

G OPEN ACCESS

Citation: Krittayaphong R, Boonyapiphat T, Aroonsiriwattana S, Ngamjanyaporn P, Lip GYH (2023) Causes of death of patients with nonvalvular atrial fibrillation in Asians. PLoS ONE 18(3): e0282455. https://doi.org/10.1371/journal. pone.0282455

Editor: Redoy Ranjan, BSMMU: Bangabandhu Sheikh Mujib Medical University, BANGLADESH

Received: October 4, 2022

Accepted: February 11, 2023

Published: March 1, 2023

Copyright: © 2023 Krittayaphong et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the paper.

Funding: This study was funded by a grant from the Heart Association of Thailand under the Royal Patronage of H.M. the King (by RK). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors declare no personal or professional conflicts of interest relating to any aspect of this paper.

RESEARCH ARTICLE

Causes of death of patients with non-valvular atrial fibrillation in Asians

Rungroj Krittayaphong^{1*}, Thanita Boonyapiphat², Suchart Aroonsiriwattana³, Pornchai Ngamjanyaporn⁴, Gregory Y. H. Lip^{5,6}

 Faculty of Medicine Siriraj Hospital, Department of Medicine, Division of Cardiology, Mahidol University, Bangkok, Thailand, 2 Lampang Hospital, Lampang, Thailand, 3 Surat Thani Hospital, Surat Thani, Thailand,
 Chonburi Hospital, Chonburi, Thailand, 5 Liverpool Centre for Cardiovascular Science at the University of Liverpool, Liverpool John Moores University and the Liverpool Heart & Chest Hospital, Liverpool, United Kingdom, 6 Faculty of Medicine, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

* rungroj.kri@mahidol.ac.th

Abstract

Objectives

The aim of this study was to determine the causes of death among Asian non-valvular atrial fibrillation (AF) patients who were registered in a nationwide AF registry, and to investigate the differences in the causes of death in AF patients compared between those who were taking and not taking oral anticoagulant (OAC).

Methods

The **CO**hort of antithrombotic use and **O**ptimal INR Level in patients with non-valvular **A**trial **F**ibrillation in Thailand (COOL-AF) study enrolled non-valvular AF patients from 27 centers in Thailand during 2014–2017 to create the COOL-AF Thailand registry. Cause of death was classified as cardiovascular (CV) death, non-CV death, or undetermined cause of death. All events were evaluated and verified by an independent adjudication committee.

Results

There was a total of 3,405 patients (mean age: 67.8 years, 41.8% female), and the mean follow-up duration was 31.8±8.7 months. Three hundred and eighty patients (11.2%) died during follow-up. CV death, non-CV death, and undetermined cause accounted for 121 (31.8%), 189 (49.7%), and 70 (18.4%) patients, respectively. Of those with a known cause of death, heart failure (10%), intracranial hemorrhage (ICH; 10%), sudden cardiac death (6.8%), and ischemic stroke (5.8%) were the most often observed causes of death. Concerning non-CV death, infection/sepsis (27.7%), cancer (5.5%), respiratory (5.2%), and major bleeding (4.5%) were the most prevalent causes of death. The use and type of OAC were found to be major determinants of ICH and major bleeding incidence.

Conclusion

Death due to ischemic stroke was responsible for only 4.7% of all deaths in Asian AF patients. Non-CV death, such as infection/sepsis or malignancy, was more far more

prevalent than CV death in Asian AF patients. An improved integrated care approach is needed to reduce the prevalence of non-CV death in Asian AF patients.

Introduction

The prevalence of non-valvular atrial fibrillation (AF) is increasing in older adults [1]. AF is a known cause of many serious complications, such as ischemic stroke from thromboembolism, heart failure, and cardiovascular death, and is associated with increased hospitalizations and healthcare costs [2,3]. Oral anticoagulants (OAC) are routinely prescribed to prevent ischemic stroke in AF patients; however, the use of OACs was reported to be associated with an increased incidence of major bleeding in Asian AF patients [4,5].

Many AF patients have comorbid conditions and adherence to an integrated care management strategy was shown to yield better clinical outcomes, including a reduction in death, stroke, bleeding, and hospitalizations [6]. Awareness of the incidence rate and causes of death of AF patients would be beneficial for focusing and improving an integrated care management strategy to care for AF patients. Healthcare systems vary widely from country to country and some treatments shown to be cost-effective in Western populations may not be cost-effective in limited resource settings [7]. For example, direct oral anticoagulants (DOACs), which have been proven to be at least as effective as warfarin for stroke prevention and cause less intracranial bleeding than warfarin, are still used less than warfarin in many Asian countries [8–10]. Differences in treatment options and patterns of antithrombotic use may lead to differences in the causes of death of AF patients among countries. Improved understanding of these important issues will improve both strategic healthcare planning and patient outcomes.

Accordingly, the aim of this study was to determine the causes of death among Asian nonvalvular AF patients who were registered in a nationwide AF registry, and to investigate the differences in the causes of death in AF patients compared between those who were taking and not taking OAC.

Materials and methods

Patients aged greater than 18 years and diagnosed with non-valvular AF were enrolled from 27 centers in Thailand into the **CO**hort of antithrombotic use and **O**ptimal INR Level in patients with non-valvular Atrial Fibrillation in Thailand (COOL-AF) study/registry during 2014–2017. The exclusion criteria were 1) rheumatic valvular disease, 2) mechanical heart valve, 3) ischemic stroke within 3 months, 4) pregnancy, 5) inability to attend follow-up visits, 6) hema-tologic disease that increased the risk of bleeding, 7) AF from transient and reversible cause, and 8) refusal to participate. The protocol for this study was approved by the Institutional Review Board of each of the 27 participating sites, and every patient that was enrolled provided written informed consent to participate in the study. The study complied with all of the principles and guidelines set forth in the 1964 Declaration of Helsinki and all of its subsequent amendments.

Study protocol

After obtaining written informed consent, each patient was interviewed and baseline data were recorded in a case record form. The data from the original case record form was then uploaded into a web-based system. All submitted data were quality checked and verified for completeness by a central data management team. The hard copy of the case record form was

sent to the central data management team for double entry and verification of data accuracy. Data-related questions or concerns were addressed to investigators at their respective study. Study monitoring was performed at all 27 study sites to ensure the quality of the data, and to confirm that investigators at each site conducted the study in accordance with both good clinical practice guidelines and the study protocol.

Data collection

Demographic data, vital signs, characteristics of AF, medical history, laboratory data, investigations data, and prescribed medications were collected at baseline. The same types of data were collected again at the 6-, 12-, 18-, 24-, and 30-month follow-up visits. During the followup, adverse event data were also recorded.

Outcomes

The primary outcome of this study was death and the cause(s) of death. The date of death was recorded and all deaths were evaluated by at least 2 members of an independent adjudication committee. The events adjudication committee developed standard procedures to assess the cause of death. Cases that were difficult to conclusively discern were discussed during adjudication team meetings.

Information specific to any death was reported by local investigators using a standardized case record form in addition to a structured narrative description of the event. The details of the death and the cause of death were then uploaded to the web-based system. When available, supporting documents, such as the death certificate, hospital discharge summary, and other records (e.g., radiology, laboratory, and pathological data), were also uploaded into the web-based system.

The cause of death was classified as cardiovascular (CV) death, non-CV death, or undetermined cause of death. CV death was defined as death due to heart failure, ischemic stroke, intracranial hemorrhage (ICH), acute myocardial infarction (AMI), sudden cardiac death (SCD), aortic aneurysm, or other CV death. Non-CV death was defined as death caused by malignancy, infection/sepsis, respiratory, hemorrhage other than CV bleeding or stroke, renal, hepatobiliary or pancreatic, gastrointestinal, trauma, senility, or other non-CV death. Death from heart failure was defined as circulatory collapse related to hypotension or symptoms/ signs of congestion at rest that may have required increased heart failure medication, including intravenous agents, in the days prior to onset. Patients may have had a previous history of heart failure or myocardial infarction. SCD was recorded in patients who 1) died suddenly and unexpectedly within 1 hour of cardiac symptom onset without preceding deterioration; 2) died unexpectedly during sleep; or, 3) died unexpectedly within 24 hours after last being seen alive. The diagnosis of SCD required the absence of severe pump failure death. Death due to ischemic stroke was defined according to the criteria for ischemic stroke. Acute onset of focal neurological deficit lasting more than 24 hours was defined as an ischemic stroke, and less than 24 hours was defined as a transient ischemic attack (TIA). Whether positive or negative, imaging data from computerized tomography (CT) or magnetic resonance imaging (MRI) of the brain were required to be uploaded into the web-based system. Major bleeding was defined according to the criteria published by the International Society of Thrombosis and Haemostasis (ISTH) [11].

Statistical analysis

All statistical analyses were performed using SPSS Statistics software version 18.0 (SPSS, Inc., Chicago, IL, USA). Continuous normally distributed data are presented as mean plus/minus

standard deviation (SD), and continuous non-normally distributed data are given as median and interquartile range (IQR). Categorical data are described as number and percentage. Comparisons of normally and non-normally distributed continuous data were performed using Student's *t*-test and Mann-Whitney U test, respectively. For comparisons of categorical data, chi-square test or Fisher's exact test was used. Hazard graphs were plotted to evaluate the increased risk of adverse outcome over time. A Cox proportional hazards model was used to compare factors that might influence the clinical outcome over time. Multivariate analysis was performed to identify factors that independently predict risk of outcome. The results of our multivariate analysis are shown as adjusted hazard ratio (aHR) and 95% confidence interval (95%CI). Data collection for this study was relatively complete with only left ventricular ejection fraction (LVEF) data missing in 15% of overall cases (512/3,405 patients), Imputation was employed to replace this missing data with substitute data. A *p*-value less than 0.05 was considered statistically significant for all tests and comparisons.

Results

We studied a total of 3,405 patients. The average age was 67.8 ± 11.3 years, and 1,424 (41.8%) were female. Fig 1 shows a flow chart that describes the enrollment and flow of patients in this study.

Outcomes

The mean follow-up duration was 31.8±8.7 months, and the median follow-up duration was 35.9 months (interquartile range [IQR]: 34.8–36.0) for a total follow-up duration of 9,026.7 person-years. Three hundred and eighty patients (11.2%) died during follow-up for an incidence rate of 4.25 per 100 person-years. Table 1 shows the baseline demographic and clinical characteristics of all patients, and compared between those who died and those who survived during follow-up. Patients who died had a significantly greater proportion of age greater than 70 years (68.4% *vs.* 41.7%, *p*<0.001), lower mean body mass index (23.6±4.6 *vs.* 25.4±4.7 kg/m², *p*<0.001), lower mean diastolic blood pressure (72.9±13.7 *vs.* 75.5±12.5, *p*<0.001), higher proportion of permanent AF (55.5% *vs.* 46.3%, *p*<0.001), more comorbidities, and significantly greater use of warfarin (73.2% *vs.* 68.2%, *p* = 0.048).

