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How Much Atrial Fibrillation Is Too Much?

The Net Clinical Benefit of Anticoagulation Therapy in Atrial Fibrillation Patients With an Intermediate CHA_2DS_2-VASc Score

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Abbreviations and Acronyms
ACC = American College of Cardiology
AF = atrial fibrillation
AHA = American Heart Association
APT= Antiplatelet therapy
BARC = Bleeding Academic Research Consortium
CI = confidence interval
ESC = European Society of Cardiology
HR = hazard ratio
HRS = Heart Rhythm Society
ICH= intracranial hemorrhage
IS = ischemic stroke
MI = myocardial infarction
NCB = net clinical benefit
NGR = nongender-related
NICE = National Institute for Health and Care Excellence
OAC = oral anticoagulation
PPV = positive predictive value
TIA = transient ischemic attack
VKA= vitamin K antagonist

Abstract

Background: Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia seen in medical practice, affecting 33.5 million people worldwide. Arterial thromboembolism, particularly ischemic stroke (IS), is a significant complication of AF. The most widely recommended tool used to evaluate AF patient's risk of IS is the CHA_2DS_2-VASc score, which assigns a numerical value to predetermined IS risk factors and allows an overall estimation of the patient's risk by adding these individual numerical values together. Current guidelines offer varying recommendations regarding oral anticoagulation (OAC) therapy use in patients with varying CHA_2DS_2-VASc scores, especially in those patients with intermediate scores, and so it is difficult for clinicians to know whether OAC use for these patients is beneficial or incurring unnecessary risk.

Objective: The purpose of this review is to evaluate the net clinical benefit (NCB) when comparing IS risk to that of hemorrhagic complications when prescribing OAC therapy to patients who have at least 1 nongender-related (NGR) risk factor for IS or an intermediate CHA_2DS_2-VASc score.

Design: Systematic literature review.

Methods: Searches were performed on the PubMed database. The search terms used were "Atrial Fibrillation" and "CHA_2DS_2-VASc" with filters for full text and English.

Results: The PubMed search resulted in finding three articles Chao T-F et al.,[1] Faucher L et al.,[2] and Joundi RA et al.[3]

Conclusions: Based on our review of the current literature, we found that the presence of even 1 NGR risk factor significantly increases a patient's risk of IS. Therefore, we agree with the European Society of Cardiology (ESC) and National Institute for Health and Care Excellence (NICE) guidelines that support considering OAC therapy in AF patients with 1 NGR risk factor, and we suggest that the American College of Cardiology, American Heart Association, and the Heart Rhythm Society (ACC/AHA/HRS) guidelines follow suit.

Introduction

AF is the most prevalent sustained cardiac arrhythmia seen in medical practice,[4] affecting an estimated 33.5 million people worldwide.[5] The prevalence of this disease is increasing, affecting 3.03 million people in the United States in 2005 and a projected 7.56 million in the United States by 2050.[6] With this increase in prevalence, in addition to the already large disease burden, the treatment of AF has become a prominent topic in medical practice.

Arterial thromboembolism, particularly IS, is a significant complication of AF. Independent of other risk factors, the risk of stroke is 5-6 times higher in AF patients than in patients without this disease,[7] and overall, one in five strokes can be attributed to AF.[8] AF hospitalizations increased by 23% between 2000 and 2010,[4] and the estimated annual cost of AF in the United States is $16-26 billion.[5] The prevalence, cost, and devastating effects of AF and its complications makes AF treatment an important issue for both patients and clinicians.

OAC therapy has been conclusively shown to reduce the risk of stroke and systemic embolism in AF patients by 64% and reduce all-cause mortality in AF patients by 26%.[2] Thus, it is one of the mainstays of treatment for many AF patients. However, there is substantial risk associated with OAC therapy due to its inhibitory effects on the body's ability to form clots. While OAC therapy dramatically reduces a patient's risk of IS, it also increases the risk of serious bleeding events such as hemorrhagic stroke. Thus, the benefit of using OAC therapy to prevent IS must be weighed against the patient's risk of hemorrhagic complications, and the decision to use OAC therapy should be prescribed only when the benefit outweighs the risk. For this study, we will define this benefit to risk ratio as the NCB. Patients with a positive NCB have a high enough risk of IS that the benefit of OAC therapy outweighs the risk of hemorrhage, and patients with a negative NCB have hemorrhage risks that outweigh the potential benefits they could receive from OAC therapy.

