European Heart Journal (2016) **37**, 1591–1602
doi:10.1093/eurheartj/ehw007

META-ANALYSIS
Arrhythmia/electrophysiology

The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis

Anand N. Ganesan[1,2,3,4], Derek P. Chew[1,2,3], Trent Hartshorne[1], Joseph B. Selvanayagam[1,2,3], Philip E. Aylward[1,2,3], Prashanthan Sanders[3,4], and Andrew D. McGavigan[1,2*]

[1]Flinders University, Sturt Road, Bedford Park, Adelaide, SA 5042, Australia; [2]Department of Cardiology, Flinders Medical Centre, Flinders Drive, Bedford Park, Adelaide, SA 5042, Australia; [3]South Australian Health and Medical Research Institute, North Terrace, Adelaide, SA 5000, Australia; and [4]Centre for Heart Rhythm Disorders, University of Adelaide and Royal Adelaide Hospital, North Terrace, Adelaide, SA 5000, Australia

Received 16 June 2015; revised 16 December 2015; accepted 7 January 2016; online publish-ahead-of-print 16 February 2016

See page 1603 for the editorial comment on this article (doi:10.1093/eurheartj/ehw014)

Aims Thromboembolic risk stratification schemes and clinical guidelines for atrial fibrillation (AF) regard risk as independent of classification into paroxysmal (PAF) and non-paroxysmal atrial fibrillation (NPAF). The aim of the current study was to conduct a systematic review evaluating the impact of AF type on thromboembolism, bleeding, and mortality.

Methods and results PubMed was searched through 27 November 2014 for randomized controlled trials, cohort studies, and case series reporting prospectively collected clinical outcomes stratified by AF type. The incidence of thromboembolism, mortality, and bleeding was extracted. Atrial fibrillation clinical outcome data were extracted from 12 studies containing 99 996 patients. The unadjusted risk ratio (RR) for thromboembolism in NPAF vs. PAF was 1.355 (95% CI: 1.169–1.571, $P < 0.001$). In the study subset off oral anticoagulation, unadjusted RR was 1.689 (95% CI: 1.151–2.480, $P = 0.007$). The overall multivariable adjusted hazard ratio (HR) for thromboembolism was 1.384 (95% CI: 1.191–1.608, $P < 0.001$). The overall unadjusted RR for all-cause mortality was 1.462 (95% CI: 1.255–1.703, $P < 0.001$). Multivariable adjusted HR for all-cause mortality was 1.217 (95% CI: 1.085–1.365, $P < 0.001$). Rates of bleeding were similar, with unadjusted RR 1.00 (95% CI: 0.919–1.087, $P = 0.994$) and adjusted HR 1.025 (95% CI: 0.898–1.170, $P = 0.715$).

Conclusion Non-paroxysmal atrial fibrillation is associated with a highly significant increase in thromboembolism and death. These data suggest the need for new therapies to prevent AF progression and further studies to explore the integration of AF type into models of thromboembolic risk.

Keywords Atrial fibrillation • Stroke • Thromboembolism • Systematic review • Meta-analysis

Clinical perspective

Atrial fibrillation (AF) is currently classified by the duration and frequency of AF episodes into paroxysmal and non-paroxysmal AF. The current study suggests that non-paroxysmal AF may be associated with an increased risk of stroke and mortality. Atrial fibrillation type may therefore need to be considered in decision making for oral anticoagulation in AF patients and the overall management of AF patients.

Clincal outlook 1

Future investigations to understand the role of AF type in decision-making for oral anticoagulation in AF patients will be needed.

Clinical outlook 2

New therapies to prevent AF progression may be important to improve the survival of AF patients.

* Corresponding author. Tel: +61 423827706; fax: +618-8204 5625. Email: andrew.mcgavigan@health.sa.gov.au

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2016. For permissions please email: journals.permissions@oup.com.

Downloaded from http://eurheartj.oxfordjournals.org/ by guest on June 12, 2016

Introduction

Atrial fibrillation (AF) is associated with an increased risk of stroke and death.[1,2] At present, the prevailing paradigm is that the risk of stroke in AF patients is independent of patient classification into paroxysmal (PAF) and non-paroxysmal forms of AF (NPAF).[3–8] Stroke risk stratification in AF is therefore based around the concept that embolic risk is driven by patient-level risk factors rather than AF type.[9,10]

To a large extent, this paradigm has been based on historical evidence demonstrating relative risk equivalence for stroke in between PAF and NPAF.[11,12] To date, no published stroke risk stratification model in AF patients has included AF type.[6,13] The consensus of PAF and NPAF stroke risk equivalence is reflected in clinical guidelines that explicitly recommend that decisions regarding oral anticoagulation (OAC) be made independently of classification into PAF or NPAF.[3,4]

Although previous systematic reviews have examined risk factors for stroke in AF,[9,10,14] to our knowledge, no systematic review has specifically investigated the role of AF type as a risk factor for thromboembolism, mortality, and bleeding. Recently, the body of evidence examining the impact of AF type on stroke risk has significantly expanded, with a series of studies exploring this issue.[15–19] In the context of this new information, we sought to re-evaluate the paradigm of stroke risk equivalence between PAF and NPAF, and the impact of AF type on mortality and bleeding risk. We therefore undertook a systematic literature review and meta-analysis of studies of prospectively collected clinical data examining the clinical outcomes in AF patients with outcome data stratified by AF type.

Methods

Study search, inclusion/exclusion criteria, and data extraction

We conducted a systematic search of PubMed to identify randomized controlled trials (RCTs), cohort studies, and case series data in which prospectively collected clinical outcome data were stratified by AF type. No specifications were placed on interventions originally evaluated in included reports. The incidence of thromboembolism, mortality, and bleeding was extracted.

In studies utilizing definitions of AF type other than in the American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) guidelines, AF types were matched with the closest contemporary definition. The term 'sustained' or 'constant' AF was grouped with NPAF. The term 'intermittent' AF was grouped with PAF.

The exclusion criteria for the primary analysis included articles failing to report outcomes stratified by AF type, and articles on topics other than AF outcomes. Review articles, commentary, conference papers, and case reports were excluded. Studies reporting outcomes in retrospectively collected data were excluded from the primary analysis, but a separate secondary analysis of these data was undertaken.

The study protocol was registered in PROSPERO (CRD42015017575). The search was conducted with a research librarian, with the search grid outlined in the Supplementary material online. The database was accessed on 27 November 2014. Two authors (A.N.G. and T.H.) reviewed titles and abstracts. Reference lists of retrieved articles were also studied to ascertain any additional relevant studies. *Figure 1* shows the number and reasons for exclusion of publications. Study quality was assessed with a modified Newcastle–Ottawa scale (Supplementary material online). The study complies with the Declaration of Helsinki.

Statistical analysis

Statistical analysis was performed with Comprehensive Meta-Analysis 2 (Biostat, Englewood, NJ, USA). Risk ratios (RRs) were computed for dichotomous variables. For adjusted hazard ratios (HRs), pooled estimates were calculated from multivariable HRs. For two articles, confidence intervals were re-calculated due to asymmetry of the log values of the published upper and lower confidence intervals.[20] Mean or median follow-up data were used to estimate effect sizes where data were provided in the form of event rates. The I^2 statistic was used as a measure of variability in observed effect estimates attributable to between-study heterogeneity.[21] For variables exhibiting mild heterogeneity ($I^2 \leq 25\%$), pooled estimates were derived with fixed effects models. For variables exhibiting more than moderate heterogeneity ($I^2 > 25\%$), pooled estimates were derived with random-effects models.[22] As an additional analysis, univariate meta-regression for unadjusted log-relative risk of thromboembolism in NPAF vs. PAF was performed utilizing $CHADS_2$ (C, congestive heart failure; H, hypertension; A, age ≥75 years; D, diabetes mellitus; S_2, prior stroke or transient ischaemic attack or thromboembolism) risk factors as candidate variables (Supplementary material online).