Causes of death

The causes and incidence rates of cardiovascular or non-cardiovascular death among the patients enrolled in this study are shown in Table 2. The incidence rate of CV death, non-CV death, and undetermined cause of death was 1.35, 2.11, and 0.78 per 100 person-years, respectively. CV death, non-CV death, and undetermined cause of death was found in 121 (31.8%), 189 (49.7%), and 70 (18.4%) patients, respectively. The rate of ischemic stroke death was 4.7%, and was nearly the same between patients taking and not taking OAC (4.7% *vs.* 4.8%, respectively). S2 Table shows the incidence rate per 100 person-years of all cause death, CV death, and non-CV death according to the pattern of OAC treatment. The adjusted hazard ratio specific to the effect of warfarin or DOAC (with or without TTR as a factor) compared to a comparator treatment condition on all cause death, CV death, and non-CV death is also shown. These data indicate that patients taking warfarin and having a TTR \geq 65% had a lower rate of death compared with those taking warfarin and having a TTR <65%, and also when compared to patients not taking OAC.

Among those with a known cause of death, the most prevalent causes of CV death were heart failure (n = 31, 10%), intracranial hemorrhage (ICH; n = 31, 10%), sudden cardiac death (n = 21, 6.8%) ischemic stroke (n = 18, 5.8%), and acute myocardial infarction (n = 13, 4.2%).



Fig 1. Flow diagram of patient enrollment and the flow of patients in this study. (Abbreviations: COOL-AF, COhort of antithrombotic use and Optimal INR Level in patients with non-valvular Atrial Fibrillation in Thailand; CV, cardiovascular).

https://doi.org/10.1371/journal.pone.0282455.g001

Variables	All (N = 3,405)	Death (n = 380)	Survival (n = 3,025)	<i>p</i> -value	
Age (years)	67.8±11.3	73.9±11.2	67.0±11.1	<0.001	
Age \geq 70 years	1,522 (44.7%)	260 (68.4%)	1,262 (41.7%)	<0.001	
Female gender	1,424 (41.8%)	167 (43.9%)	1,257 (41.6%)	0.373	
Body mass index (kg/m ²)	25.2±4.7	23.6±4.6	25.4±4.7	<0.001	
Systolic blood pressure (mmHg)	128.5±18.4	128.6±19.7	128.5±18.3	0.893	
Diastolic blood pressure (mmHg)	75.2±12.7	72.9±13.7	75.5±12.5	<0.001	
Pulse (bpm)	77.4±16.2	77.6±16.0	77.3±16.2	0.741	
Time since diagnosis of AF (years)	3.4±4.3	3.5±4.7	3.4±4.3	0.519	
Atrial fibrillation				<0.001	
• Paroxysmal	1,148 (33.7%)	91 (23.9%)	1,057 (34.9%)		
• Persistent	645 (18.9%)	78 (20.5%)	567 (18.7%)		
• Permanent	1,612 (47.3%)	211 (55.5%)	1,401 (46.3%)		
Symptomatic AF	2,620 (76.9%)	286 (75.3%)	2,334 (77.2%)	0.409	
History of heart failure	913 (26.8%)	139 (36.6%)	774 (25.6%)	<0.001	
History of CAD	547 (16.1%)	89 (23.4%)	458 (15.1%)	<0.001	
CIED	341 (10.0%)	47 (12.4%)	294 (9.7%)	0.105	
History of ischemic stroke/TIA	592 (17.4%)	90 (23.7%)	502 (16.6%)	0.001	
Diabetes mellitus	839 (24.6%)	126 (33.2%)	713 (23.6%)	<0.001	
Hypertension	2,330 (68.4%)	286 (75.3%)	2,044 (67.6%)	0.002	
Current smoker	678 (19.9%)	81 (21.3%)	597 (19.7%)	0.467	
Dyslipidemia	1,917 (56.3%)	236 (62.1%)	1,681 (55.6%)	0.015	
Renal replacement therapy	40 (1.2%)	12 (3.2%)	28 (0.9%)	0.001	
Dementia	29 (0.9%)	8 (2.1%)	21 (0.7%)	0.012	
Systemic embolism	25 (0.7%)	9 (2.4%)	16 (0.5%)	0.001	
History of peripheral vascular disease	44 (1.3%)	12 (3.2%)	32 (1.1%)	0.001	
History of carotid occlusive disease	8 (0.2%)	1 (0.3%)	7 (0.2%)	0.904	
History of stent use	253 (46.2%)	44 (49.4%)	209 (45.5%)	0.499	
History of CABG	65 (12.0%)	14 (15.7%)	51 (11.2%)	0.232	
History of alcohol abuse	140 (4.1%)	14 (3.7%)	126 (4.2%)	0.656	
History of bleeding	324 (9.5%)	54 (14.2%)	270 (8.9%)	0.001	
CHA ₂ DS ₂ -VASc score	3.07±1.68	3.95±1.64	2.96±1.65	<0.001	
• Low	287 (8.4%)	8 (2.1%)	279 (9.2%)		
• Intermediate	548 (16.1%)	24 (6.3%)	524 (17.3%)		
• High	2,570 (75.5%)	348 (91.6%)	2,222 (73.5%)		
HAS-BLED score	1.54±1.01	2.01±1.07	1.48±0.98	<0.001	
• 0	490 (14.4%)	20 (5.3%)	470 (15.5%)		
• 1-2	2,375 (69.8%)	249 (65.5%)	2,126 (70.3%)		
•>3	540 (15.9%)	111 (29.2%)	429 (14.2%)		
Chronic kidney disease	1,756 (51.6%)	285 (75.0%)	1,471 (48.6%)	<0.001	
Anemia	1,293 (38.0%)	228 (60.0%)	1,065 (35.5%)	<0.001	
Left ventricular ejection fraction	60.2±13.7	59.1±15.0	60.3±13.6	0.129	
Antiplatelet	892 (26.2%)	114 (30.0%)	778 (25.7%)	0.074	
Anticoagulant	2,568 (75.4%)	296 (77.9%)	2,272 (75.1%)	0.234	
• Warfarin	2,340 (68.7%)	278 (73.2%)	2,062 (68.2%)	0.048	
• DOAC	228 (6.7%)	18 (4.7%)	210 (6.9%)	0.105	
Beta blocker	2,477 (72.7%)	266 (70.0%)	2,211 (73.1%)	0.202	
	· · · · · ·	A second s			

Table 1. Baseline demographic and clinical characteristics of all patients, and compared between those who died and those who survived during follow-up.

(Continued)

Table 1. (Continued)

Variables	All (N = 3,405)	Death (n = 380)	Survival (n = 3,025)	<i>p</i> -value
Calcium channel blocker	935 (27.5%)	130 (34.2%)	805 (26.6%)	0.002
Digitalis	539 (15.8%)	61 (16.1%)	478 (15.8%)	0.899
MRA	280 (8.2%)	43 (11.3%)	237 (7.8%)	0.020
Statin	2,014 (59.1%)	247 (65.0%)	1,767 (58.4%)	0.014
ACEI/ARB	1,557 (45.7%)	180 (47.4%)	1,377 (45.5%)	0.496
NSAID/Cox-2 inhibitor	83 (2.4%)	7 (1.8%)	76 (2.5%)	0.425

Data presented as mean ± standard deviation or number and percentage.

A *p*-value<0.05 indicates statistical significance (bold and italic).

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; bpm, beats per minute; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHA₂DS₂-VASc, congestive heart failure, hypertension, age \geq 75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female); CIED, cardiac implantable electronic device; DOAC, direct oral anticoagulant; HAS-BLED, Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage; MRA, mineralocorticoid receptor antagonist; NSAID, non-steroidal anti-inflammatory drug; TIA, transient ischemic attack.

https://doi.org/10.1371/journal.pone.0282455.t001

Table 2. The causes of cardiovascular or non-cardiovascular death among the patients enrolled in this study.

Causes of death (N = 3,405)	n	% of the whole group (N = 3,405)	Rate per 100 person- years	% of those who died (n = 380)	% of those with a known cause of death (n = 310)	% of death
Cardiovascular death	121	3.6%	1.35	31.8%	39.0%	% of CV death (n = 121)
• Heart failure	31	0.9%	0.35	8.2%	10.0%	25.6%
• ICH	31	0.9%	0.35	8.2%	10.0%	25.6%
Ischemic stroke	18	0.5%	0.20	4.7%	5.8%	14.9%
• SCD	21	0.6%	0.23	5.5%	6.8%	17.4%
• AMI	13	0.4%	0.15	3.4%	4.2%	10.7%
Aortic aneurysm	2	0.1%	0.02	0.5%	0.6%	1.7%
• Other CV death	5	0.1%	0.06	1.3%	1.6%	4.1%
Non-cardiovascular death	189	5.6%	2.11	49.7%	61.0%	% of non-CV death (n = 189)
• Infection/sepsis	86	2.5%	0.96	22.6%	27.7%	45.5%
• Malignancy	17	0.5%	0.19	4.5%	5.5%	9.0%
• Hemorrhage other than CV bleeding or stroke	14	0.4%	0.16	3.7%	4.5%	7.4%
Respiratory	16	0.5%	0.18	4.2%	5.2%	8.5%
• Senility	8	0.2%	0.09	2.1%	2.6%	4.2%
• Trauma	7	0.2%	0.08	1.8%	2.3%	3.7%
Neurological	7	0.2%	0.08	1.8%	2.3%	3.7%
• Renal	5	0.1%	0.06	1.3%	1.6%	2.6%
• Hepatobiliary or pancreatic	4	0.1%	0.04	1.1%	1.3%	2.1%
 Gastrointestinal 	2	0.1%	0.02	0.5%	0.6%	1.1%
• Other non-CV death	23	0.7%	0.26	6.1%	7.4%	12.2%
Undetermined	70	2.1%	0.78	18.4%		
Total	380	11.2%	4.25	100.0%		

Abbreviations: AMI, acute myocardial infarction; CV, cardiovascular; ICH, intracranial hemorrhage; SCD, sudden cardiac death.

https://doi.org/10.1371/journal.pone.0282455.t002

Concerning non-CV death, the most prevalent causes of death were infection/sepsis (n = 86, 27.7%), malignancy (n = 17, 5.5%), respiratory (n = 16, 5.2%), and hemorrhage other than CV bleeding or stroke (n = 14, 4.5%).