There are a number of tools available to help clinicians predict how high a patient's risk of IS is and therefore help determine whether OAC therapy is warranted. The most widely recommended tool for patients with nonvalvular AF is the $CHADS_2$-VASc score,[9] which assigns a numerical value to pre-determined IS risk factors and allows an overall estimation of the patient's risk by adding these individual numerical values together.

The CHA_2DS_2-VASc score assigns 1 point for congestive heart failure, 1 point for hypertension, 2 points for age ≥75 years, 1 point for diabetes mellitus, 2 points for having a history of previous stroke/transient ischemic attack (TIA)/thromboembolism, 1 point for vascular disease (including myocardial infarction (MI), complex aortic plaque, and peripheral arterial disease), 1 point for age 65-74, and 1 point for being female (see table 1).[2]

Once the CHA_2DS_2-VASc score has been determined, patients are typically categorized in one of two ways. Some studies identify patients as having low, intermediate, or high risk of IS based on their overall CHA_2DS_2-VASc score. Typically, patients with a score of 0 are considered to have low risk, patients with a score of 1 are considered to have intermediate risk, and patients with a score of 2 or higher are considered to have high risk.[10]

Table 1. The CHA_2DS_2-VASc Score for Calculating Stroke Risk in AF Patients[2]

Risk Factor	Points Assigned for Risk Factor
(C) Congestive heart failure	1
(H) Hypertensive	1
(A) Age ≥75 years	2
(D) Diabetes mellitus	1
(S) Stroke/TIA	2
(V) Vascular Disease	1
(A) Age between 65-74	1
(Sc) Sex category (female)	1
Total Possible Points	**10**

Other studies focus only on NGR risk factors. While being female automatically adds one point to the patient's overall CHA_2DS_2-VASc score due to research that shows a higher risk of stroke in female AF patients versus men, there is evidence that some of this research was focused on older populations and that the age factor may have conferred more risk than the female factor in these studies.[9] So, while being female may increase a patient's risk of IS, the numerical point it adds to the CHA_2DS_2-VASc score may not confer as high of a degree of risk as the other risk factors, and therefore may not warrant OAC therapy if it is the only risk factor present.[9] The studies that focus only on NGR risk factors when assessing the NCB of OAC therapy classify patients according to the number of NGR risk factors they have.

It is also important to recognize that the risk factors included in the CHA_2DS_2-VASc score confer varying degrees of risk[1] and that each patient may also have comorbidities or other confounding factors which affect their overall risk of IS. Therefore, it is always important to consider which risk factors are contributing to a patient's overall risk and what other factors need to be considered when assessing their NCB.

Current guidelines agree that OAC therapy is warranted in AF patients with more than 2 stroke risk factors and not warranted in patients with 0 risk factors.[9] This reflects that the NCB of OAC therapy is positive for patients with more than 2 risk factors (that is, their potential benefit from OAC outweighs their risk of bleeding) and negative for patients with no risk factors (that is, their risk of bleeding outweighs their potential benefits from OAC therapy). Current guidelines vary, however, regarding recommendations about OAC in patients with 1 NGR risk factor or an intermediate CHA_2DS_2-VASc score (see table 2), and it is difficult for clinicians to know whether OAC is beneficial or incurring unnecessary risk in these patients.