Results

A total of 6252 citations were retrieved. After initial screening of abstracts and titles on general criteria, 5936 citations were excluded, and 317 citations were selected for a secondary review. From these citations, 12 journal articles were identified, referencing 10 published RCTs or pooled RCT series and 2 prospective observational cohort studies.[11,12,15–18,23–27]

Baseline characteristics of included studies

The baseline characteristics of included studies are presented in *Tables 1* and *2*. A total of 99 996 patients were included from 12 studies. Included studies were published from 1990 to 2015. Sample size varied from 409 to 21 109 patients. Ten studies included data from large-scale, prospective, multicentre RCTs. Two studies were prospectively collected case series. Follow-up varied from 1 to 2.8 years. The mean age of patients varied from 62 to 73 years. The proportion of female patients varied from 27 to 43%. $CHADS_2$ scores were reported in five studies, and CHA_2DS_2VASc [C, congestive heart failure or left ventricular systolic dysfunction; H, hypertension; A_2, age ≥75 years; D, diabetes mellitus; S_2, previous stroke or transient ischaemic attack or thromboembolism; V, vascular disease; A, age 65–74 years; Sc, sex category (i.e. female sex)] scores were reported in two studies.

Impact of atrial fibrillation type on thromboembolism

Stroke or systemic embolism data were reported in 12 studies representing 99 996 patients. The pooled unadjusted estimate for the annualized risk of thromboembolism in NPAF patients was 2.17% per annum (95% CI: 1.81–2.53% per annum). The pooled

Downloaded from http://eurheartj.oxfordjournals.org/ by guest on June 12, 2016

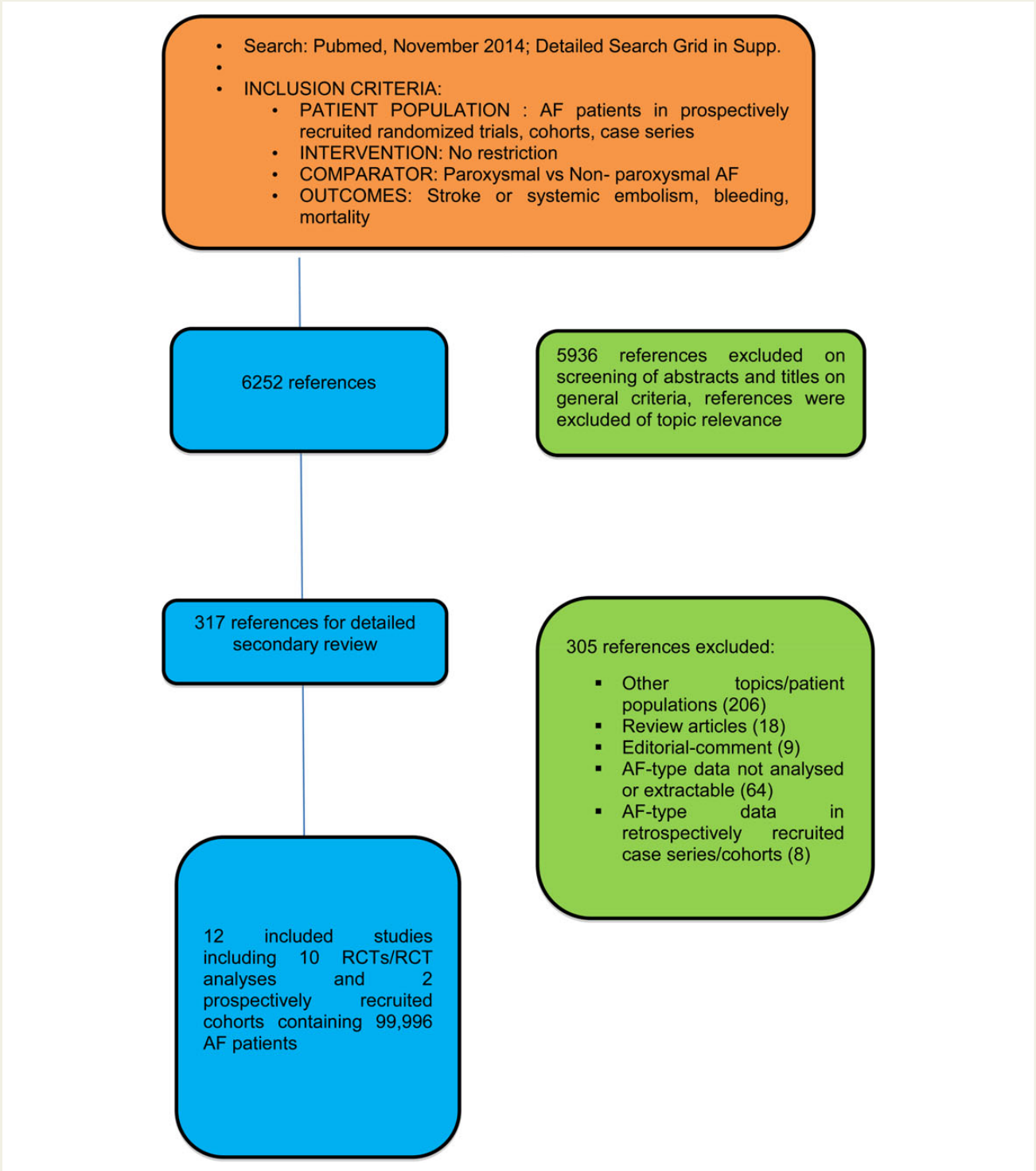


Figure 1 Search flow diagram. Search flow diagram for included studies. The study included eight randomized controlled trials and two prospective cohorts, reporting data from 99 996 patients.

unadjusted estimate for the annualized risk of thromboembolism in PAF patients was 1.50% per annum (95% CI: 1.23–1.76% per annum). The pooled unadjusted RR for thromboembolism in NPAF patients was 1.355 (95% CI: 1.169–1.571, $P < 0.001$, *Figure 2A*). The variable I^2 was moderate at 57.8%. Multivariable adjusted HRs for thromboembolism were reported in 7 of 12 studies, representing 58 421 patients (see Supplementary material online for complete table of adjustment covariates, but each of these studies provided adjusted data for stroke risk factors including age, gender, hypertension, heart failure, previous thromboembolism, and