Fig 2 shows the cumulative event rate of all death, CV death, non-CV death, undetermined cause of death, ischemic stroke death, and major bleeding death; the components of CV death; and, the components of non-CV death. The rate of non-CV death was higher than the rate of CV death throughout the follow-up period. The main causes of CV death were heart failure and ICH, and the rates of these two causes of death were at similar levels throughout the study period. Females demonstrated a trend toward an increased risk of death due to ischemic stroke compared to males. No significant difference between genders was observed for any of the other causes of death.

Subgroup analyses

S1 Fig shows the incidence rates of clinical outcomes per 100 person-years compared between OAC and no OAC, warfarin with TTR <65% and \geq 65%, and warfarin and DOAC. These data indicate that OAC increased the crude risk of ICH death more than two-fold compared to the no OAC groups. Warfarin with a TTR <65% increased the risk of ICH death more than two-fold when compared to warfarin with a TTR \geq 65%. Similarly, warfarin increased risk of ICH death more than two-fold compared to DOACs.

Deaths related to bleeding, such as ICH and non-ICH major bleeding, tended to be increased in patients on OAC compared to no OAC, in those taking warfarin with a TTR <65% compared to \geq 65%, and in those taking warfarin compared to DOACs.

S1 Table shows the incidence rate of fatal and all ischemic stroke, major bleeding, and ICH according to the pattern of OAC treatment. Among overall events, OAC decreased ischemic stroke from 1.93 to 1.37 per 100 person-years, but increased major bleeding from 1.13 to 2.63 per 100 person-years, and increased ICH from 0.27 to 0.95 per 100 person-years.

Despite a decrease in the ischemic stroke incidence rate, warfarin increased the rate of major bleeding and ICH. DOACs exerted greater benefit compared to warfarin relative to a reduction in ischemic stroke, major bleeding, and ICH. Regarding fatal events, OAC did not reduce fatal ischemic stroke, but did increase the incidence rate of major bleeding and ICH. The crude incidence rates of ischemic stroke, major bleeding and ICH among those taking DOACs were similar to those from patients not taking OAC, and were much lower than the incidence rates from those taking warfarin. Among those taking warfarin, patients with a TTR \geq 65% had a lower incidence of ischemic stroke, major bleeding, and ICH compared to those with a TTR <65%.

Fig 3 shows the causes of death per 100 person-years compared between patients aged <70 and ≥ 70 years, and compared between males and females. Patients aged ≥ 70 years had a significantly increased risk of death due to ischemic stroke, ICH, infection/sepsis, malignancy, and other non-CV death compared to those aged <70 years.

Multivariate analysis

The independent predictors of all-cause death from multivariate analysis were older age, low body mass index (BMI), persistent or permanent AF, history of heart failure, ischemic stroke, type 2 diabetes mellitus (T2D), CKD, and anemia (Fig 4). The independent predictors of CV death were low BMI, persistent or permanent AF, history of CAD, and T2D. The independent predictors of non-CV death were persistent or permanent AF, history of ischemic stroke, T2D, history of bleeding, and anemia (Fig 4).



Fig 2. Cumulative event rate of (A) all death, CV death, non-CV death, undetermined death, ischemic stroke death, and major bleeding death; (B) the components of CV death; and, (C) the components of non-CV death. (**Abbreviations:** AMI, acute myocardial infarction; CV, cardiovascular; HF, heart failure; ICH, intracranial hemorrhage; SCD, sudden cardiac death).

https://doi.org/10.1371/journal.pone.0282455.g002

Discussion

The results of this prospective multicenter nationwide AF registry found that death due to ischemic stroke accounts for only 4.7% of all deaths in Asian patients with AF. This finding



Fig 3. The causes of death per 100 person-years compared between patients aged <70 and ≥70 years (A), and compared between males and females (B). A *p*-value<0.05 indicates statistical significance. (**Abbreviations:** AMI, acute myocardial infarction; CV, cardiovascular; HF, heart failure; ICH, intracranial hemorrhage; SCD, sudden cardiac death).

https://doi.org/10.1371/journal.pone.0282455.g003

suggests that in addition to seeking to prevent ischemic stroke via the use of OACs, the management of Asian patients with AF should include a more holistic or integrated care approach to patient management in order to prevent other types of CV death and non-CV death.

Stroke prevention in patients with AF is a major goal of treatment many clinical practice guidelines [12–15]. Ischemic stroke from AF leads to more disability and higher mortality compared to non-AF-related stroke [16,17]. As such, one might perceive that to reduce mortality in patients with AF, we should focus only on the use of OAC; however, OAC use has both benefits and drawbacks. Although OAC does confer stroke prevention benefit, it is at the same time associated with an increased risk of bleeding, which is sometimes fatal [18]. Therefore, a careful evaluation of the risks and benefits of OAC is needed before starting OAC treatment, and shared decision-making between the physician and the patient/family is recommended [12].

All-cause dea	ath	CV death		Non-CV death	
	Adjusted HR (95% CI)		Adjusted HR (95% CI)		Adjusted HR (95% CI)
Age ≥70 years —	1.68 (1.27-2.23)		1.23 (0.77-1.98)		- 1.82 (1.21-2.74)
Female	1.08 (0.86-1.36)		1.24 (0.83-1.88)		0.87 (0.63-1.21)
BMI ≥25 kg/m ² -	0.60 (0.48-0.76)	i	0.52 (0.35-0.79)		0.73 (0.53-1.01)
Pulse ≥100 bpm	0.92 (0.64-1.33)		1.08 (0.59-1.97)		0.83 (0.48-1.44)
AF type					
- Permanent	1.56 (1.14-2.12)		1.76 (1.02-3.03)		1.60 (1.02-2.51)
- Persistent —	1.67 (1.29-2.16)		1.87 (1.17-2.97)		1.74 (1.21-2.51)
Symptomatic AF	1.04 (0.82-1.33)		0.85 (0.57-1.28)		1.13 (0.81-1.60)
History of heart failure	1.35 (1.07-1.71)		1.50 (0.99-2.26)		1.17 (0.83-1.63)
History of CAD	1.13 (0.86-1.49)		1.67 (1.06-2.64)		1.02 (0.69-1.52)
CIED	1.20 (0.88-1.65)		1.26 (0.72-2.21)		1.26 (0.81-1.96)
History of IS/TIA	1.35 (1.06-1.74)		1.24 (0.79-1.96)		1.68 (1.20-2.35)
Diabetes mellitus —	1.39 (1.10-1.76)		1.60 (1.06-2.41)		1.40 (1.01-1.94)
Hypertension -	1.10 (0.86-1.42)		1.49 (0.93-2.39)		1.09 (0.76-1.56)
Smoking	1.08 (0.82-1.42)		1.24 (0.77-2.00)		0.91 (0.62-1.35)
Dyslipidemia 😽 🗖 🗖	1.13 (0.90-1.42)		0.94 (0.63-1.40)		1.36 (0.98-1.89)
History of PAD	1.67 (0.93-3.01)		2.00 (0.80-5.01)		1.16 (0.43-3.17)
History of bleeding	1.30 (0.97-1.75)		0.83 (0.45-1.53)		1.61 (1.10-2.37)
CKD	- 1.49 (1.11-2.01)		1.51 (0.91-2.51)	÷-•	1.43 (0.94-2.19)
Anemia 🗕	- 1.47 (1.16-1.87)		1.10 (0.73-1.66)		1.83 (1.30-2.60)
LVEF <50%	1.13 (0.86-1.48)		1.10 (0.69-1.77)		1.04 (0.69-1.56)
Antiplatelet	1.06 (0.78-1.43)		1.11 (0.67-1.86)		0.90 (0.58-1.40)
Warfarin -	0.90 (0.66-1.24)		1.08 (0.62-1.89)		0.75 (0.48-1.19)
NOAC	0.74 (0.43-1.29)		0.94 (0.36-2.47)		0.48 (0.20-1.13)
Lum	L L	rum ra	L.	r r r r r	
0.4 1	4 0.3	1	6 0.2	1	4
Hazard ratio (9	5%CI)	Hazard ratio (95%CI)		Hazard ratio (95%Cl)	

Fig 4. Forest plots showing the predictors of all-cause death, CV death, and non-CV death. (Abbreviations: AF, atrial fibrillation; AMI, acute myocardial infarction; BMI, body mass index; bpm, beats per minute; CAD, coronary artery disease; CI, confidence interval; CIED, cardiac implantable electronic device; CKD, chronic kidney disease; CV, cardiovascular; HF, heart failure; HR, hazard ratio; ICH, intracranial hemorrhage; IS, ischemic stroke; LVEF, left ventricular ejection fraction; NOAC, non-vitamin K antagonist oral anticoagulant; PAD, peripheral arterial disease; SCD, sudden cardiac death; TIA, transient ischemic attack).

https://doi.org/10.1371/journal.pone.0282455.g004

Concerning the increased risk of bleeding in AF patients on OAC, ICH was reported to have a 30-day mortality rate of 43% compared to 9% for non-ICH bleeding [18]. Data from the Get With The Guidelines–Stroke registry during 2013–2016 revealed that among 141,311 patients with ICH, the use of DOACs was associated with significantly lower in-hospital mortality compared to warfarin (adjusted odds ratio: 0.75) [19].

Patients with AF commonly have multimorbidity, including T2D, hypertension, and renal dysfunction, which leads to death from many other causes besides ischemic stroke [20,21]. Management adherence to a holistic or integrated care pathway has been introduced to emphasize not only stroke prevention, but also patient-centered symptom-directed decisions on rate or rhythm control, and comorbidity and lifestyle management [22]. However, a multi-disciplinary strategy is needed to provide comprehensive care to AF patients since this level of comprehensive care could not be managed or delivered by the cardiologist alone.

Table 3 summarizes the causes of death among patients from the COOL-AF study compared to those reported from 5 other previously published studies [20,21,23–25]. These studies include the GARFIELD-AF study [21], the FUSHIMI-AF study [25], the Loire Valley AF project [20], national insurance data [24], and DOAC clinical trials [23]. The incidence rate of allcause death in AF patients was 3.8–6.3 per 100 person-years, CV death accounted for 26–64% of all deaths, and CV death accounted for 32–68% among those with a known cause of death. Most of the published data indicates that CV death accounts for less than half of all-cause deaths, while non-CV death accounted for more than half of all deaths. Among CV deaths, heart failure was the most common cause of CV death followed by SCD and AMI.

