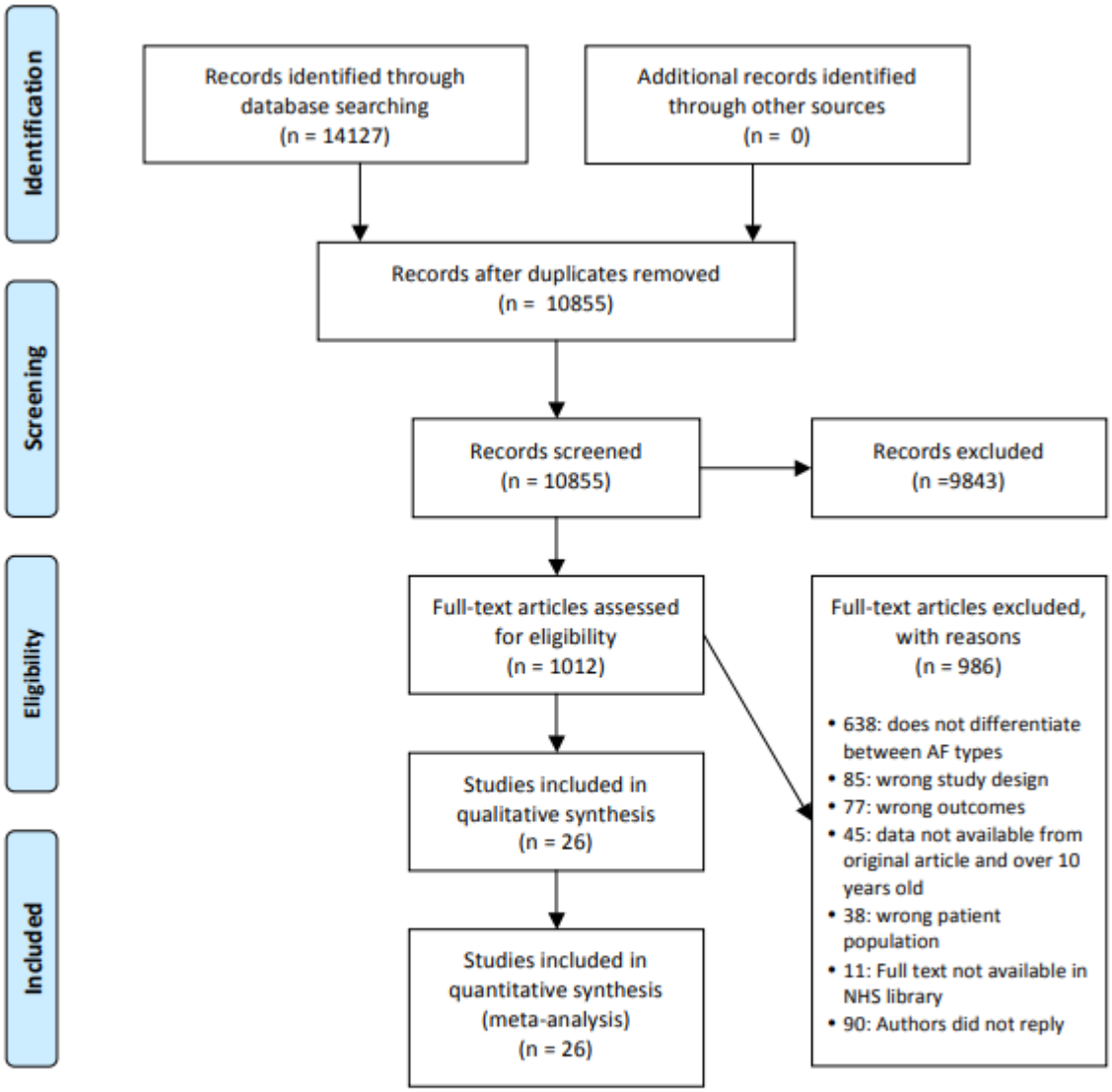
## FIGURES & FIGURES LEGENDS

**Figure 1:** PRISMA for study selection. The final analysis included 26 studies, reporting data from 23,054 patients.

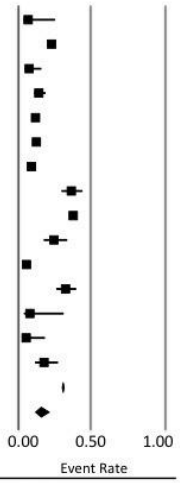



*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.* PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

**Figure 2:** Thromboembolic estimated event rates for non-paroxysmal (NPAF) and paroxysmal atrial fibrillation (PAF) patients and the direct comparison by odds ratio of the risk of thromboembolic recurrence.