Downloaded from http://eurheartj.oxfordjournals.org/ by guest on June 12, 2016

Table 1 Baseline characteristics for included randomized controlled trials

Study name	Year	Study type	Patient number (*n*)	Patient numbers by AF type		Inclusion criteria	Comparators	Oral anticoagulation (%)	Follow-up duration
				PAF	NPAF				
AVERROES and ACTIVE A[19]	2015	RCT analysis of aspirin treated patients from the AVERROES and ACTIVE A trials	6563	1576	4720 (persistent 1136) (permanent 3854)	ACTIVE A: AF with one stroke risk factor and a contraindication for OAC; AVERROES: AF with one risk factor for stroke and patients unsuitable for warfarin	ACTIVE A: clopidogrel plus aspirin AVERROES: apixaban vs. aspirin	All patients in analysis on aspirin without OAC	ACTIVE A: 18 months; AVERROES: 20 months
ROCKET-AF[18]	2014	RCT analysis of patients from the ROCKET-AF trial	14 264	2514	11 548 (persistent 11 548)	Non-valvular AF plus high risk of stroke	Rivaroxaban vs. warfarin	100	707 days
ARISTOTLE[16]	2013	RCT analysis of patients from the ARISTOTLE trial	18 201	2786	15 412	AF and at least one risk factor for stroke	Apixaban vs. warfarin	100	1.8 years
GISSI-AF[17]	2013	RCT analysis	1234	771	463	ECG-documented symptomatic AF or previous cardioversion	Valsartan vs. placebo	PAF: 24.9%-warfarin Persistent: 87.26%-warfarin	1 year
RE-LY[15]	2012	RCT analysis of patients from the RE-LY trial	18 467	5943	12 164 (persistent 5789) (permanent 6475)	AF and risk factor for stroke	Dabigatran vs. warfarin	100%	2 years
ENGAGE AF-TIMI-38[26]	2013	RCT data from ENGAGE AF TIMI-48 RCT	21 099	5366	15 733 (persistent 4868) (permanent 10 865)	AF and risk factors for stroke ($CHADS_2 \geq 2$)	Edoxaban vs. warfarin	100%	2.8 years
Euro Heart Survey[25]	2008	Prospective observational	4133	1509	2624 (persistent 1109) (permanent 1515)	Hospitalized or ambulant AF patients	No comparator	Paroxysmal 51% NPAF 78%	1 year
SPORTIF[24]	2008	RCT analysis of SPORTIF III and V trials	7329	836	6493 (persistent 6493)	Non-valvular AF at moderate to high risk for thromboembolism	Ximelagatran vs. warfarin	100%	SPORTIF III: 18 months; SPORTIF V: 20 months
ACTIVE W[12]	2007	RCT	6697	1202	5495 (Sustained AF 5495)	AF and at least one risk factor for stroke	Aspirin plus clopidogrel vs. warfarin	PAF: 54.8% NPAF: 79.8%	1.3 years

Downloaded from http://eurheartj.oxfordjournals.org/ by guest on June 12, 2016

ELAT[27]	2004	Prospective observational	409	159 (defined as intermittent AF)	250 (defined as constant AF)	Outpatients with constant or intermittent AF	No comparator	36% of whole cohort on OAC; OAC not stratified by AF type	101 months
SPAF[11]	2000	RCT analysis of patients from SPAF trials treated with aspirin or aspirin plus fixed-dose warfarin	2012	460	1552	SPAF I–III trial patients Documented intermittent or sustained AF without mitral stenosis or valve prostheses	Aspirin vs. fixed-dose warfarin	All patients included in analysis on aspirin without full-dose OAC	2 years
BAATAF[23]	1990	RCT analysis	420	70 (defined as intermittent AF)	350 (defined as sustained AF)	Chronic non-rheumatic sustained or intermittent AF	Aspirin vs. adjusted dose warfarin	Warfarin or no therapy	2.3 years

Table 2 **Patient characteristics in included studies**

Study name	$CHADS_2$-NPAF	$CHADS_2$-PAF	CHA_2DS_2VASc-NPAF	CHA_2DS_2VASc-PAF	Age (years) (mean/ median)	Female (%)	Previous stroke or systemic embolism (%)	Hypertension (%)	Diabetes mellitus (%)	Heart failure (%)
AVERROES/ACTIVE A	–	–	3.47	3.1	69	42	10	87	19	35
ROCKET-AF	3.5	3.5	4.9	4.9	73	40	55	91	40	63
ARISTOTLE	2.1	2	–	–	69	35	19	90	35	30
GISSI-AF	–	–	–	–	68	39	6	85	15	8
RE-LY	2.15	2.1	–	–	72	36	20	79	23	32
ENGAGE AF-TIMI-48	–	–	–	–	72	38	28	93	36	57
Euro Heart Survey	–	–	–	–	67	43	12	65	18	36
SPORTIF	–	–	–	–	71	31	21	77	24	37
ACTIVE W	2.04	1.79	–	–	70	34	17	81	30	17
ELAT	–	–	–	–	62	36	23	47	18	32
SPAF	–	–	–	–	69	29	8	53	15	19
BAATAF	–	–	–	–	68	28	3	51	20	35

Downloaded from http://eurheartj.oxfordjournals.org/ by guest on June 12, 2016

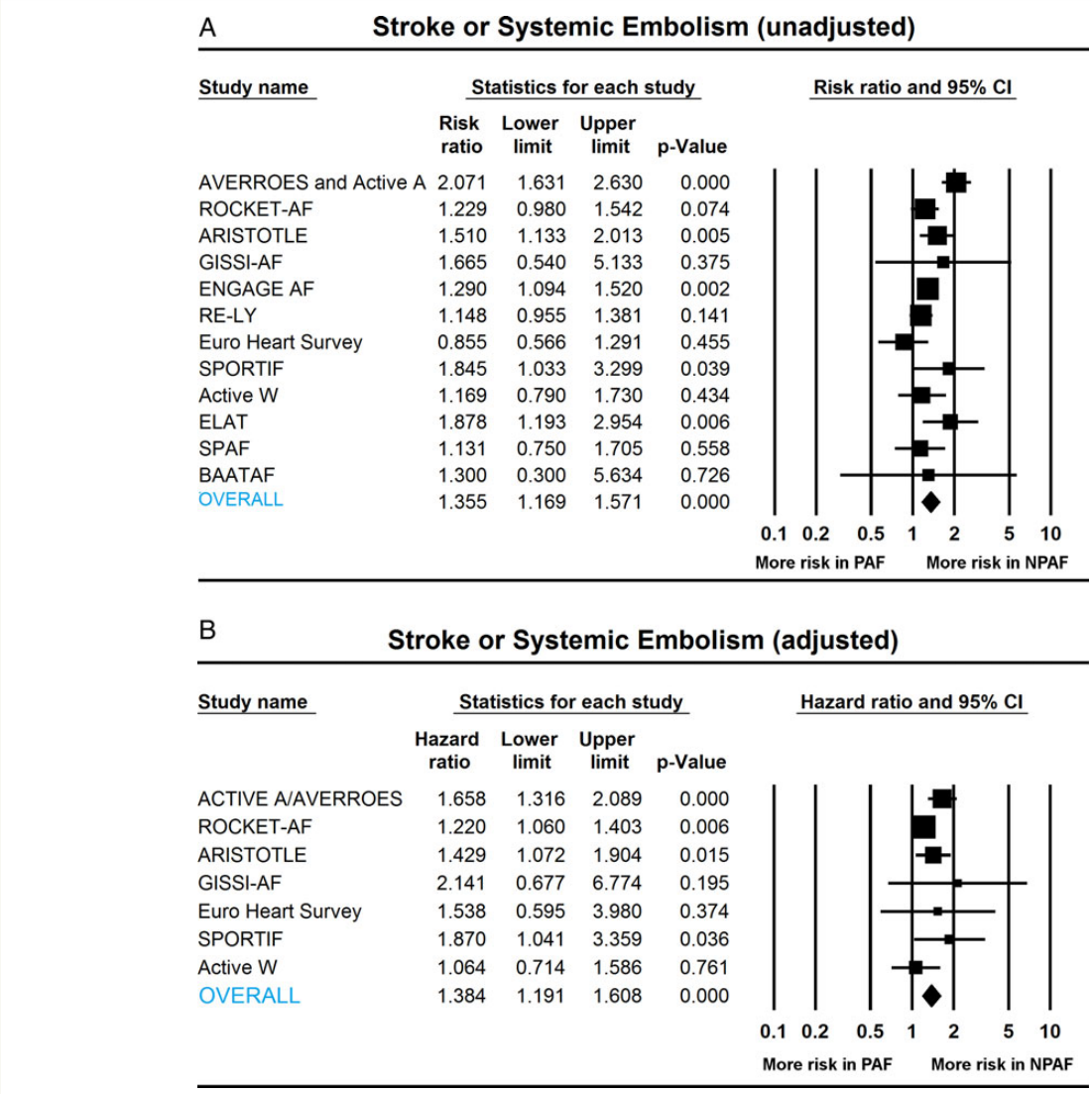


Figure 2 Stroke or systemic embolism. Stroke and systemic embolism data were reported for non-paroxysmal atrial fibrillation and paroxysmal atrial fibrillation in 12 studies ($n = 99\,996$ patients). The pooled risk ratio for stroke in non-paroxysmal atrial fibrillation patients was 1.355 (95% CI: 1.169–1.571, $P < 0.001$, $I^2 = 61.8\%$) (*A*). Multivariable adjusted hazard ratios were reported in seven studies ($n = 58\,421$ patients). The pooled adjusted hazard ratio for thromboembolism in non-paroxysmal atrial fibrillation vs. paroxysmal atrial fibrillation was 1.384 (95% CI: 1.191–1.608, $P < 0.001$, $I^2 = 28.841\%$) (*B*).