Table 2. Organization Anticoagulation Guidelines[11, 12, 13]

Organization	Sex Category	CHA_2DS_2-VASc Score 0	1	≥2
ACC/AHA/HRS	Men	No therapy	Oral anticoagulation, aspirin, or no therapy	Oral anticoagulation
	Women	N/A	Oral anticoagulation, aspirin, or no therapy	Oral anticoagulation
ESC and NICE	Men	No therapy	Oral anticoagulation	Oral anticoagulation
	Women	N/A	No therapy	Oral anticoagulation

Key: ACC: American College of Cardiology, AHA: American Heart Association, ESC: European Society of Cardiology, HRS: Heart Rhythm Society, NICE: National Institute for Health and Care Excellence

The NICE 2014 guidelines recommend considering OAC for men with a CHA_2DS_2-VASc score of 1 and offering OAC to all patients with a CHA_2DS_2-VASc score of 2, taking bleeding risk into account. Options for OAC should also be discussed with the patient and the decision should be based on clinical features and preference.[13]

The 2014 AHA/ACC/HRS guideline recommends OAC for patients with a CHA_2DS_2-VASc score of 2 or greater and for patients with a prior stroke or TIA regardless of their CHA_2DS_2-VASc score.[11] The guideline states that either no antithrombotic therapy, treatment with OAC, or treatment with aspirin may be considered for patients with a CHA_2DS_2-VASc score of 1, and that it is reasonable to omit all antithrombotic therapy for patients with a CHA_2DS_2-VASc score of 0.[11]

The 2016 ESC guidelines recommend the use of OAC in all AF patients unless they are at low risk for IS based on the CHA_2DS_2-VASc score or have true contraindications for anticoagulation.[12] The ESC defines low risk for men as a score of 0. For the purposes of gender classification, the ESC considers women without other stroke risk factors to correspond with a CHA_2DS_2-VASc score of 0 and therefore considers them low risk.[12] Regardless of gender, the ESC guidelines consider all patients with AF and 1 NGR stroke risk factor to have a CHA_2DS_2-VASc score of 1. Thus all patients with a CHA_2DS_2-VASc score of 1 or more should be treated with OAC therapy unless contraindications indicate otherwise.[12]

The objective of this study is to review available scholarly literature and make a recommendation regarding the use of OAC therapy in patients with an intermediate CHA_2DS_2-VASc score. We developed the following clinical question to guide our study:

Clinical Question: In patients with nonvalvular AF who have at least 1 NGR risk factor for IS or an intermediate CHA_2DS_2-VASc score, does prescribing OAC therapy as compared to not prescribing OAC therapy have a positive NCB when comparing IS risk to risk of hemorrhagic complications?

Methods

A literature search was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). On September 15, 2016, the PubMed database was searched using the terms "Atrial Fibrillation" and "CHA_2DS_2-VASc." Inclusion criteria was limited to meta-analysis and observational retrospective cohort study designs. Studies were included if their population consisted of patients with nonvalvular AF and risk stratification of IS using the CHA_2DS_2-VASc score. Studies were excluded if the patient population included valvular AF, if IS was not a measured endpoint, and if risk assessment tools other than the CHA_2DS_2-VASc score were used. 691 articles were screened and 575 articles were excluded because they focused on variables outside our defined clinical question. Of the remaining 116 articles assessed for eligibility, 113 full text articles were excluded because they did not meet the analytical criteria. This left 3 studies to include in our qualitative synthesis: 1 meta-analysis and 2 retrospective cohorts. A schematic flowchart of the article search and selection process can be seen in figure 1.