From previous studies, ICH accounted for 2–6% of all deaths. In our study and in contrast, ICH accounted for 8% of all deaths and was the shared leading cause of CV death with HF death. In the present study, OAC increased the crude risk of ICH death more than two-fold compared to the no OAC groups. Warfarin users with a TTR <65% had a two-fold increased

Table 3. Cause of death of patients with atrial fibrillation from COOL-AF study compared to some of the previously published data.

YearYearJone-2010J000-2013J011-2012J005-2010Number of patientsS4083896215411404571683CourtyTuilaidGlobalFrance, UK, DenmakKorcaIp anGlobalAsian1000.25NA10073.675.7Female1062.5NA10073.675.7Female41.844.48840.24035.40Dabets mallus46.477.541.164.16379.94Dabets mallus56.341.11542.144.4NA*Sonking19.934.812.213.4014.170Dabets mallus56.341.11542.144.1NA*Sonking19.934.812.218.518.111.1*Identification2.6.820.64944.1514.1*Identification10.417.28.815.518.519.4*Identification10.417.28.815.518.619.2*Identification7.410.33.02.93.3.819.2*Identification7.51.51.51.51.51.5Identification or median)3.13.714.15.51.5Identification or median3.11.11.71.410.0DASC2.73.81.51.51.51.51.51.5Identifica	Cause of death (N = 3,405)	COOL-AF	GARFIELD [26]	Loire Valley-AF [20]	Korean-NHIS [24]	FUSHIMI [25]	4 DOAC trials [23]
Number opticitizity94059406940697103CountryThailand10012Nacc UK, DemakNorea10400.63-Asian0012NA0.0010.06.5-1.41Age (Man or median)67.87.17.16.3.97.3.67.5.7Bernale48.44.84.8.04.0.04.0.03.5.4.0Dahes medinas66.47.1.71.5.52.2.42.3.52.3.4.0Diplipitarian66.44.1.71.6.14.1.4NA*NA*Stroking19.93.8.81.0.21.8.51.8.11.9.5CAD19.41.7.28.88.15.51.6.11.9.5Schwing16.11.9.92.0.03.4.81.9.51.5.1Schwing/TAA1.6.11.7.28.81.8.11.9.51.5.1Schwing/TAA1.6.11.7.23.81.0.32.1.5.7CAD stape-5-1.4.11.7.23.81.0.32.1.5.7CAD stape-5-1.4.11.7.23.81.0.32.1.5.7CATA_DS_VXSAScore (mean ormelian)1.5.1.5.11.2.21.7.51.8.4OAC7.7.40.0NA1.0.11.0.61.8.4OAC7.7.40.0NA1.0.11.0.61.8.4OAC7.7.40.0NA1.0.11.5.11.4.1OAC7.7.40.0NA1.0.11.5.11.4.1OAC <td< td=""><td>Year of enrollment</td><td>2014-2017</td><td>2010-2014</td><td>2000-2010</td><td>2002-2013</td><td>2011-2012</td><td>2005-2010</td></td<>	Year of enrollment	2014-2017	2010-2014	2000-2010	2002-2013	2011-2012	2005-2010
CourtyInstantGoldalFrance, UK, DermarkKoreaJipanGelokalAtan10025NA1006.5154Age (den or mediant)6.731716.397.307.7-3Fenda41.841.48840.22.322.3-00Dabetes mediancy48.41754.121.637.91.5Dabetes mediancy6.847.751.114.114.4NA*Dabetes mediancy1.93.481.214.41NA*NA*Sonking1.93.441.124.41NA*NA*NA*Bardiancy2.631.94.141.71.211.81.11*Ischeni stroke/TA2.631.91.121.81.15	Number of patients	3405	28628	8962	15411	4045	71683
Asian10010067.8717163.9100.6515.4Age (Mean or median)67.867.871.77163.970.575.7Fenale41.844.43.860.240.03.5.0Dubets millins24.621.71522.023.5230Dyspletnino56.341.115.542.144.4NA*Snaking19.934.812.018.514.1NA*Bert failure26.820.649.024.42.72.6-3.1CAD16.119.920.03.8.810.515.515.5CKD stap 5-516.419.218.019.219.219.2Permanet AF47.312.738.010.340.167.8CKD styp 5-51.51.51.218.410.510.1CALADS-VAS core (mean or median)1.51.51.21.810.0OAC62.717.70NA1050DAG62.717.51.51.21.61.5CALADS-VAS core (mean or median)1.51.51.62.834OAC62.77.9501.62.81.6DAG62.77.71.62.83.11.37DAG62.77.9501.62.83.1CALADS-VAS core (mean or median)1.51.51.61.62.8DAG7.7 <td>Country</td> <td>Thailand</td> <td>Global</td> <td>France, UK, Denmark</td> <td>Korea</td> <td>Japan</td> <td>Global</td>	Country	Thailand	Global	France, UK, Denmark	Korea	Japan	Global
Age (Manor median)67.871.67.967.977.9Penale41.844.43840.24035-40Pender onlines64.627.715222323-40Hypertonsion68.477.54164.46379-94Displayfindina65.877.54164.46379-94Smoking19.934.81218.5NANASmoking19.934.81218.5NANAShoring19.934.81218.518.419-55Schoring Stroke/TA17.412.2815.518.819-55CKD stage 3-5710.47NA4991-21Permanet AF47.311.213.810.341.167-83CHA Stroke (mean or median)3.133.02.93.382.1-3.5°DAC (mean or median)3.133.02.93.82.1-3.5°DAC (mean or median)3.133.02.93.82.1-3.5°DAC (mean or median)3.13.13.01.21.53.6 <td>Asian</td> <td>100</td> <td>25</td> <td>NA</td> <td>100</td> <td>100</td> <td>6.5-15.4</td>	Asian	100	25	NA	100	100	6.5-15.4
Fende41.844.43840.240.035-40Diabetes mellius24.621.715222323-00Dysiptedmia56.3411542.144NA*Dysiptemia56.3411542.144NA*Smoking19.934.81218.5NANAHart falure26.820.649242732-63CAD16.119.92034.815.514-17 ^b Schemic Strök/TA17.412.28810.341.167-83CKD stage 3-5-10.47NA4919-21Permanet AF47.312.73810.341.167-83CKD stage 3-5-10.47NA4919-21Permanet AF47.312.73810.341.167-83CKD stage 3-5-15.51.21.751.84100DAC75.463.35817.954100DAC75.446.3556.35.54.63CAC75.43.835.56.35.54.63Incidence rate of deathAutighated42.53.835.56.35.54.63Cachoscalar death2.111.372.37NA3.11.37Inderet and of death2.121.753.846.13.8Cachoscalar death	Age (Mean or median))	67.8	71	71	63.9	73.6	70-73
Dables24.621.7152223.8220Hypertension68.477.541646379-94Displajedima56.34116.216.477.518.5NANA*Smoking19.934.812.218.5NANA*Bear fullers12.810.412.418.5NA14.1CAD16.119.920.034.815.518.819-51Edentiorlok/TA17.412.28.810.341.167-83CD stags 5.517.812.213.810.341.167-83CHA,DS/XAS: core (man or median)3.133.02.93.382.1-35*DACC75.463.35.817.95.410.0DACS75.463.35.817.95.410.0DACS75.464.35.8NA4.45.0DACS75.464.35.8NA4.45.0Cardinance for dent13.814.52.97NA0.02.91Cardenz of dent13.51.552.97NA0.13.1	Female	41.8	44.4	38	40.2	40	35-40
Hypersonion68.477.54164.63.79.94Dysliplemia56.3411542.18.4NADastanging19.934.812.218.5NANAHart falture26.820.649.034.815.515.531.6CAD16.119.920.034.815.514.1.9 ¹⁰ Ichenic stok/TIA17.412.2815.518.419-37CKD stog 3-517.410.47NA49.919.21Permanent AF31.33.02.93.382.1-3.5*CHAjDS, VAS core (mean or median)15.115.51.21.51.60DAC6.717.40.817.90.016.0DACS6.717.70NA44.050DACS6.717.70NA44.050DACS6.717.70NA44.050DACS6.717.70NA44.050DACS6.717.60.81.653.151.653.15AttiplateI6.714.51.5516.63.153.16Cadoracal catch6.71.552.97NA0.02.91Dacionacia catch1.351.555.516.63.163.13AttiplateI1.351.552.97NA0.02.91Dacionacia catch3.844.052.911.65 <td>Diabetes mellitus</td> <td>24.6</td> <td>21.7</td> <td>15</td> <td>22</td> <td>23</td> <td>23-40</td>	Diabetes mellitus	24.6	21.7	15	22	23	23-40
pyspidemia56.3.1115.42.1.44.NASnoking19.934.81218.5NANAHart fultre26.820.624.024.023.2.5363CAD10.419.920.034.815.014.1 ⁻⁵ Ischenic strok/TIA17.412.2815.518.019-51CD stag.5-510.117.7NA49.919-21Pernanet AF47.312.738.010.341.167.83CHASUS Socre (mean or median)3.13.02.93.362.1-3.5"DACC75.465.33.817.95.4100DACA6.717.00NA4050DACA6.717.70.6NA4.450DACA6.8746.35.8NA4.450DACA6.8714.52.97NA0.450Antipaled2.022.793.56.35.54.63Indeter ste of death1.351.552.97NA0.92.91Non-cordioxcular death1.351.572.97NA0.92.91Indeter ste of death1.351.576.35.56.613.85Cardioxcular death1.552.97NA0.92.91Internation0.181.371.371.371.371.37Cardioxcular death1.552.97NA3.0 <t< td=""><td>Hypertension</td><td>68.4</td><td>77.5</td><td>41</td><td>64</td><td>63</td><td>79–94</td></t<>	Hypertension	68.4	77.5	41	64	63	79–94
Smoking19934.81218.5NANAHardinue26.820.649242732-63CAD16.119.920.034.815.514.17bIschmistrok/TIA17.412.0815.518.819-51CKD stag 3-5-10.47.7NA49.919-21Permanet AF47.312.78.810.341.167-83CHA,by,VAS core (mean or median)3.13.02.93.882.1-3.5*BAS-BLED core (mean or median)7.546.3.33.6817.95.41.00DAC7.546.3.315.51.121.751.84CAC7.546.3.46.8NA4.01.00DACS6.717.70NA10.05.0Variaria6.62.87.73.51.6.63.4Aniptalet2.622.7.93.56.35.54.6.3Incidener at of death1.351.552.9.7NA3.13.1Incidener at of death2.131.3.72.9.7NA3.13.1Incidener at of death1.351.556.35.54.6.3Incidener at of death2.131.3.71.4.11.4.1Incidener at of death2.131.5.71.6.11.4.1Incidener at of death1.351.5.56.33.5.54.6.3Incidener at of death2.151.5.7<	Dyslipidemia	56.3	41	15	42.1	44	NA ^a
Hartfulure26.820.649242732-63CAD16.119.92034.817.514-17bCAD schemic stok/TIA17.412815.51819-51CKD stage 3-57.410.47NA49.919-21Permanet AF47.312.73810.341.167-83CMAJSS_VAS core (mean or median)3.13.33.02.93.382.1-35*HAS-BLED score (mean or median)1.51.51.21.751.84OAC6.6717.10NA10050DACA6.746.358NA4450Antiplatel6.8746.358NA4450Incidence rate of death77.84556.35.54.63Cardiovacular death1.351.552.97NA0.92.91Non-ardiovacular death1.351.572.37NA3.11.37Underscalar death1.352.97NA3.11.370.41Cardiovacular death1.85%0.910.16NA1.50.41Cardiovacular death3.18%40.554.1382.5.564Cardiovacular death3.18%40.554.1382.5.564Cardiovacular death3.18%40.57.53.3NA0.62.7Cardiovacular death5.5%7.53.3NA0.6 </td <td>Smoking</td> <td>19.9</td> <td>34.8</td> <td>12</td> <td>18.5</td> <td>NA</td> <td>NA</td>	Smoking	19.9	34.8	12	18.5	NA	NA