diabetes mellitus). The pooled adjusted HR for thromboembolism in NPAF patients vs. PAF was 1.384 (95% CI: 1.191–1.608, $P < 0.001$, $I^2 = 28.841\%$, *Figure 2B*).

Impact of atrial fibrillation type on all-cause mortality

All-cause mortality was reported in six studies representing outcomes in 45 570 patients. The pooled unadjusted estimate for annualized mortality rate in NPAF was 3.89% per annum (95% CI: 3.04–4.74% per annum, $P < 0.001$). The pooled unadjusted estimate for annualized mortality rate in PAF was 2.79% per annum (95% CI: 2.11–3.47% per annum, $P < 0.001$). The pooled unadjusted relative risk for all-cause mortality in NPAF vs. PAF patients was 1.462 (95% CI: 1.255–1.703, $P < 0.001$, $I^2 = 39.4\%$, *Figure 3A*).

Multivariable adjusted mortality data were reported in four studies representing 41 028 patients (see Supplementary material online for complete table of adjustment covariates). The pooled adjusted HR for mortality with NPAF was 1.217 (95% CI: 1.085–1.365, $P < 0.001$, $I^2 = 0.0\%$, *Figure 3B*).

Impact of atrial fibrillation type on the risk of bleeding

Major bleeding data were reported by AF type in seven studies representing 92 532 patients. The RR for bleeding in NPAF vs. PAF was 0.986 (95% CI: 0.917–1.060, $P = 0.700$, $I^2 = 3.6\%$, *Figure 4A*). Multivariable adjusted HRs for bleeding were reported in five studies representing 44 210 patients (see Supplementary material online for table of adjustment covariates). The pooled adjusted

Downloaded from http://eurheartj.oxfordjournals.org/ by guest on June 12, 2016

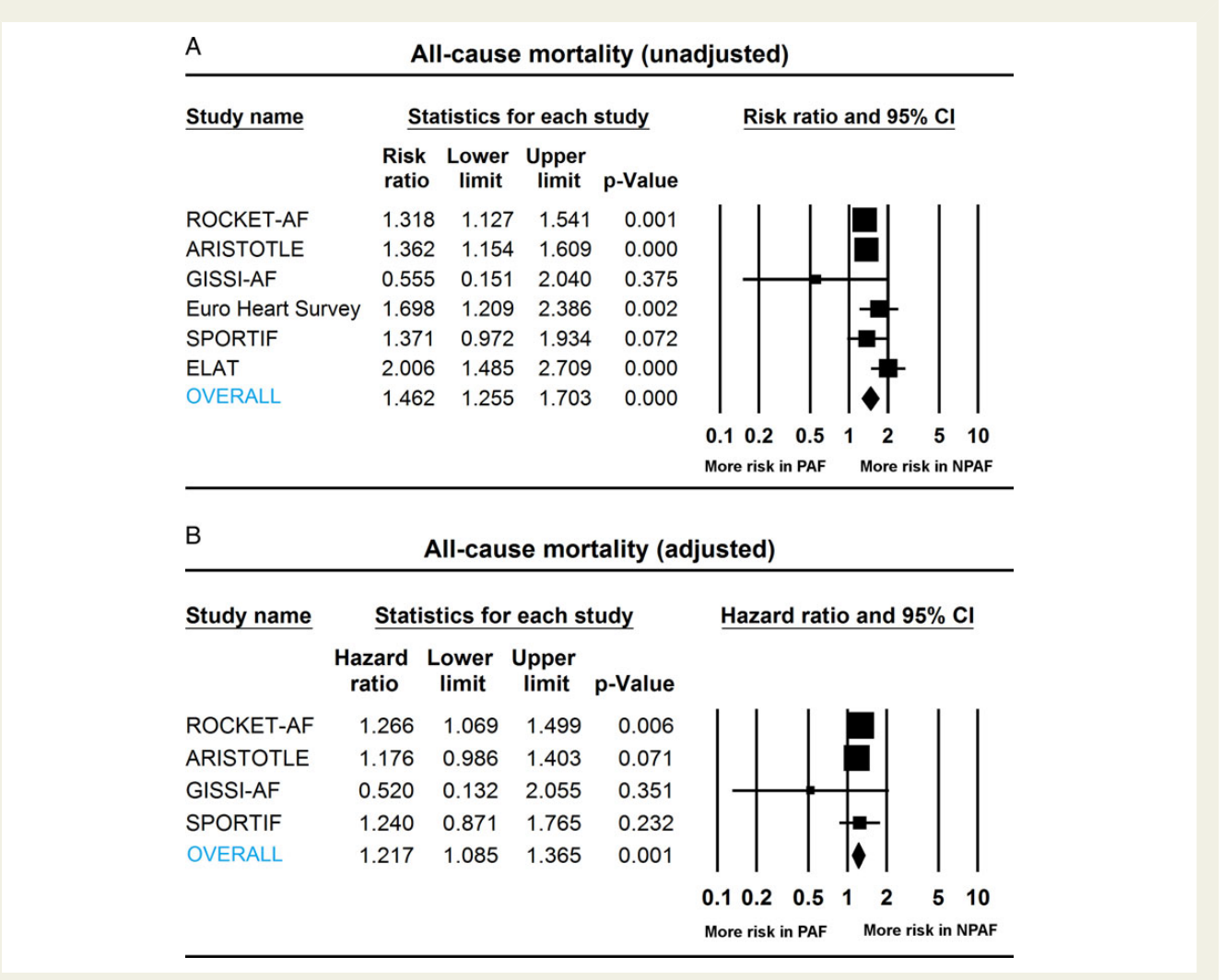


Figure 3 All-cause mortality. All-cause mortality was reported in six studies ($n = 45\,570$ patients). The pooled unadjusted relative risk for all-cause mortality in non-paroxysmal atrial fibrillation vs. paroxysmal atrial fibrillation patients was 1.462 (95% CI: 1.255–1.703, $P < 0.001$, $I^2 = 39.4\%$) (*A*). Multivariable adjusted hazard ratios for mortality were reported in four studies ($n = 41\,028$ patients). The pooled adjusted hazard ratio for mortality with non-paroxysmal atrial fibrillation was 1.217 (95% CI: 1.085–1.365, $P < 0.001$, $I^2 = 0.0\%$) (*B*).

HR for major bleeding was 1.025 (95% CI: 0.898–1.170, $P = 0.715$, *Figure 4B*).