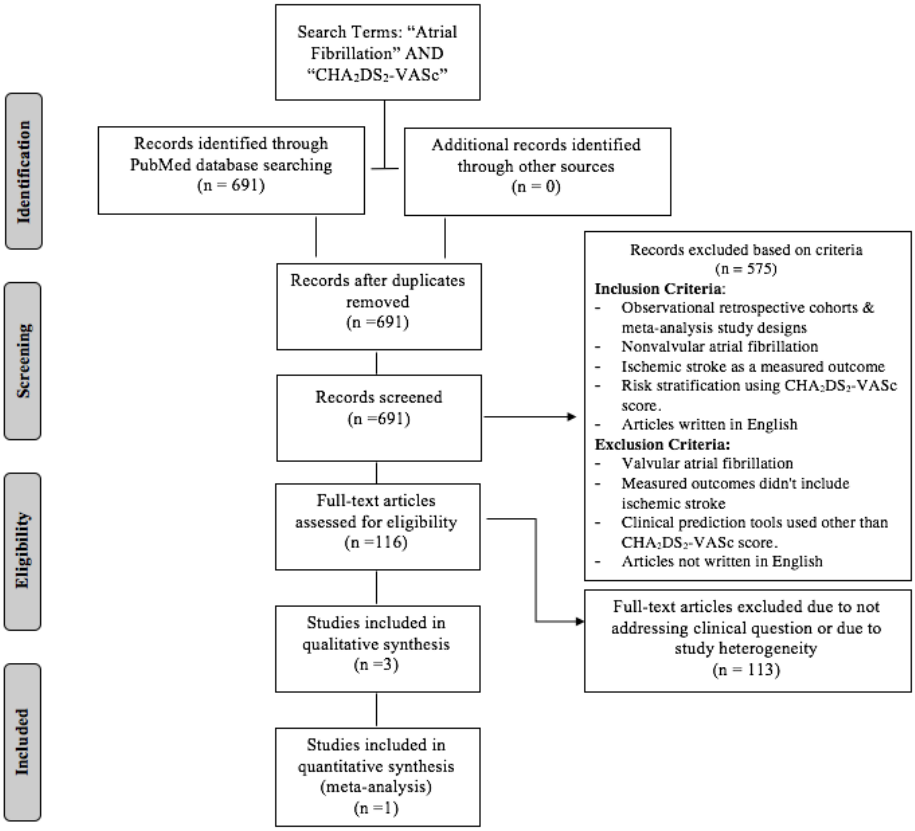

Figure 1. PRISMA Article Selection Criteria

Results

Study 1:

Should Atrial Fibrillation Patients With 1 Additional Risk Factor of the CHA_2DS_2-VASc Score (Beyond Sex) Receive Oral Anticoagulation?[1]

Study Objective:

To determine whether the presence of a single NGR risk factor increases the annual rate of IS in Taiwanese AF patients aged 20 years and older and to determine the degree of risk that each CHA_2DS_2-VASc risk factor actually confers.

Study Design:

The study used the National Health Insurance Research Database (NHIRD) of the Taiwan National Health Research Institutes. The National Health Insurance System is a mandatory universal healthcare program offering comprehensive medical care to Taiwanese residents. Patient's original ID numbers were encrypted to protect their privacy. They identified patients with a diagnosis of AF using the International Classification of Disease-Ninth Revision-Clinical Modification code, only when it was a discharge diagnosis or confirmed more than twice in an outpatient department. This method was also used to determine comorbid conditions.

After accounting for inclusion and exclusion criteria (Table 3), a total of 186,570 patients were enrolled.

Table 3. Study 1 Inclusion and Exclusion Criteria

Using the NHIRD of the Taiwan National Health Research Institutes, patients meeting the following criteria were identified:

Inclusions Criteria	Exclusion Criteria
1. Patients in the NHIRD system from January 1, 1996 to December 31, 2011 2. AF patients 20 years of age or older	1. History or warfarin therapy 180 days before and 90 days after the diagnosis of AF 2. History of any antiplatelet therapy (APT) including aspirin, clopidogrel, dipyridamole, and ticlopidine 180 days before and 90 after the diagnosis of AF

The CHA_2DS_2-VASc score was then calculated for each patient. The total number of males enrolled with 1 NGR risk factor was 12,935 (CHA_2DS_2-VASc score of 1), and the total number of females enrolled with 1 NGR risk factor was 7,900 (CHA_2DS_2-VASc score of 2).

The clinical end point of the study was to determine the occurrence of IS with concomitant imaging studies of the brain including computed tomography or magnetic resonance imaging using the NHIRD (which is reported to have a 94% accuracy rate, a positive predictive value (PPV) of 88.4%, and a sensitivity of 97.3% for diagnosing IS). A PPV is the probability of actually having a disease (i.e. IS) if a positive test result is obtained. A test's sensitivity demonstrates its ability to correctly identify patients with a disease (to identify true positive).