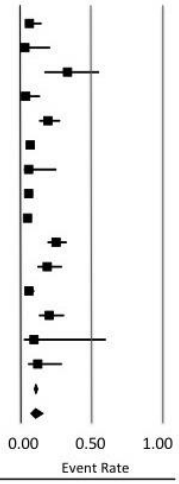
2A Thromboembolic Recurrence Rate in Non-Paroxysmal Atrial Fibrillation

| Model | Study name | Event rate | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|
| | Al-Khalili 2016 | 0.042 | 0.006 | 0.244 | -3.069 | 0.002 |
| | Azoulay 2012 | 0.215 | 0.203 | 0.228 | -34.325 | 0.000 |
| | Britton 1984 | 0.049 | 0.016 | 0.142 | -5.002 | 0.000 |
| | Friberg 2010 | 0.121 | 0.083 | 0.173 | -9.307 | 0.000 |
| | Koga 2016 | 0.096 | 0.077 | 0.119 | -18.185 | 0.000 |
| | Ntaios 2013 | 0.103 | 0.080 | 0.132 | -15.202 | 0.000 |
| | Paciaroni 2018 | 0.066 | 0.053 | 0.082 | -22.346 | 0.000 |
| | Petty 1998 | 0.362 | 0.287 | 0.446 | -3.192 | 0.001 |
| | Rietbrock 2008 | 0.376 | 0.365 | 0.387 | -21.455 | 0.000 |
| | Straszewski 2009 | 0.233 | 0.155 | 0.333 | -4.678 | 0.000 |
| | Tanaka 2016 | 0.030 | 0.015 | 0.058 | -9.732 | 0.000 |
| | Tsivgoulis 2005 | 0.319 | 0.248 | 0.400 | -4.194 | 0.000 |
| | Yamanouchi 1988 | 0.056 | 0.008 | 0.307 | -2.753 | 0.006 |
| | Yanagisawa 2016 | 0.027 | 0.004 | 0.168 | -3.535 | 0.000 |
| | Yu 2018 | 0.159 | 0.091 | 0.265 | -5.055 | 0.000 |
| Fixed | | 0.296 | 0.289 | 0.304 | -45.789 | 0.000 |
| Random | | 0.134 | 0.090 | 0.193 | -8.314 | 0.000 |




2B Thromboembolic Recurrence Rate in Paroxysmal Atrial Fibrillation

| Model | Study name | Event rate | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|
| | Al-Khalili 2016 | 0.049 | 0.016 | 0.142 | -5.002 | 0.000 |
| | Britton 1984 | 0.016 | 0.001 | 0.206 | -2.907 | 0.004 |
| | Christensen 2014 | 0.333 | 0.158 | 0.571 | -1.386 | 0.166 |
| | Grond 2013 | 0.020 | 0.003 | 0.131 | -3.831 | 0.000 |
| | Friberg 2010 | 0.187 | 0.119 | 0.280 | -5.469 | 0.000 |
| | Koga 2016 | 0.055 | 0.037 | 0.081 | -13.514 | 0.000 |
| | Liantinioti 2017 | 0.043 | 0.006 | 0.252 | -3.023 | 0.003 |
| | Ntaios 2013 | 0.043 | 0.025 | 0.075 | -10.486 | 0.000 |
| | Paciaroni 2018 | 0.035 | 0.025 | 0.049 | -18.143 | 0.000 |
| | Petty 1998 | 0.248 | 0.181 | 0.330 | -5.440 | 0.000 |
| | Straszewski 2009 | 0.182 | 0.106 | 0.293 | -4.713 | 0.000 |
| | Tanaka 2016 | 0.045 | 0.023 | 0.087 | -8.448 | 0.000 |
| | Tsivgoulis 2005 | 0.197 | 0.118 | 0.310 | -4.541 | 0.000 |
| | Yamanouchi 1988 | 0.083 | 0.005 | 0.622 | -1.623 | 0.105 |
| | Yanagisawa 2016 | 0.111 | 0.036 | 0.293 | -3.396 | 0.001 |
| Fixed | | 0.092 | 0.079 | 0.107 | -27.296 | 0.000 |
| Random | | 0.090 | 0.054 | 0.146 | -8.203 | 0.000 |