Secondary analyses of unadjusted risk of stroke or systemic embolism

Secondary analyses were undertaken to explore the key finding of increased thromboembolic risk in NPAF and identify potential sources of heterogeneity. We firstly undertook a cumulative analysis, in which studies were ordered by publication year. It became clear that a statistically significant increase in NPAF vs. PAF RR for stroke first became clear after the SPORTIF publication, which remained consistent as further studies including novel oral anticoagulant (NOAC) agents were added (*Figure 5A*).

To address the issue of standardization of AF type definition, a subgroup analysis in studies utilizing definitions of AF type after the AHA/ACC/European Society of Cardiology (ESC) guidelines of 2006 was included. In this analysis including seven studies with 84 067 patients, the RR of stroke or systemic embolism was 1.334 (95% CI: 1.103–1.614, $P = 0.003$, *Figure 5B*).

A subgroup analysis was undertaken to explore the effect of OAC. Three studies reported data in patients exclusively not on OAC (SPAF, ACTIVE A/AVERROES analysis, and ACTIVE W). In these studies, the RR of thromboembolism in NPAF vs. PAF was 1.689 (95% CI: 1.151–2.480, $P = 0.007$, *Figure 5C*). Five studies reported data where all patients received OAC (either warfarin or NOAC). In these studies, the unadjusted RR of stroke or systemic embolism in NPAF vs. PAF was 1.274 (95% CI: 1.149–1.414, $P < 0.001$, *Figure 5D*).

Meta-regression

To explore the mechanisms for the unadjusted increased risk of stroke and thromboembolism in NPAF vs. PAF, exploratory

Downloaded from http://eurheartj.oxfordjournals.org/ by guest on June 12, 2016

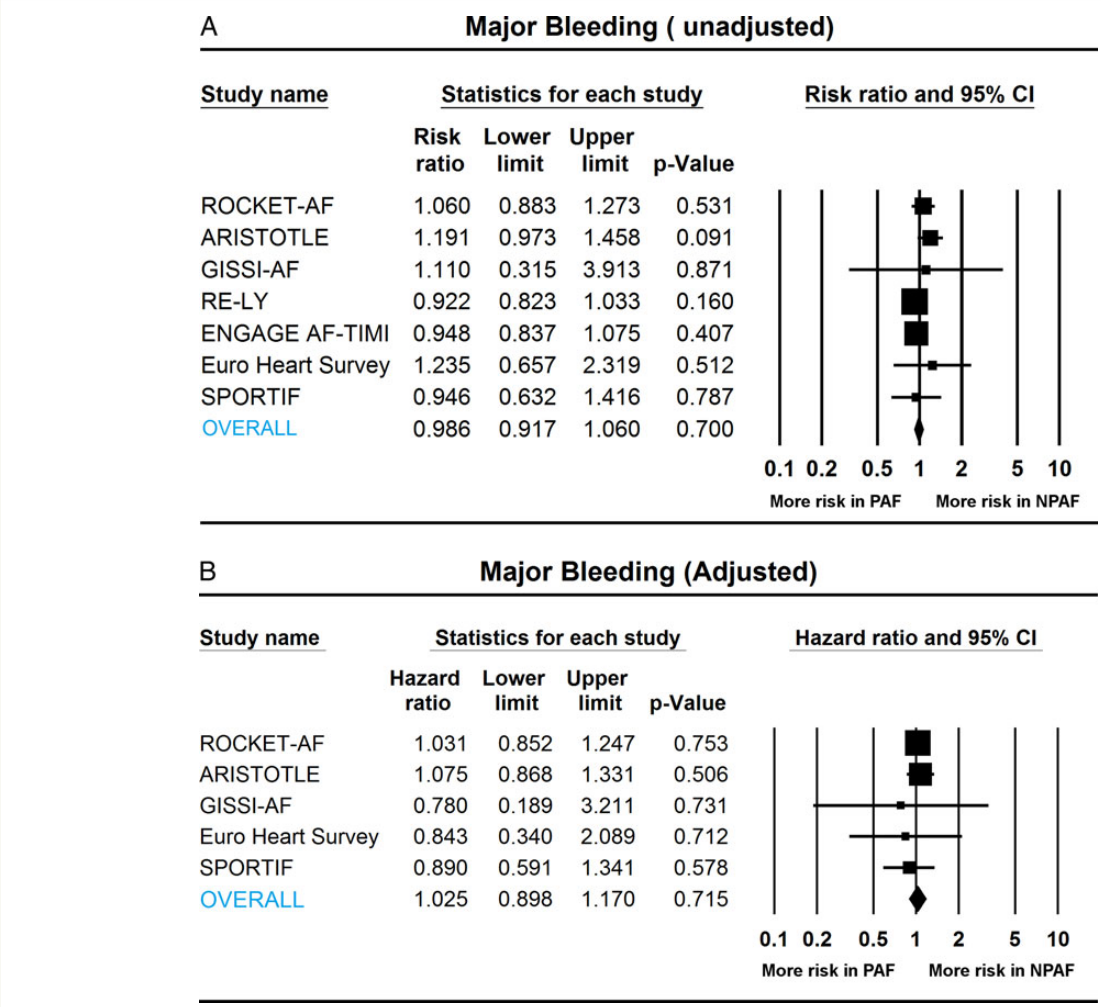


Figure 4 Risk of bleeding. Major bleeding data were reported in 6 of 10 studies representing 62 677 patients. The risk ratio for bleeding in non-paroxysmal atrial fibrillation vs. paroxysmal atrial fibrillation was 0.986 (95% CI: 0.917–1.060, $P = 0.700$, $I^2 = 3.6\%$) (*A*). Multivariable adjusted hazard ratios for bleeding were reported in five studies representing 44 210 patients. The pooled adjusted hazard ratio for major bleeding was 1.025 (95% CI: 0.898–1.170, $P = 0.715$) (*B*).

univariate meta-regression analysis was undertaken with study-level candidate variables including age, female gender, hypertension, previous stroke or systemic thromboembolism, diabetes mellitus, and heart failure. None of these study-level covariates was a significant predictor of the increased risk of stroke and systemic embolism identified in the meta-analysis of unadjusted thromboembolism data (Supplementary material online). This suggests, at least the study-level variables, that AF type may be an independent predictor of stroke or systemic embolism.

Retrospective studies evaluating impact of atrial fibrillation type on the risk of stroke or systemic embolism

As a supplementary analysis, we performed a meta-analysis of the risk of stroke in the 10 studies reporting on retrospective outcome data relating to AF type and stroke or systemic embolism (Supplementary material online). In these studies, the pooled RR for stroke or systemic embolism in NPAF patients was 1.456 (95% CI: 1.137–1.865, $P = 0.003$, $I^2 = 72.4\%$). When combined with the prospective studies, the overall pooled RR for stroke or systemic embolism in NPAF patients was 1.335 (95% CI: 1.185–1.504, $P < 0.001$, $I^2 = 63.4\%$), consistent with the point estimate in the primary analysis.