CAD16.119.92034.81514-17 ^h Ischemic strok/TIA17.412815.518.919-57CRD stag 3-510.47NA4919-21Permanent AF47.312.73810.341.167-83CHA JDS_VAS core (mean or median)3.133.02.93.882.1-3.5"DAS ELD sore (mean or median)1.51.51.21.751.84100OAC75.463.35817.954100DACA6.71.70NA4450Warfarin6.8746.358NA4450Marfarin26.227.93516.62.834Incidence rate of death2.11.372.37NA0.92.91Cardiorascular death1.351.552.97NA0.92.91Cardiorascular death1.331.552.97NA0.92.91Cardiorascular death1.381.652.97NA0.92.91Cardiorascular death3.181.552.97NA0.92.91Cardiorascular death1.341.451.453.832.556.4Interaccular death3.181.652.97NA0.92.91Cardiorascular death3.181.653.83.13.13.1Cardiorascular death3.181.653.82.56.4 <t< td=""><td>Heart failure</td><td>26.8</td><td>20.6</td><td>49</td><td>24</td><td>27</td><td>32-63</td></t<>	Heart failure	26.8	20.6	49	24	27	32-63
ischemic stroke/TIA17.412.2815.51819-55CKD store 3.40.047.7NA4.919-21CKD store 3.47.33.100.116.78.310.34.196.78.3CHApDS2-VASe score (mean or median)3.13.03.02.93.382.1-3.5"HAS-BLD score (mean or median)1.51.51.51.21.751.84OAC6.71.70NA1050DAGS6.71.70NA4.450AntiplateI6.874.635.8NA4.450AntiplateI6.874.635.81.662.84.63Cardiovascular deth1.21.373.162.86.7AltighteI1.253.8.52.97NA0.92.11Cardiovascular deth1.31.372.37NA3.11.37Cardiovascular deth2.111.372.37NA3.11.41Cause of Deth77.84.86.11.31.37Intercarnial Branci3.8%40.55.4.13.82.5.56.4Interarnial Res3.8%40.55.4.13.82.5.56.4Cardiovascular deth3.8%40.55.4.13.82.5.56.4Interarnial Branci3.8%40.55.4.13.82.5.56.4Interarnial Res3.8%40.55.4.13.82.5.5 <td>CAD</td> <td>16.1</td> <td>19.9</td> <td>20</td> <td>34.8</td> <td>15</td> <td>14–17^b</td>	CAD	16.1	19.9	20	34.8	15	14–17 ^b
CKD stage 3-5Image with the stand state of the stand state of the stand state of the	Ischemic stroke/TIA	17.4	12	8	15.5	18	19–55
Permanent AF47.312.73810.341.167-83CHA,DS,-VAS score (mean or median)3.13.02.93.382.1-3.5"HAS-BLED score (mean or median)1.51.51.21.751.84OAC75.463.35811.954100DAACs6.71.70NA1059Warfarin68.746.358NA4450Antiplatelet26.227.93516.62834Incidence rate of death4.253.835.56.35.54.63Cardiovascular death1.351.552.97NA0.92.91Non-cardiovascular death1.351.552.97NA1.131.37Cardiovascular death2.111.372.37NA3.11.37Cardiovascular death3.18%40.554.1NA1.50.41Cardiovascular death3.18%40.554.1NA1.564Cardiovascular death3.18%40.554.1NA1.414Intracmial hemorrhage8.2%NA4.1NA2.16Ischemic stroke4.7%5.16.77.84.866Sudden cardia death5.5%7.53.3NA0.62.7Acute myocardial infarction3.4%5.9NA5.01.333Adite myocardial infarction3.4%5.9<	CKD stage 3–5		10.4	7	NA	49	19-21
CHA2DS-vASc score (mean or median)3.133.02.93.382.1-3.5"HAS-BLD score (mean or median)1.51.51.51.21.751.84HAS-BLD score (mean or median)75.463.35817.954.4100DACa6.71.70NA1050Warfarin68.746.358.8NA44.450Antipatelet26.227.935.616.62834.63Incidence rate of death1.355.56.5.35.5.54.63Alf death1.352.97NA0.92.91Non-ardioxascular death1.311.372.37NA0.9Non-ardioxascular death1.311.372.37NA1.31Undetermined0.780.910.16NA1.50.41Cardioxacular death1.8%40.554.18.82.5.56.4Cardioxacular death5.2%10.82.923.214.414Cardioxacular death5.5%7.53.3NA0.62.7Cardioxacular death5.5%7.53.3NA0.62.7Acter maycardial infarction3.4%5.9NA5.01.33.6Sudden cardiac death5.5%7.53.3NA0.62.7Acter maycardial infarction3.4%5.9NA5.01.33.6Marcardioxacular death5.5%7.53.3 <t< td=""><td>Permanent AF</td><td>47.3</td><td>12.7</td><td>38</td><td>10.3</td><td>41.1</td><td>67-83</td></t<>	Permanent AF	47.3	12.7	38	10.3	41.1	67-83
HAS-BLED score (mean or median)1.51.51.21.751.84OAC75.463.35817.954100DOACs6.7170NA1050Warfarin68.746.358NA4450Antiplated26.227.935.516.628.034Incidenc rate of death42.538.35.56.35.54.63Cardiovascular death1.351.552.97NA0.92.91Non-catiovascular death2.111.372.37NA3.11.37Undetermined0.849.016NA3.11.471.44Cause of Death11.921.923.2314.414Intracranial hemorrhage8.2%10.82.923.214.414Intracranial hemorrhage5.5%7.53.3NA0.62.7Schein cardia ceath5.5%7.53.3NA0.62.7Acute myocardial infarction3.4%5.9NA5.03.13.1Other Cycleath1.3%7.53.3NA0.62.7Acute myocardial infarction3.5%7.53.3NA0.62.7Acute myocardial infarction3.5%7.53.3NA0.62.7Acute myocardial infarction3.5%7.53.3NA3.13.1Acute myocardial infarction3.5%1.67.4 <t< td=""><td>CHA₂DS₂-VASc score (mean or median)</td><td>3.1</td><td>3</td><td>3.0</td><td>2.9</td><td>3.38</td><td>2.1-3.5^c</td></t<>	CHA ₂ DS ₂ -VASc score (mean or median)	3.1	3	3.0	2.9	3.38	2.1-3.5 ^c
OAC75.463.35817.954100DOACs6.7170NA1050Warfarin6.7170NA1050Marfarin26.227.93516.62834Incidence rate of death26.227.9356.35.56.35.5All death4.253.835.56.35.54.63Cardiovascular death1.151.572.97NA3.11.37Non-cardiovascular death0.780.910.16NA1.50.41Cardiovascular death31.8%40.5154.13825.56.6Cardiovascular death31.8%10.910.16NA1.50.41Cardiovascular death31.8%10.82.923.2214.414Intracranial hemorrhage8.2%10.82.923.2214.414Intracranial hemorrhage8.2%7.53.3NA0.13.7Suden cardiac death5.5%7.53.3NA2.26Nort cardiovascular death1.3%7.53.3NA2.26Nort cardiovascular death1.3%7.53.3NA2.26Nort cardiovascular death1.3%7.53.3NA2.26Nort cardiovascular death1.3%7.53.3NA2.26Nort cardiovascular death1.3%7.57.6 <td>HAS-BLED score (mean or median)</td> <td>1.5</td> <td>1.5</td> <td>1.5</td> <td>1.2</td> <td>1.75</td> <td>1.84</td>	HAS-BLED score (mean or median)	1.5	1.5	1.5	1.2	1.75	1.84
DACs6.7170NA1050Warinin68.746.358NA4450Antipatelet26.227.93516.62834Incidence rate of death4.253.835.56.35.54.63All death4.253.835.56.35.54.63Cardiovascular death1.351.552.97NA0.92.91Non-cardiovascular death0.780.910.16NA3.11.37Cadiovascular death0.780.910.16NA1.50.41Cause of Death0.780.910.16NA1.50.41Cardiovascular death3.8%10.829.23.214.414Intracrania hemorrhage8.2%NA4.11NA2.16Ischemic stroke4.7%5.16.77.84.86Sudde cardiac death5.5%7.53.3NA0.627Acute myocardia infarction3.4%5.9NA5.01.33Other CV death1.3%5.9NA5.01.33Infection/sepis2.6%6.717.6NA2.26Non-cardiovascular death4.9%35.842.7NA3.01.13Infection/sepis2.6%6.717.6NA3.430Infection/sepis2.6%6.717.6NA3.13 <t< td=""><td>OAC</td><td>75.4</td><td>63.3</td><td>58</td><td>17.9</td><td>54</td><td>100</td></t<>	OAC	75.4	63.3	58	17.9	54	100
Warfarin68.746.358NA4450Antiplatel26.227.93516.62.834Incidence rate of death4.253.835.56.35.54.63Cardiovascular death4.253.835.56.33.11.37On-cardiovascular death1.351.152.97NA0.92.91Non-cardiovascular death2.111.372.37NA3.11.37Undermined0.780.910.16NA1.50.41Cause of Death11.71.73.82.556.4Cause of Death31.8%40.554.13.82.556.4Heart Failure8.2%10.82.923.214.414Intracraila hemorrhage8.2%7.53.3NA0.62.7Sudden cardiac death5.5%7.53.3NA0.62.7Acute myocardial infarction3.4%5.9NA5.01.33Ortic aneurysm0.5%7.53.3NA0.62.7Acute myocardial infarction3.4%5.9NA5.01.33Ortic capesis2.2%6.717.6NANANAOther CV death1.3%11.17.3NA2.26Non-cardiovascular death4.9%3.011.823.423.110Infection/sepsis2.2%6.717.6NA <t< td=""><td>DOACs</td><td>6.7</td><td>17</td><td>0</td><td>NA</td><td>10</td><td>50</td></t<>	DOACs	6.7	17	0	NA	10	50
Antiplatelet 26.2 27.9 35 16.6 28 34 Incidence rate of death	Warfarin	68.7	46.3	58	NA	44	50
Incidence rate of deathImage: state of deathImage: state of deathImage: state of deathAll death4.253.835.56.35.54.63Cardiovascular death1.351.552.97NA0.92.91Non-cardiovascular death2.111.372.37NA3.11.37Case of Death0.780.910.16NA1.50.41Cardiovascular death31.8%40.554.13.825.564Heart Failure8.2%10.82.923.214.414Intracranial hemorrhage8.2%NA4.1NA2.16Sudden cardiac death5.5%7.53.3NA0.627Acute myocardial infarction3.4%5.9NA5.01.33Abrit canurysm0.5%NA0.8NA0.627Other CV death1.3%11.17.3NA2.26Non-ardiovascular death4.5%NA0.8NANANAOther CV death1.3%11.17.3NA2.26Non-ardiovascular death4.5%10.311.823.423.110Infection/sepsis2.2.6%6.717.6NA1.43Malignancy4.5%10.311.823.423.110Hemorrhage that neither CV bleeding or struck3.7%4.8%2.6NANA2Senile2.1%	Antiplatelet	26.2	27.9	35	16.6	28	34
All death4.253.835.56.35.54.63Cardiovascular death1.351.552.97NA0.92.91Non-cardiovascular death2.111.372.37NA3.11.37Undetermined0.780.910.16NA1.50.41Cause of Death	Incidence rate of death						