2C Thromboembolic Recurrence Risk in Non-Paroxysmal versus Paroxysmal Atrial Fibrillation

| Model | Study name | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|
| | Al-Khalili 2016 | 0.841 | 0.083 | 8.503 | -0.147 | 0.883 |
| | Britton 1984 | 3.769 | 0.189 | 75.305 | 0.868 | 0.385 |
| | Friberg 2010 | 0.598 | 0.305 | 1.172 | -1.498 | 0.134 |
| | Koga 2016 | 1.821 | 1.130 | 2.934 | 2.461 | 0.014 |
| | Ntaios 2013 | 2.536 | 1.334 | 4.820 | 2.839 | 0.005 |
| | Paciaroni 2018 | 1.944 | 1.268 | 2.981 | 3.051 | 0.002 |
| | Petty 1998 | 1.722 | 1.014 | 2.924 | 2.013 | 0.044 |
| | Straszewski 2009 | 1.364 | 0.612 | 3.038 | 0.759 | 0.448 |
| | Tanaka 2016 | 0.646 | 0.238 | 1.755 | -0.856 | 0.392 |
| | Tsivgoulis 2005 | 1.911 | 0.947 | 3.858 | 1.807 | 0.071 |
| | Yamanouchi 1988 | 0.943 | 0.033 | 26.632 | -0.035 | 0.972 |
| | Yanagisawa 2016 | 0.222 | 0.022 | 2.264 | -1.270 | 0.204 |
| Fixed | | 1.573 | 1.278 | 1.936 | 4.280 | 0.000 |
| Random | | 1.466 | 1.083 | 1.985 | 2.476 | 0.013 |

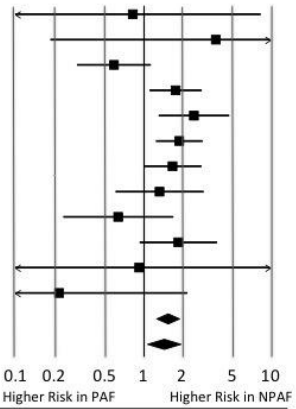
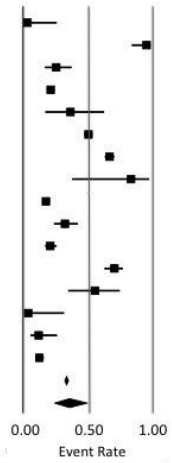


**Figure 3:** All cause mortality estimated event rates for non-paroxysmal (NPAF) and paroxysmal atrial fibrillation (PAF) patients and the direct comparison by odds ratio of the risk of all-cause mortality.

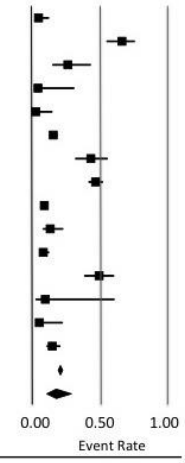
3A All-Cause Mortality Rate in Non-Paroxysmal Atrial Fibrillation

| Model | Study name | Event rate | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|
| | Al-Khalili 2016 | 0.020 | 0.001 | 0.251 | -2.724 | 0.006 |
| | Baturova 2017 | 0.955 | 0.836 | 0.989 | 4.207 | 0.000 |
| | Britton 1984 | 0.246 | 0.154 | 0.369 | -3.769 | 0.000 |
| | Koga 2016 | 0.202 | 0.175 | 0.232 | -15.192 | 0.000 |
| | Levy 1999 | 0.357 | 0.157 | 0.624 | -1.054 | 0.292 |
| | Marini 2005 | 0.499 | 0.464 | 0.533 | -0.070 | 0.944 |
| | Ntaios 2013 | 0.665 | 0.624 | 0.704 | 7.469 | 0.000 |
| | Önundarson 1987 | 0.833 | 0.369 | 0.977 | 1.469 | 0.142 |
| | Palomaki 2017 | 0.165 | 0.148 | 0.183 | -25.601 | 0.000 |
| | Straszewski 2009 | 0.314 | 0.225 | 0.419 | -3.364 | 0.001 |
| | Tanaka 2016 | 0.199 | 0.156 | 0.251 | -9.146 | 0.000 |
| | Tsivgoulis 2005 | 0.702 | 0.622 | 0.772 | 4.656 | 0.000 |
| | Wolf 1978 | 0.550 | 0.336 | 0.747 | 0.446 | 0.655 |
| | Yamanouchi 1988 | 0.026 | 0.002 | 0.310 | -2.519 | 0.012 |
| | Yanagisawa 2016 | 0.108 | 0.041 | 0.255 | -3.986 | 0.000 |
| | Zolotovskaya 2018 | 0.113 | 0.084 | 0.150 | -12.274 | 0.000 |
| Fixed | | 0.322 | 0.307 | 0.337 | -21.693 | 0.000 |
| Random | | 0.345 | 0.227 | 0.484 | -2.173 | 0.030 |