Study quality

Study quality was assessed with a modified Newcastle–Ottawa scale, with summary information provided in Supplementary material online. Study quality in the 12 studies contributing to the primary analysis was considered overall strong. All studies were from the representative AF populations. Follow-up duration was adequate

Downloaded from http://eurheartj.oxfordjournals.org/ by guest on June 12, 2016

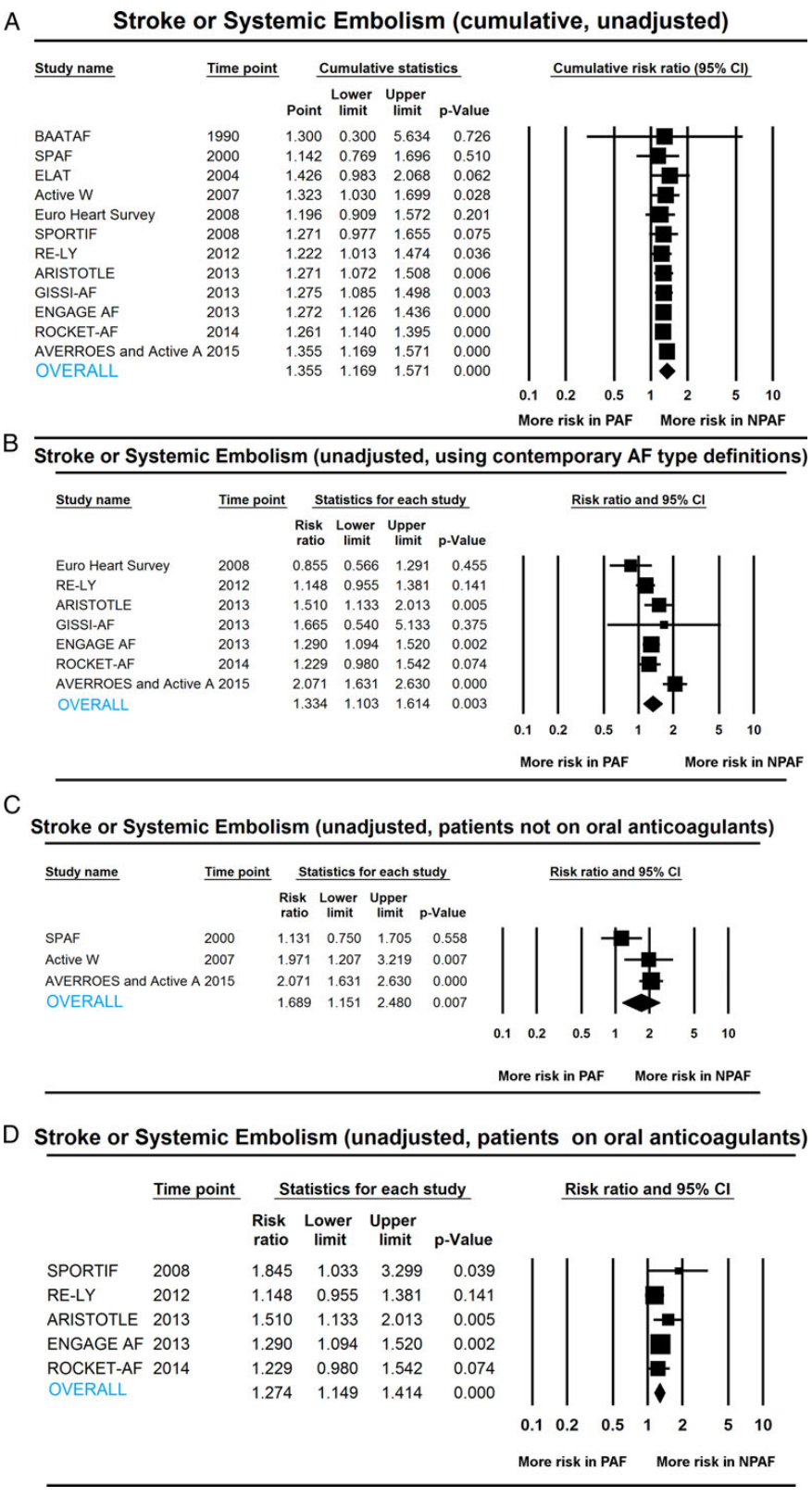


Figure 5 Secondary analyses of unadjusted thromboembolic risk data. A cumulative meta-analysis of the unadjusted thromboembolism was undertaken with studies ordered by year of publication (*A*). Statistical significance showing increased rates of stroke in non-paroxysmal atrial fibrillation vs. paroxysmal atrial fibrillation patients was achieved after the SPORTIF trial. In the subgroup of studies utilizing contemporary definitions of atrial fibrillation type, the risk ratio of stroke or systemic embolism was 1.334 (95% CI: 1.103–1.614, $P = 0.003$) (*B*). In the subgroup of studies reporting data in patients not on oral anticoagulation, pooled unadjusted risk ratio of stroke or systemic embolism was 1.689 (95% CI: 1.151–2.480, $P = 0.007$) (*C*). In the subgroup of studies where all patients were anticoagulated with either NOAC or warfarin, the pooled unadjusted risk ratio for stroke or systemic embolism was 1.288 (95% CI: 1.100–1.507) (*D*).

Downloaded from http://eurheartj.oxfordjournals.org/ by guest on June 12, 2016

in all studies. Outcome assessment involved blinded adjudication in 8 of 10 studies. Outcomes adjusted for baseline covariates were reported in 7 of 10 studies.

Discussion

Temporally based classification of AF into PAF and NPAF has gained widespread acceptance in clinical practice.[3,4] The principal finding of our study is that NPAF is associated with a significantly increased risk of thromboembolism and death compared with PAF. This finding was consistently observed in data adjusted for baseline stroke risk factors. The effect of NPAF and thromboembolic risk was significantly larger in studies of patients not on OAC, but remained present in the subset of studies where all patients were on OAC. Increased stroke risk was observed in the subset of studies utilizing contemporary definitions of AF type published after the AHA/ACC/ESC guidelines of 2006.

In considering these findings, it should further be noted that AF type is known to be dynamic. Paroxysmal atrial fibrillation is known to progress to NPAF in many patients over time.[28–30] Our study utilized data sets that classified patients at baseline only, which may have a potentially dilutive effect on the impact of NPAF. Therefore, the effect size of AF type on thromboembolism and mortality could potentially be underestimated in this study.

The primary analysis aggregated prospectively collected data in >99 000 patients. The quality of the included studies was strong, with most of the data acquired from contemporary representative AF populations with at least moderate risk of stroke. Included studies were multicentre, prospectively recruited, with well-defined outcome assessments and patterns of follow-up, increasing the reliability of source data. A separate analysis of retrospectively collected data also identified an increased risk of thromboembolism in NPAF.

Impact of atrial fibrillation type on the risk of stroke and systemic thromboembolism

Historically, the risk of thromboembolism has been considered to be independent of AF type.[3,4,11,12] Previous systematic reviews of risk factors for stroke in AF patients have not identified AF type as an important prognostic risk factor for thromboembolism.[9,10,31] Atrial fibrillation stroke risk prediction models have in general not included AF type,[6–8,13] perhaps because hospitalization/discharge databases used as derivation and validation cohorts have not included data coded by AF type. This consensus of risk equivalence between AF types is reflected in Class I and IIa recommendations in current North American[3] and European AF[4] guidelines. The data presented in the current study suggest that the current paradigm of thromboembolic risk equivalence between NPAF and PAF may need to be re-evaluated. Future studies exploring the impact of integration of AF type in thromboembolic risk models may be required.

Impact of atrial fibrillation type on the risk of mortality

Although AF itself is known to be associated with increased mortality,[2,32] the current study represents the largest aggregated AF patient data set to demonstrate increased mortality in NPAF vs. PAF patients. The mechanisms by which NPAF patients experienced increased mortality were unable to be investigated; however, potential mechanisms include worsened heart failure,[32] or more severe stroke events,[33] or perhaps a higher burden of non-cardiovascular illness. The association of NPAF with mortality suggests that prevention of AF progression may potentially not only impact on AF symptom burden or stroke risk, but could also potentially improve survival.

Atrial fibrillation type—driving force or risk marker?