Cardiovascular death1.351.552.97NA0.92.91Non-cardiovascular death2.111.372.37NA3.11.37Undermined0.780.910.16NA1.50.41Cause of Death777107Cardiovascular death31.8%40.554.13825.564Heart Failure8.2%10.82.9.23.214.414Intracranial hemorrhage8.2%NA4.1NA2.16Schemic stroke4.7%5.16.77.84.86Suden cardiac death5.5%7.53.3NA0.627Acute myocardial infarction3.4%5.9NA5.01.33Other CV death1.3%11.17.3NA2.26Non-cardiovascular death49.7%35.842.7NA5430Infection/sepsis22.6%6.717.6NA17.38Malignancy4.5%10.311.823.42.110Hemorrhage that neither CV bleeding or stroke3.7%4.8 ⁴ 2.6NANA2Senile2.1%NANANA133Senile2.1%NANANA13Infection/sepsis22.6%6.717.6NA1.33Senile3.7%4.8 ⁴ 2.6NANA2Res	All death	4.25	3.83	5.5	6.3	5.5	4.63
Non-cardiovascular death 2.11 1.37 2.37 NA 3.1 1.37 Undetermined 0.78 0.91 0.16 NA 1.5 0.41 Causo of Death	Cardiovascular death	1.35	1.55	2.97	NA	0.9	2.91
Undetermined0.780.910.16NA1.50.41Cause of DeathIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIIII	Non-cardiovascular death	2.11	1.37	2.37	NA	3.1	1.37
Cause of DeathImage: Cause of Death<	Undetermined	0.78	0.91	0.16	NA	1.5	0.41
Cardiovascular death31.8%40.554.13825.564Heart Failure8.2%10.829.23.214.414Intracranial hemorrhage8.2%NA4.1NA2.16Ischemic stroke4.7%5.16.77.84.86Sudden cardiac death5.5%7.53.3NA0.627Acute myocardial infarction3.4%5.9NA5.01.33Aortic aneurysm0.5%NA0.8NANANAOther CV death1.3%11.17.3NA2.26Non-cardiovascular death49.7%35.842.7NA5430Infection/sepsis22.6%6.717.6NA17.38Malignancy4.5%10.311.823.423.110Hemorrhage that neither CV bleeding or stroke3.7%4.8 ^d 2.6NANA2Senile2.1%NANA4.5NANA1Yauma1.8%NANAA.5NANA1Neurological1.8%NANANANANANAReal1.3%NA2.7NANANAHenorthage that neither CV bleeding or stroke3.7%4.8 ^d 2.6NANANASenile1.8%NANANANANANa1.8%NANANANANA <td>Cause of Death</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	Cause of Death						
Heart Failure8.2%10.829.23.214.414Intracranial hemorrhage8.2%NA4.1NA2.16Ischemic stroke4.7%5.16.77.84.86Sudden cardiac death5.5%7.53.3NA0.627Acute myocardial infarction3.4%5.9NA5.01.33Aortic aneurysm0.5%NA0.8NANANAOther CV death1.3%11.17.3NA2.26Non-cardiovascular death49.7%35.842.7NA5430Infection/sepsis22.6%6.717.6NA17.38Malignancy4.5%10.311.823.423.110Hemorrhage that neither CV bleeding or stroke3.7%4.8 ^d 2.6NANA2Senile2.1%NANA4.5NA1Prauma1.8%NANANANA1Neurological1.8%NA2.7NA3.2NAReal1.3%NA2.7NANA1Neurological1.8%NANANANANAReal1.3%NA1.6NANANAReal1.3%NANANANA0.3Gastrointestinal0.5%NANANANANA	Cardiovascular death	31.8%	40.5	54.1	38	25.5	64
Intracranial hemorrhage8.2%NA4.1NA2.16Ischemic stroke4.7%5.16.77.84.86Sudden cardiac death5.5%7.53.3NA0.627Acute myocardial infarction3.4%5.9NA5.01.33Aortic aneurysm0.5%NA0.8NANANAOther CV death1.3%11.17.3NA2.26Non-cardiovascular death49.7%35.842.7NA5430Infection/sepsis22.6%6.717.6NA17.38Malignancy4.5%10.311.823.423.110Hemorrhage that neither CV bleeding or stroke3.7%4.8 ^d 2.6NANA2Senile2.1%NANA4.5NA1.33Nama1.8%NANANA131Neurological1.8%NANANA13Renal1.3%NA1.6NANANARenal1.3%NA1.6NA0.33Senile1.3%NA1.6NANA0.3Renal1.3%NANANA0.333Senile1.3%NANANANA0.3Senile0.5%NANANANA0.3Senile1.3%NA1.6NAN	Heart Failure	8.2%	10.8	29.2	3.2	14.4	14
Ischemic stroke4.7%5.16.77.84.86Sudden cardiac death5.5%7.53.3NA0.627Acute myocardial infarction3.4%5.9NA5.01.33Aortic aneurysm0.5%NA0.8NANANAOther CV death1.3%11.17.3NA2.26Non-cardiovascular death49.7%35.842.7NA5.430Infection/sepsis22.6%6.717.6NA17.38Malignancy4.5%10.311.823.423.110Hemorrhage that neither CV bleeding or stroke3.7%4.8 ⁴ 2.6NANA2Senile2.1%NANA4.5NA1.33Senile1.8%NANA4.5NA13Neurological1.8%NA2.7NANA1Renal1.3%NA2.7NANANARenal1.3%NA1.6NANARenal1.3%NA1.6NA0.3Renal1.3%NA1.6NANA0.3Senile1.3%NANANANANANaNA1.6NA3.2NARenal1.3%NANANANA0.3Senile1.3%NANANANANARenal1.3%NA<	Intracranial hemorrhage	8.2%	NA	4.1	NA	2.1	6
Sudden cardiac death 5.5% 7.5 3.3 NA 0.6 27 Acute myocardial infarction 3.4% 5.9 NA 5.0 1.3 3 Aortic aneurysm 0.5% NA 0.8 NA NA NA Other CV death 1.3% 11.1 7.3 NA 2.2 6 Non-cardiovascular death 49.7% 35.8 42.7 NA 54 30 Infection/sepsis 22.6% 6.7 17.6 NA 17.3 8 Malignancy 4.5% 10.3 11.8 23.4 23.1 10 Hemorrhage that neither CV bleeding or stroke 3.7% 4.8 ^d 2.6 NA NA 2 Respiratory 4.2% 8.0 3.2 8.4 4.1 3 Senile 2.1% NA NA NA NA 1 Neurological 1.8% NA 2.7 NA NA NA Neurological 1.3%	Ischemic stroke	4.7%	5.1	6.7	7.8	4.8	6
Acute myocardial infarction3.4%5.9NA5.01.33Aortic aneurysm0.5%NA0.8NANANAOther CV death1.3%11.17.3NA2.26Non-cardiovascular death49.7%35.842.7NA5430Infection/sepsis22.6%6.717.6NA17.38Malignancy4.5%10.311.823.423.110Hemorrhage that neither CV bleeding or stroke3.7%4.8 ^d 2.6NANA2Respiratory4.2%8.03.28.44.13Senile2.1%NANANANANANama1.8%NANANANANANama1.8%NA1.6NA3.2NAHepatobiliary or pancreatic1.1%NANANANA0.3Gastrointestinal0.5%NANANANANANA	Sudden cardiac death	5.5%	7.5	3.3	NA	0.6	27
Aortic aneurysm0.5%NA0.8NANANAOther CV death1.3%11.17.3NA2.26Non-cardiovascular death49.7%35.842.7NA5430Infection/sepsis22.6%6.717.6NA17.38Malignancy4.5%10.311.823.423.110Hemorrhage that neither CV bleeding or stroke3.7%4.8d2.6NANA2Respiratory4.2%8.03.28.44.13Senile2.1%NANANANA1Neurological1.8%NA2.7NANANARenal1.3%NA1.6NA3.2NAHepatobiliary or pancreatic1.1%NANANANA0.3Gastrointestinal0.5%NANANANANANA	Acute myocardial infarction	3.4%	5.9	NA	5.0	1.3	3
Other CV death 1.3% 11.1 7.3 NA 2.2 6 Non-cardiovascular death 49.7% 35.8 42.7 NA 54 30 Infection/sepsis 22.6% 6.7 17.6 NA 17.3 8 Malignancy 4.5% 10.3 11.8 23.4 23.1 10 Hemorrhage that neither CV bleeding or stroke 3.7% 4.8 ^d 2.6 NA NA 2 Respiratory 4.2% 8.0 3.2 8.4 4.1 3 Senile 2.1% NA NA NA NA 1 Neurological 1.8% NA 2.7 NA NA 1 Renal 1.3% NA 2.7 NA NA NA Hepatobiliary or pancreatic 1.1% NA NA NA 0.3 Gastrointestinal 0.5% NA NA NA NA NA	Aortic aneurysm	0.5%	NA	0.8	NA	NA	NA
Non-cardiovascular death 49.7% 35.8 42.7 NA 54 30 Infection/sepsis 22.6% 6.7 17.6 NA 17.3 8 Malignancy 4.5% 10.3 11.8 23.4 23.1 10 Hemorrhage that neither CV bleeding or stroke 3.7% 4.8 ^d 2.6 NA NA 2 Respiratory 4.2% 8.0 3.2 8.4 4.1 3 Senile 2.1% NA NA NA NA 1 Yauma 1.8% NA NA A.5 NA NA Neurological 1.8% NA 2.7 NA NA 1 Renal 1.3% NA 2.7 NA NA NA Hepatobiliary or pancreatic 1.1% NA 1.6 NA 3.2 NA Gastrointestinal 0.5% NA NA NA NA NA NA	Other CV death	1.3%	11.1	7.3	NA	2.2	6
Infection/sepsis22.6%6.717.6NA17.38Malignancy4.5%10.311.823.423.110Hemorrhage that neither CV bleeding or stroke3.7%4.8 ^d 2.6NANA2Respiratory4.2%8.03.28.44.13Senile2.1%NANA4.5NANATrauma1.8%NANANANA1Neurological1.8%NA1.6NA3.2NAHepatobiliary or pancreatic1.1%NANANA0.3Gastrointestinal0.5%NANANANANA	Non-cardiovascular death	49.7%	35.8	42.7	NA	54	30
Malignancy4.5%10.311.823.423.110Hemorrhage that neither CV bleeding or stroke3.7%4.8d2.6NANA2Respiratory4.2%8.03.28.44.13Senile2.1%NANA4.5NANATrauma1.8%NANANA1Neurological1.8%NA2.7NANANARenal1.3%NA1.6NA3.2NAHepatobiliary or pancreatic1.1%NANANANA0.3Gastrointestinal0.5%NANANANANANA	Infection/sepsis	22.6%	6.7	17.6	NA	17.3	8
Hemorrhage that neither CV bleeding or stroke3.7%4.8d2.6NANA2Respiratory4.2%8.03.28.44.13Senile2.1%NANA4.5NANATrauma1.8%NANANA1Neurological1.8%NA2.7NANANARenal1.3%NA1.6NA3.2NAHepatobiliary or pancreatic1.1%NANANANA0.3Gastrointestinal0.5%NANANANANANA	Malignancy	4.5%	10.3	11.8	23.4	23.1	10
Respiratory4.2%8.03.28.44.13Senile2.1%NANAA.5NANATrauma1.8%NANANANA1Neurological1.8%NA2.7NANANARenal1.3%NA1.6NA3.2NAHepatobiliary or pancreatic1.1%NANANANA0.3Gastrointestinal0.5%NANANANANANA	Hemorrhage that neither CV bleeding or stroke	3.7%	4.8 ^d	2.6	NA	NA	2
Senile2.1%NANA4.5NANATrauma1.8%NANANANA1Neurological1.8%NA2.7NANANARenal1.3%NA1.6NA3.2NAHepatobiliary or pancreatic1.1%NANANA0.3Gastrointestinal0.5%NANANANANA	Respiratory	4.2%	8.0	3.2	8.4	4.1	3
Trauma1.8%NANANA1Neurological1.8%NA2.7NANANARenal1.3%NA1.6NA3.2NAHepatobiliary or pancreatic1.1%NANANA0.3Gastrointestinal0.5%NANANANANA	Senile	2.1%	NA	NA	4.5	NA	NA
Neurological1.8%NA2.7NANANARenal1.3%NA1.6NA3.2NAHepatobiliary or pancreatic1.1%NANANA0.3Gastrointestinal0.5%NANANANANA	Trauma	1.8%	NA	NA	NA	NA	1
Renal1.3%NA1.6NA3.2NAHepatobiliary or pancreatic1.1%NANANANA0.3Gastrointestinal0.5%NANANANANA	Neurological	1.8%	NA	2.7	NA	NA	NA
Hepatobiliary or pancreatic1.1%NANANANA0.3Gastrointestinal0.5%NANANANANA	Renal	1.3%	NA	1.6	NA	3.2	NA
Gastrointestinal 0.5% NA NA NA NA NA NA	Hepatobiliary or pancreatic	1.1%	NA	NA	NA	NA	0.3
	Gastrointestinal	0.5%	NA	NA	NA	NA	NA