3B All-Cause Mortality Rate in Paroxysmal Atrial Fibrillation

| Model | Study name | Event rate | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|
| | Al-Khalili 2016 | 0.031 | 0.008 | 0.115 | -4.803 | 0.000 |
| | Baturova 2017 | 0.677 | 0.555 | 0.779 | 2.789 | 0.005 |
| | Britton 1984 | 0.258 | 0.135 | 0.437 | -2.573 | 0.010 |
| | Christensen 2014 | 0.026 | 0.002 | 0.310 | -2.519 | 0.012 |
| | Grond 2013 | 0.010 | 0.001 | 0.141 | -3.233 | 0.001 |
| | Koga 2016 | 0.145 | 0.115 | 0.182 | -13.012 | 0.000 |
| | Marini 2005 | 0.436 | 0.312 | 0.569 | -0.941 | 0.347 |
| | Ntaios 2013 | 0.473 | 0.415 | 0.532 | -0.901 | 0.368 |
| | Palomaki 2017 | 0.075 | 0.063 | 0.090 | -25.183 | 0.000 |
| | Straszewski 2009 | 0.121 | 0.062 | 0.224 | -5.253 | 0.000 |
| | Tanaka 2016 | 0.067 | 0.039 | 0.115 | -8.788 | 0.000 |
| | Tsivgoulis 2005 | 0.500 | 0.382 | 0.618 | 0.000 | 1.000 |
| | Yamanouchi 1988 | 0.083 | 0.005 | 0.622 | -1.623 | 0.105 |
| | Yanagisawa 2016 | 0.037 | 0.005 | 0.221 | -3.197 | 0.001 |
| | Zolotovskaya 2018 | 0.137 | 0.091 | 0.201 | -7.825 | 0.000 |
| Fixed | | 0.195 | 0.178 | 0.213 | -25.181 | 0.000 |
| Random | | 0.163 | 0.088 | 0.281 | -4.612 | 0.000 |




3C All-Cause Mortality Risk in Non-Paroxysmal versus Paroxysmal Atrial Fibrillation

| Model | Study name | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|
| | Al-Khalili 2016 | 0.518 | 0.024 | 11.188 | -0.419 | 0.675 |
| | Baturova 2017 | 10.023 | 2.212 | 45.405 | 2.990 | 0.003 |
| | Britton 1984 | 0.938 | 0.347 | 2.532 | -0.127 | 0.899 |
| | Koga 2016 | 1.489 | 1.081 | 2.052 | 2.435 | 0.015 |
| | Levy 1999 | 0.193 | 0.007 | 5.603 | -0.957 | 0.338 |
| | Marini 2005 | 1.285 | 0.741 | 2.229 | 0.894 | 0.371 |
| | Ntaios 2013 | 2.210 | 1.643 | 2.973 | 5.243 | 0.000 |
| | Palomaki 2017 | 2.424 | 1.924 | 3.056 | 7.501 | 0.000 |
| | Straszewski 2009 | 3.318 | 1.392 | 7.905 | 2.707 | 0.007 |
| | Tanaka 2016 | 3.442 | 1.784 | 6.643 | 3.686 | 0.000 |
| | Tsivgoulis 2005 | 2.357 | 1.290 | 4.306 | 2.789 | 0.005 |
| | Yanagisawa 2016 | 3.152 | 0.332 | 29.924 | 1.000 | 0.318 |
| | Zolotovskaya 2018 | 0.801 | 0.455 | 1.410 | -0.770 | 0.442 |
| Fixed | | 1.985 | 1.734 | 2.274 | 9.919 | 0.000 |
| Random | | 1.896 | 1.429 | 2.515 | 4.434 | 0.000 |