A key question is whether the increased risk of thromboembolism in NPAF occurs as a consequence of an increased prevalence of clinical co-morbidities, or operates causally as an independent risk factor. Supporting the notion of AF type as an independent risk factor, were the pooled adjusted estimates for thromboembolic risk and death. Additionally, no association of AF type was seen with major bleeding, which would be expected if there were substantial differences in the distribution of clinical co-morbidities between NPAF and PAF. The absence of an association with bleeding supports the hypothesis that the associations of NPAF with thromboembolism and death may be a specific effect attributable to AF type.

Limitations

A number of important questions could not be answered in the study. First, there was insufficient data to analyse the impact of permanent vs. persistent AF. Second, although it was clear that NPAF increases stroke risk, we could not assess whether NPAF-related excess thromboembolic risk applies uniformly across all levels of $CHADS_2/CHA_2DS_2VASc$. Integrating AF type into existing stroke scoring systems would clearly be most important in the low/moderate risk group of $CHADS_2/CHA_2DS_2VASc$ of 0–1, as clearly patients with $CHADS_2/CHA_2DS_2VASc \geq 2$ would be recommended for OAC on the basis of clinical risk factors. Integration of NPAF into $CHADS_2/CHA_2DS_2VASc$ is of particular salience because of differences in OAC guidelines between North America and Europe, where two different approaches are utilized for $CHADS_2/CHA_2DS_2VASc$ 1 patients.[3,4] We could not, however, in this study assess the number of patients who would be reclassified with modified stroke scoring systems incorporating NPAF as an extra risk marker.

Conclusions

Non-paroxysmal atrial fibrillation is associated with a highly significant increase in thromboembolism and death. These data suggest the need for new therapies to prevent AF progression and further studies to explore the integration of AF type into models of thromboembolic risk.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Downloaded from http://eurheartj.oxfordjournals.org/ by guest on June 12, 2016

Authors' contributions

A.N.G. and D.P.C. performed statistical analysis. A.D.M. handled funding and supervision. A.N.G. and T.H. acquired the data. A.N.G. and A.D.M. conceived and designed the research. A.N.G. drafted the manuscript. A.N.G., D.P.C., T.H., P.E.A., P.S., J.B.S., and A.D.M. made critical revision of the manuscript for key intellectual content.

Acknowledgements

The authors acknowledge the support of Mr Michael Draper, of the University of Adelaide Barr Smith Library, for assistance with the development of the study search.

Funding

A.N.G. is supported by an Australian Early Career Health Practitioner Fellowship from the National Health and Medical Research Council of Australia (NHMRC). D.P.C. and P.S. are supported by the National Heart Foundation of Australia. P.S. is supported by a Practitioner Fellowship of the NHMRC.

Conflict of interest: J.B.S. has received lecture and/or consulting fees from Medtronic, St Jude Medical, Biotronik, Bayer, and Boehringer Ingelheim and research funding from Biotronik and St Jude Medical. P.S. has served on the advisory board of Biosense-Webster, Medtronic, St Jude Medical, Sanofi-Aventis, and Merck, Sharpe and Dohme; received lecture and/or consulting fees from Biosense-Webster, Medtronic, St Jude Medical, Boston Scientific, Merck, Sharpe and Dohme, Biotronik, and Sanofi-Aventis; and received research funding from Medtronic, St Jude Medical, Boston Scientific, Biotronik, and Sorin. A.D.M.has served on the advisory board of St Jude Medical and Boston Scientific; and received lecture and/or consulting fees from Biotronik, Medtronic, St Jude Medical, Boston Scientific, and Bayer.

References

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;**22**:983–988.
2. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998;**98**:946–952.
3. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW, American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. *J Am Coll Cardiol* 2014;**64**:e1–e76.
4. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH, ESC Committee for Practice Guidelines. Guidelines for the management of atrial fibrillation: Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace* 2010;**12**:1360–1420.
5. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohloser SH, Hindricks G, Kirchhof P, ESC Committee for Practice Guidelines. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. *Eur Heart J* 2012;**33**:2719–2747.
6. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;**285**:2864–2870.
7. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach. *Chest* 2010;**137**:263–272.
8. Singer DE, Chang Y, Borowsky LH, Fang MC, Pomernacki NK, Udaltsova N, Reynolds K, Go AS. A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: the ATRIA study stroke risk score. *J Am Heart Assoc* 2013;**2**:e000250.
9. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. *Neurology* 2007;**69**:546–554.
10. Hughes M, Lip GY. Stroke and thromboembolism in atrial fibrillation: a systematic review of stroke risk factors, risk stratification schema and cost effectiveness data. *Thromb Haemost* 2008;**99**:295–304.
11. Hart RG, Pearce LA, Rothbart RM, McAnulty JH, Asinger RW, Halperin JL, Stroke Prevention in Atrial Fibrillation Investigators. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. *J Am Coll Cardiol* 2000;**35**:183–187.
12. Hohnloser SH, Pajitnev D, Pogue J, Healey JS, Pfeffer MA, Yusuf S, Connolly SJ. Incidence of stroke in paroxysmal versus sustained atrial fibrillation in patients taking oral anticoagulation or combined antiplatelet therapy: an ACTIVE W Substudy. *J Am Coll Cardiol* 2007;**50**:2156–2161.
13. Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB, Larson MG, Kannel WB, Benjamin EJ. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA* 2003;**290**:1049–1056.
14. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994;**154**:1449–1457.
15. Flaker G, Ezekowitz M, Yusuf S, Wallentin L, Noack H, Brueckmann M, Reilly P, Hohnloser SH, Connolly S. Efficacy and safety of dabigatran compared to warfarin in patients with paroxysmal, persistent, and permanent atrial fibrillation: results from the RE-LY study. *J Am Coll Cardiol* 2012;**59**:854–855.
16. Al-Khatib SM, Thomas L, Wallentin L, Lopes RD, Gersh B, Garcia D, Ezekowitz J, Alings M, Yang H, Alexander JH, Flaker G, Hanna M, Granger CB. Outcomes of apixaban vs. warfarin by type and duration of atrial fibrillation: results from the ARISTOTLE trial. *Eur Heart J* 2013;**34**:2464–2471.
17. Disertori M, Franzosi MG, Barlera S, Cosmi F, Quintarelli S, Favero C, Cappellini G, Fabbri G, Maggioni AP, Staszewsky L, Moroni LA, Latini R, GISSI-AF Investigators. Thromboembolic event rate in paroxysmal and persistent atrial fibrillation: data from the GISSI-AF trial. *BMC Cardiovasc Disord* 2013;**13**:28.
18. Steinberg BA, Hellkamp AS, Lokhnygina Y, Patel MR, Breithardt G, Hankey GJ, Becker RC, Singer DE, Halperin JL, Hacke W, Nessel CC, Berkowitz SD, Mahaffey KW, Fox KA, Califf RM, Piccini JP. Higher risk of death and stroke in patients with persistent vs. paroxysmal atrial fibrillation: results from the ROCKET-AF trial. *Eur Heart J* 2015;**36**:288–296.
19. Vanassche T, Lauw MN, Eikelboom JW, Healey JS, Hart RG, Alings M, Avezum A, Diaz R, Hohnloser SH, Lewis BS, Shestakovska O, Wang J, Connolly SJ. Risk of ischaemic stroke according to pattern of atrial fibrillation: analysis of 6563 aspirin-treated patients in ACTIVE-A and AVERROES. *Eur Heart J* 2015;**36**:281–287a.
20. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med* 1998;**17**:2815–2834.
21. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;**21**:1539–1558.
22. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177–188.
23. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med* 1990;**323**:1505–1511.
24. Lip GY, Frison L, Grind M. Stroke event rates in anticoagulated patients with paroxysmal atrial fibrillation. *J Intern Med* 2008;**264**:50–61.
25. Nieuwlaat R, Dinh T, Olsson SB, Camm AJ, Capucci A, Tieleman RG, Lip GY, Crijns HJ. Should we abandon the common practice of withholding oral anticoagulation in paroxysmal atrial fibrillation? *Eur Heart J* 2008;**29**:915–922.
26. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM, ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;**369**:2093–2104.
27. Stollberger C, Chnupa P, Abzieher C, Langer T, Finsterer J, Klem I, Hartl E, Wehinger C, Schneider B. Mortality and rate of stroke or embolism in atrial fibrillation during long-term follow-up in the embolism in left atrial thrombi (ELAT) study. *Clin Cardiol* 2004;**27**:40–46.
28. De Vos CB, Breithardt G, Camm AJ, Dorian P, Kowey PR, Le Heuzey JY, Naditch-Brule L, Prystowsky EN, Schwartz PJ, Torp-Pedersen C, Weintraub WS, Crijns HJ. Progression of atrial fibrillation in the REgistry on Cardiac rhythm disORDers assessing the control of Atrial Fibrillation cohort: clinical correlates and the effect of rhythm-control therapy. *Am Heart J* 2012;**163**:887–893.
29. Camm AJ, Breithardt G, Crijns H, Dorian P, Kowey P, Le Heuzey JY, Merioua I, Pedrazzini L, Prystowsky EN, Schwartz PJ, Torp-Pedersen C, Weintraub W. Real-life observations of clinical outcomes with rhythm- and rate-control therapies for