(Continued)

Table 3. (Continued)

Cause of death (N = 3,405)	COOL-AF	GARFIELD [26]	Loire Valley-AF [20]	Korean-NHIS [24]	FUSHIMI [25]	4 DOAC trials [23]
Others non-CV death	6.1%	10.8	6.0	NA	6.2	5
Undetermined	18.4%	23.7	3.2	NA	20.4	6

^aNA = not available.

^bHistory of myocardial infarction[.]

^cCHAD_S score.

^dGARFIELD reported fatal major bleeding separate from CV or non-CV cause of death which included fatal ICH and fatal bleeding from non-ICH cause.

Abbreviations: AF, atrial fibrillation; CHA2DS2-VASc, congestive heart failure, hypertension, age \geq 75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female); CHADs, congestive heart failure, hypertension, age \geq 75 years, diabetes mellitus, stroke [double weight]; COOL-AF, COhort of antithrombotic use and Optimal INR Level in patients with non-valvular Atrial Fibrillation in Thailand; CV, cardiovascular; GARFIELD, Global Anticoagulant Registry in the Field-Atrial Fibrillation; HAS-BLED, Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/ alcohol usage; ICH, intracranial hemorrhage; TIA, transient ischemic attack.

https://doi.org/10.1371/journal.pone.0282455.t003

risk of ICH death compared to those with a TTR \geq 65%. Similarly, warfarin increased the risk of ICH death more than two-fold compared to DOAC users. Hence, giving OAC (particularly, warfarin with TTR <65%) for stroke prevention increased the risk of major bleeding that exceeded the benefit of preventing ischemic stroke. Asian population was reported to be at greater risk for major bleeding and ICH compared to non-Asians [27,28]. Moreover, the results of a previously published meta-analysis of DOACs trials revealed DOACs to be more effective and safe in Asians than in non-Asians [29]; therefore, DOACs should be the preferred OAC in Asian population.

The rates of death related to ICH or major bleeding in our study were higher than those reported from previous studies (Table 3). This finding may be related to a higher use of warfarin and lower use of DOACs in our study compared to other studies. Regarding non-CV death, our results show that the proportion of deaths from non-CV causes, especially infection or sepsis, was higher than previous studies. As such, the strategy to reduce mortality in patients with AF should not focus primarily on stroke prevention, but should include adjunct strategies to minimize bleeding complications and to appropriately prevent and treat infection.

Limitations

This study has some mentionable limitations. First, the results of this study were derived from data collected from large tertiary hospitals, which could limit their generalizability to community-based populations. Second, the cause of death was undetermined in 18.4% of patients who died, but this proportion is similar to those reported from previous studies, as shown in Table 3. Third, our study reports associations, but not causality. Fourth, the main OAC used in our study was warfarin (which is commonly used globally, especially in low-to-middle income countries) and the rate of DOAC use was comparatively low, which may limit the generalizability of our results. Fifth, his study results aren't generalisable across the world and current trends of DOAC use. The results are important at local level especially in low-middle income countries. Efforts in prescribing DOACS instead of warfarin or in alternative, in obtaining better TTR should be encouraged in your population. Finally, we did not have data specific to the causes of death among healthy population to perform age- and gender-matched comparisons with the patients in our study cohort. This is due to the fact that the registry from which our data was collected enrolled only AF patients.

Conclusion

Death due to ischemic stroke was responsible for only 4.7% of all deaths in Asian AF patients. Non-CV death, such as infection/sepsis or malignancy, was more far more prevalent than CV death in Asian AF patients. The use and type of OAC were found to be major determinants of ICH and major bleeding incidence. An improved integrated care approach is needed to reduce the prevalence of non-CV death in Asian AF patients.

Supporting information

S1 Fig. The incidence rates of clinical outcomes per 100 person-years compared between OAC and no OAC (A); warfarin with TTR <65% and \geq 65% (B); and, warfarin and DOAC. A p-value<0.05 indicates statistical significance. (PDF)

S1 Table. Incidence rate of patient outcomes per 100 person-years according to the type of treatment and the time in therapeutic range. (PDF)

S2 Table. Incidence rate per 100 person-years of all cause death, CV death, and non-CV death according to the pattern of OAC treatment. Adjusted hazard ratio specific to the effect of warfarin or DOAC (with or without TTR as a factor) compared to a comparator treatment condition on all cause death, CV death, and nonCV death. (PDF)

Acknowledgments

The authors gratefully acknowledge Mr. Ahthit Yindeengam for his assistance with data management and statistical analysis.

Author Contributions

Conceptualization: Rungroj Krittayaphong, Gregory Y. H. Lip.

Data curation: Rungroj Krittayaphong, Thanita Boonyapiphat, Suchart Aroonsiriwattana, Pornchai Ngamjanyaporn, Gregory Y. H. Lip.

Formal analysis: Rungroj Krittayaphong.

Funding acquisition: Rungroj Krittayaphong.

Investigation: Rungroj Krittayaphong.

Methodology: Rungroj Krittayaphong.

Project administration: Rungroj Krittayaphong.

Supervision: Rungroj Krittayaphong, Gregory Y. H. Lip.

Writing - original draft: Rungroj Krittayaphong, Gregory Y. H. Lip.

Writing – review & editing: Rungroj Krittayaphong, Thanita Boonyapiphat, Suchart Aroonsiriwattana, Pornchai Ngamjanyaporn, Gregory Y. H. Lip.

References

1. Lippi G, Sanchis-Gomar F, Cervellin G. Global epidemiology of atrial fibrillation: An increasing epidemic and public health challenge. International journal of stroke: official journal of the International Stroke

Society. 2021; 16(2):217–21. Epub 2020/01/21. https://doi.org/10.1177/1747493019897870 PMID: 31955707.