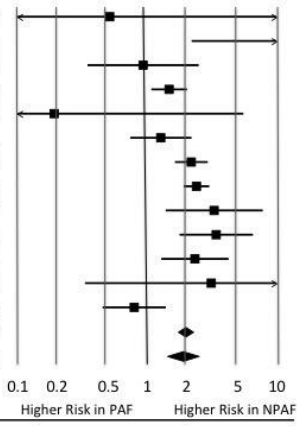


**Figure 4:** The estimated event rates of major haemorrhage for non-paroxysmal (NPAF) and paroxysmal atrial fibrillation (PAF) and the direct comparison by odds ratio of the risk of major haemorrhage.

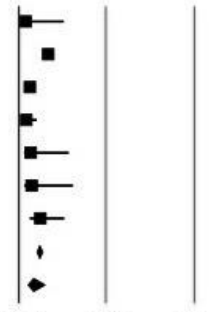
4A

## Major Haemorrhage Rate in Non-Paroxysmal Atrial Fibrillation

| Model | Study name | Event rate | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|
| | Al-Khalili 2016 | 0.020 | 0.001 | 0.251 | -2.724 | 0.006 |
| | Azoulay 2012 | 0.155 | 0.126 | 0.190 | -13.482 | 0.000 |
| | Koga 2016 | 0.045 | 0.032 | 0.062 | -17.429 | 0.000 |
| | Straszewski 2009 | 0.023 | 0.006 | 0.088 | -5.224 | 0.000 |
| | Wolf 1978 | 0.050 | 0.007 | 0.282 | -2.870 | 0.004 |
| | Yamanouchi 1988 | 0.056 | 0.008 | 0.307 | -2.753 | 0.006 |
| | Yanagisawa 2016 | 0.108 | 0.041 | 0.255 | -3.986 | 0.000 |
| Fixed | | 0.099 | 0.083 | 0.118 | -22.468 | 0.000 |
| Random | | 0.063 | 0.029 | 0.131 | -6.519 | 0.000 |

Statistics for each study

Event rate and 95% CI



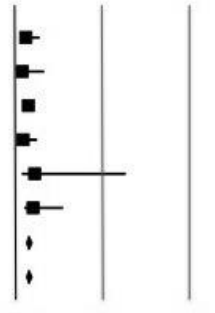

4B

## Major Haemorrhage Rate in Paroxysmal Atrial Fibrillation

| Model | Study name | Event rate | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|
| | Al-Khalili 2016 | 0.031 | 0.008 | 0.115 | -4.803 | 0.000 |
| | Grond 2013 | 0.010 | 0.001 | 0.141 | -3.233 | 0.001 |
| | Koga 2016 | 0.046 | 0.030 | 0.070 | -13.235 | 0.000 |
| | Straszewski 2009 | 0.015 | 0.002 | 0.100 | -4.143 | 0.000 |
| | Yamanouchi 1988 | 0.083 | 0.005 | 0.622 | -1.623 | 0.105 |
| | Yanagisawa 2016 | 0.074 | 0.019 | 0.252 | -3.437 | 0.001 |
| Fixed | | 0.044 | 0.030 | 0.063 | -15.392 | 0.000 |
| Random | | 0.044 | 0.030 | 0.063 | -15.392 | 0.000 |

Statistics for each study

Event rate and 95% CI




4C

## Major Haemorrhage Risk in Non-Paroxysmal versus Paroxysmal Atrial Fibrillation

| Model | Study name | Odds ratio | Lower limit | Upper limit | Z-Value | p-Value |
|---|---|---|---|---|---|---|
| | Al-Khalili 2016 | 0.518 | 0.024 | 11.188 | -0.419 | 0.675 |
| | Koga 2016 | 0.972 | 0.552 | 1.711 | -0.098 | 0.922 |
| | Straszewski 2009 | 1.548 | 0.137 | 17.443 | 0.353 | 0.724 |
| | Yamanouchi 1988 | 0.943 | 0.033 | 26.632 | -0.035 | 0.972 |
| | Yanagisawa 2016 | 1.515 | 0.257 | 8.941 | 0.459 | 0.646 |
| Fixed | | 1.011 | 0.606 | 1.688 | 0.043 | 0.966 |
| Random | | 1.011 | 0.606 | 1.688 | 0.043 | 0.966 |

Statistics for each study

Odds ratio and 95% CI