Downloaded from http://eurheartj.oxfordjournals.org/ by guest on June 12, 2016

atrial fibrillation RECORDAF (Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation). *J Am Coll Cardiol* 2011;**58**:493–501.
30. Kerr CR, Humphries KH, Talajic M, Klein GJ, Connolly SJ, Green M, Boone J, Sheldon R, Dorian P, Newman D. Progression to chronic atrial fibrillation after the initial diagnosis of paroxysmal atrial fibrillation: results from the Canadian Registry of Atrial Fibrillation. *Am Heart J* 2005;**149**:489–496.
31. Pisters R, Lane DA, Marin F, Camm AJ, Lip GY. Stroke and thromboembolism in atrial fibrillation. *Circ J* 2012;**76**:2289–2304.
32. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation* 2003;**107**:2920–2925.
33. Deguchi I, Fukuoka T, Hayashi T, Maruyama H, Sehara Y, Kato Y, Horiuchi Y, Nagamine Y, Sano H, Tanahashi N. Clinical outcomes of persistent and paroxysmal atrial fibrillation in patients with stroke. *J Stroke Cerebrovasc Dis* 2014;**23**:2840–2844.

CARDIOVASCULAR FLASHLIGHT

doi:10.1093/eurheartj/ehv609
Online publish-ahead-of-print 9 November 2015

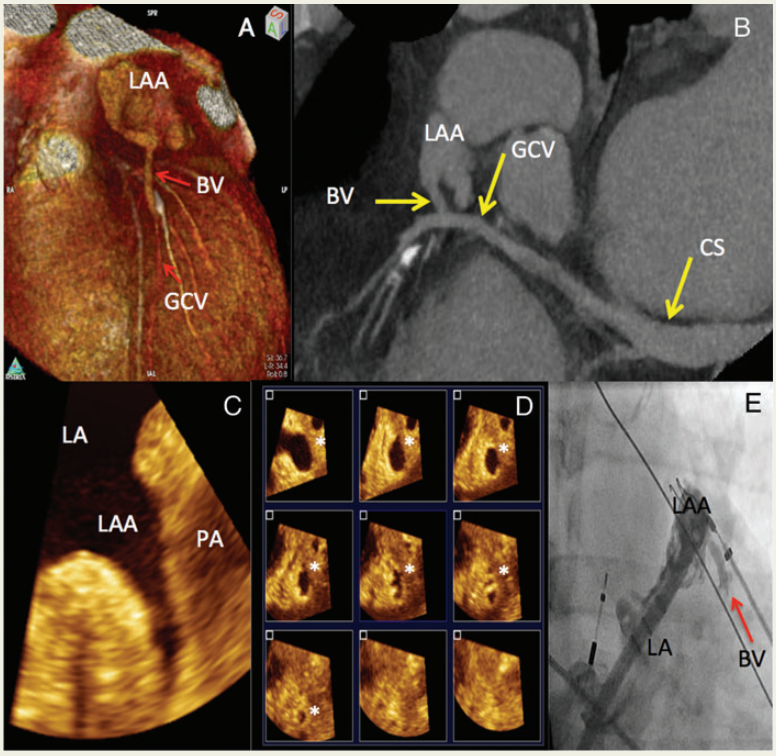
Left atrial appendage to great cardiac vein fistula complicating watchman left atrial appendage closure

Sreekanth Vemulapalli[1,2]*, Lynne M. Hurwitz Koweek[3], Todd L. Kiefer[1], Kevin P. Jackson[1], and Jonathan P. Piccini[1,2]

[1]Division of Cardiology, Department of Medicine, Duke University Medical Center, Box 3026, Durham, NC 27710, USA; [2]Duke Clinical Research Institute, Durham, NC, USA; and [3]Department of Radiology, Duke University Medical Center, USA

* Corresponding author. Tel: +1 919 668 8917, Fax: +1 919 668 7026, Email: sreekanth.vemulapalli@duke.edu

A 67-year-old man with persistent atrial fibrillation, recurrent gastrointestinal bleeding, and recent percutaneous coronary intervention presented for evaluation of left atrial appendage (LAA) closure. Pre-procedural TEE revealed an EF of >55%, an intact interatrial septum and no evidence of LAA thrombus. Pre-procedural CT revealed a vessel connecting the anterior tip of the LAA to the great cardiac vein (*Panel 1*). Intraprocedural LAA angiography confirmed the presence of this bridging vein from the anterior tip of the LAA to the great cardiac vein.



The advent of percutaneous LAA closure techniques has brought renewed interest in LAA anatomy related to thrombosis risk and suitability for epicardial vs. transseptal closure techniques. Multiple studies have reported a correlation between stroke risk and LAA flow velocity and LAA anatomy. While LAA anatomy varies, there are no previous reports of the presence of a bridging vein and its impact on LAA flow velocity and stroke risk.

Similarly, the impact of an LAA bridging vein on LAA closure techniques is unknown. Lariat epicardial closure would be anatomically prohibitive given the location of the bridging vein. While endocardial device closure may successfully occlude the os of the LAA and result in thrombotic occlusion of the bridging vein, the bridging vein also presents a potential conduit for LAA thrombus to the right atrium. In this case, a 30 mm WATCHMAN device was successfully placed. Transoesophageal echocardiogram at 45 days demonstrated no LAA flow around the device and the patient was transitioned off warfarin to aspirin and clopidogrel.

Panel (*A*) Three-dimensional volume rendered reconstruction of the patient's pre-procedure cardiac computed tomography. (*B*) Curved multiplanar reconstruction of the patient's pre-procedure cardiac computed tomography. (*C*) Two-dimensional transoesophageal echocardiogram of the pre-procedure left atrial appendage at 45°. (*D*) Three-dimensional transoesophageal echocardiogram short-axis multiplanar reconstruction slices of the left atrial appendage from superior to inferior. (*E*) Intraprocedure contrast fluoroscopy of the left atrial appendage. BV, bridging vein; CS, coronary sinus; LA, left atrium; LAA, left atrial appendage; GCV, great cardiac vein; *, left atrial appendage.

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2015. For permissions please email: journals.permissions@oup.com.

Downloaded from http://eurheartj.oxfordjournals.org/ by guest on June 12, 2016