- Son MK, Lim NK, Kim HW, Park HY. Risk of ischemic stroke after atrial fibrillation diagnosis: A national sample cohort. PloS one. 2017; 12(6):e0179687. Epub 2017/06/22. https://doi.org/10.1371/journal. pone.0179687 PMID: 28636620; PubMed Central PMCID: PMC5479557.
- Burdett P, Lip GYH. Atrial Fibrillation in the United Kingdom: Predicting Costs of an Emerging Epidemic Recognising and Forecasting the Cost Drivers of Atrial Fibrillation-related costs. European heart journal Quality of care & clinical outcomes. 2020. Epub 2020/12/22. https://doi.org/10.1093/ehjqcco/qcaa093 PMID: 33346822.
- Wong JM, Maddox TM, Kennedy K, Shaw RE. Comparing Major Bleeding Risk in Outpatients With Atrial Fibrillation or Flutter by Oral Anticoagulant Type (from the National Cardiovascular Disease Registry's Practice Innovation and Clinical Excellence Registry). The American journal of cardiology. 2020; 125(10):1500–7. Epub 2020/04/12. https://doi.org/10.1016/j.amjcard.2020.02.028 PMID: 32276760.
- Kim HK, Tantry US, Smith SC Jr., Jeong MH, Park SJ, Kim MH, et al. The East Asian Paradox: An Updated Position Statement on the Challenges to the Current Antithrombotic Strategy in Patients with Cardiovascular Disease. Thromb Haemost. 2021; 121(4):422–32. Epub 2020/11/11. <u>https://doi.org/10. 1055/s-0040-1718729 PMID: 33171520</u>.
- Romiti GF, Pastori D, Rivera-Caravaca JM, Ding WY, Gue YX, Menichelli D, et al. Adherence to the 'Atrial Fibrillation Better Care' Pathway in Patients with Atrial Fibrillation: Impact on Clinical Outcomes-A Systematic Review and Meta-Analysis of 285,000 Patients. Thromb Haemost. 2021. Epub 2021/05/22. https://doi.org/10.1055/a-1515-9630 PMID: 34020488.
- Dilokthornsakul P, Nathisuwan S, Krittayaphong R, Chutinet A, Permsuwan U. Cost-Effectiveness Analysis of Non-Vitamin K Antagonist Oral Anticoagulants Versus Warfarin in Thai Patients With Non-Valvular Atrial Fibrillation. Heart Lung Circ. 2020; 29(3):390–400. Epub 2019/04/20. <u>https://doi.org/10.1016/j.hlc.2019.02.187</u> PMID: 31000364.
- Liu T, Yang HL, Gu L, Hui J, Omorogieva O, Ren MX, et al. Current status and factors influencing oral anticoagulant therapy among patients with non-valvular atrial fibrillation in Jiangsu province, China: a multi-center, cross-sectional study. BMC cardiovascular disorders. 2020; 20(1):22. Epub 2020/01/18. https://doi.org/10.1186/s12872-020-01330-6 PMID: <u>31948390</u>; PubMed Central PMCID: PMC6964080.
- Bahuleyan CG, Namboodiri N, Jabir A, Lip GYH, Koshy AG, Shifas BM, et al. One-year clinical outcome of patients with nonvalvular atrial fibrillation: Insights from KERALA-AF registry. Indian Heart J. 2021; 73(1):56–62. Epub 2021/03/15. https://doi.org/10.1016/j.ihj.2020.11.152 PMID: 33714410; PubMed Central PMCID: PMC7961260.
- Krittayaphong R, Winijkul A, Methavigul K, Wongtheptien W, Wongvipaporn C, Wisaratapong T, et al. Risk profiles and pattern of antithrombotic use in patients with non-valvular atrial fibrillation in Thailand: a multicenter study. BMC cardiovascular disorders. 2018; 18(1):174. https://doi.org/10.1186/s12872-018-0911-4 PMID: 30144802; PubMed Central PMCID: PMC6109333.
- Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the S, Standardization Committee of the International Society on T, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. Journal of thrombosis and haemostasis: JTH. 2005; 3(4):692–4. https://doi.org/10.1111/j.1538-7836.2005.01204.x PMID: 15842354.
- Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2020; 42(5):373–498. https://doi.org/10. 1093/eurheartj/ehaa612 PMID: 32860505.
- January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr., et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2019; 74(1):104–32. https://doi.org/10.1016/j.jacc.2019.01.011 PMID: 30703431.
- Lip GYH, Banerjee A, Boriani G, Chiang CE, Fargo R, Freedman B, et al. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. Chest. 2018; 154(5):1121–201. https:// doi.org/10.1016/j.chest.2018.07.040 PMID: 30144419.
- 15. Chao TF, Joung B, Takahashi Y, Lim TW, Choi EK, Chan YH, et al. 2021 Focused Update Consensus Guidelines of the Asia Pacific Heart Rhythm Society on Stroke Prevention in Atrial Fibrillation: Executive Summary. Thromb Haemost. 2022; 122(1):20–47. Epub 2021/11/14. https://doi.org/10.1055/s-0041-1739411 PMID: 34773920; PubMed Central PMCID: PMC8763451 and received research funds from Samjin, Medtronic, and Abbott. No fees have been received directly or personally. Y.T.: Research grants from Medtronic Japan, Boston Scientific, Japan Lifeline, WIN International, Abbott and Biosense-Webster, and speaker honoraria from Abbott and Biosense-Webster. G.Y. H. L.: Consultant and

speaker for BMS/Pfizer, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are received personally. The other authors report no conflict of interest.

- Yiin GS, Howard DP, Paul NL, Li L, Mehta Z, Rothwell PM, et al. Recent time trends in incidence, outcome and premorbid treatment of atrial fibrillation-related stroke and other embolic vascular events: a population-based study. Journal of neurology, neurosurgery, and psychiatry. 2017; 88(1):12–8. Epub 2015/10/22. https://doi.org/10.1136/jnnp-2015-311947 PMID: 26487646; PubMed Central PMCID: PMC5256147.
- Kongbunkiat K, Kasemsap N, Travanichakul S, Thepsuthammarat K, Tiamkao S, Sawanyawisuth K. Hospital mortality from atrial fibrillation associated with ischemic stroke: a national data report. Int J Neurosci. 2015; 125(12):924–8. https://doi.org/10.3109/00207454.2014.986266 PMID: 25387068.
- Held C, Hylek EM, Alexander JH, Hanna M, Lopes RD, Wojdyla DM, et al. Clinical outcomes and management associated with major bleeding in patients with atrial fibrillation treated with apixaban or warfarin: insights from the ARISTOTLE trial. Eur Heart J. 2015; 36(20):1264–72. Epub 2014/12/17. https:// doi.org/10.1093/eurheartj/ehu463 PMID: 25499871.
- Inohara T, Xian Y, Liang L, Matsouaka RA, Saver JL, Smith EE, et al. Association of Intracerebral Hemorrhage Among Patients Taking Non-Vitamin K Antagonist vs Vitamin K Antagonist Oral Anticoagulants With In-Hospital Mortality. JAMA. 2018; 319(5):463–73. Epub 2018/01/27. https://doi.org/10.1001/ jama.2017.21917 PMID: 29372247; PubMed Central PMCID: PMC5839299.
- Fauchier L, Villejoubert O, Clementy N, Bernard A, Pierre B, Angoulvant D, et al. Causes of Death and Influencing Factors in Patients with Atrial Fibrillation. The American journal of medicine. 2016; 129 (12):1278–87. Epub 2016/08/01. https://doi.org/10.1016/j.amjmed.2016.06.045 PMID: 27476087.
- Bassand JP, Accetta G, Camm AJ, Cools F, Fitzmaurice DA, Fox KA, et al. Two-year outcomes of patients with newly diagnosed atrial fibrillation: results from GARFIELD-AF. Eur Heart J. 2016; 37 (38):2882–9. <u>https://doi.org/10.1093/eurheartj/ehw233</u> PMID: <u>27357359</u>; PubMed Central PMCID: PMC5070447.
- Lip GYH. The ABC pathway: an integrated approach to improve AF management. Nat Rev Cardiol. 2017; 14(11):627–8. https://doi.org/10.1038/nrcardio.2017.153 PMID: 28960189.
- Gomez-Outes A, Lagunar-Ruiz J, Terleira-Fernandez AI, Calvo-Rojas G, Suarez-Gea ML, Vargas-Castrillon E. Causes of Death in Anticoagulated Patients With Atrial Fibrillation. J Am Coll Cardiol. 2016; 68 (23):2508–21. Epub 2016/12/10. https://doi.org/10.1016/j.jacc.2016.09.944 PMID: 27931607.
- Lee E, Choi EK, Han KD, Lee H, Choe WS, Lee SR, et al. Mortality and causes of death in patients with atrial fibrillation: A nationwide population-based study. PloS one. 2018; 13(12):e0209687. Epub 2018/ 12/27. https://doi.org/10.1371/journal.pone.0209687 PMID: <u>30586468</u>; PubMed Central PMCID: PMC6306259.
- An Y, Ogawa H, Yamashita Y, Ishii M, Iguchi M, Masunaga N, et al. Causes of death in Japanese patients with atrial fibrillation: The Fushimi Atrial Fibrillation Registry. European heart journal Quality of care & clinical outcomes. 2019; 5(1):35–42. Epub 2018/07/19. <u>https://doi.org/10.1093/ehjqcco/qcy033</u> PMID: 30020445.
- Bassand JP, Accetta G, Al Mahmeed W, Corbalan R, Eikelboom J, Fitzmaurice DA, et al. Risk factors for death, stroke, and bleeding in 28,628 patients from the GARFIELD-AF registry: Rationale for comprehensive management of atrial fibrillation. PloS one. 2018; 13(1):e0191592. Epub 2018/01/26. <u>https://doi.org/10.1371/journal.pone.0191592</u> PMID: <u>29370229</u>; PubMed Central PMCID: PMC5784935.
- Shen AY, Yao JF, Brar SS, Jorgensen MB, Chen W. Racial/ethnic differences in the risk of intracranial hemorrhage among patients with atrial fibrillation. J Am Coll Cardiol. 2007; 50(4):309–15. Epub 2007/ 07/31. https://doi.org/10.1016/j.jacc.2007.01.098 PMID: 17659197.
- Chiang CE, Wang KL, Lin SJ. Asian strategy for stroke prevention in atrial fibrillation. Europace: European pacing, arrhythmias, and cardiac electrophysiology: journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2015; 17 Suppl 2:ii31–9. https://doi.org/10.1093/europace/euv231 PMID: 26842113.
- Wang KL, Lip GY, Lin SJ, Chiang CE. Non-Vitamin K Antagonist Oral Anticoagulants for Stroke Prevention in Asian Patients With Nonvalvular Atrial Fibrillation: Meta-Analysis. Stroke. 2015; 46(9):2555–61. Epub 2015/08/26. https://doi.org/10.1161/STROKEAHA.115.009947 PMID: 26304863; PubMed Central PMCID: PMC4542566.