Data was presented using mean +/- standard deviation. An unpaired 2-tailed student *t* test was used to analyze continuous variables. A t test is used to determine the presence of a statistically significant difference between two variables.[14] Incidence rates of stroke were calculated by dividing the number of events by person-time at risk with a 95% confidence interval (CI) estimated by using the Fisher exact test. The CI is a range of outcome values that the authors are 95% confident contain the actual result. Risk of IS was assessed using the Cox regression analysis. A Cox regression analysis looks at several variables that occur over one specific event in time or survival. Statistical significance was set at $p<0.05$ and all statistical analyses were carried out by using Statistical Package for Social Science (SPSS) 17.0 software.

Study Results:

The mean age of male patients enrolled was 59.1+/- 11.3 years and the mean age of female patients enrolled was 59.1 +/- 10.2 years. The most prevalent risk factor for males was age between 65-74 years and for females was hypertension.

Among the male AF patients with a CHA_2DS_2-VASc score of 1 (12,935) there were 1,858 patients who experienced an IS during follow-up (5.2 years +/- 4.3 years), resulting in an average annual stroke rate of 2.75%. This rate ranges from 1.96%/year for patients with vascular disease to 3.50%/year for patients aged 65-74 years. When comparing males with a CHA_2DS_2-VASc score of 1 to those with a CHA_2DS_2-VASc score of 0 the hazard ratio (HR) of IS was 2.385 (95% CI: 2.184-2.604; $p<0.001$) (Table 4). A HR expresses how many times more or less likely an exposed person (i.e. with AF) develops an outcome (i.e. IS) relative to an unexposed person. Therefore males with a score of 1 are 2.385 times more likely to have an IS compared to those with a score of 0.

Of the female AF patients with a CHA_2DS_2-VASc score of 2 (7,900), 1,174 (14.9%) experienced IS during follow-up (5.9+/- 4.4 years) resulting in an average annual stroke rate of 2.55%. The annual stroke rate ranged from 1.91% for patients with hypertension to 3.34% for patients aged 65-74. When comparing females with a CHA_2DS_2-VASc score of 2 to those with a CHA_2DS_2-VASc score of 1 the HR of IS was 2.251 (95% CI: 2.024-2.404; $p<0.001$), therefore females with a score of 2 are 2.251 times more likely to have an IS compared to those with a score of 1. (Table 5).

Table 4. Risk of Ischemic Stroke in AF Male Patients (CHA_2DS_2-VASc score of 1)

Risk Factor Components of CHA_2DS_2-VASc Score	# of events	Person-Years	Annual Stroke Rate % (95% CI)	Hazard Ratio (95% CI)*	P value
Congestive Heart Failure	265	11,246	2.37 (2.10-2.67)	2.060 (1.788-2.373)	<0.001
Hypertension	477	21,888	2.18 (1.99-2.38)	1.946 (1.731-2.189)	<0.001
Age 65-74 years	874	24,982	3.50 (3.27-3.74)	3.085 (2.790-3.410)	<0.001
Diabetes mellitus	156	5,263	2.96 (2.52-3.47)	2.655 (2.230-3.161)	<0.001
Vascular Disease	84	4,294	1.96 (1.56-2.42)	1.681 (1.333-2.120)	<0.001
Total	1,858	67,673	2.75 (2.62-2.87)	2.385 (2.184-2.604)	<0.001
* The risk of IS was compared to those with a CHA_2DS_2-VASc Score of 0 using the Cox regression analysis					

Table recreated from Study 1[1]

Table 5. Risk of Ischemic Stroke in AF Female Patients (CHA_2DS_2-VASc score of 2: Female plus 1 Additional Stroke Risk Factor)

Risk Factor Components of CHA_2DS_2-VASc Score	# of events	Person-Years	Annual Stroke Rate % (95% CI)	Hazard Ratio (95% CI)*	P value
Congestive Heart Failure	181	8,151	2.22 (1.91-2.57)	1.984(1.672-2.353)	<0.001
Hypertension	303	15,864	1.91(1.70-2.14)	1.711 (1.481-1.976)	<0.001
Age 65-74 years	521	15,602	3.34 (3.06-3.64)	3.031 (2.678-3.431)	<0.001
Diabetes mellitus	110	3,823	2.88 (2.37-3.47)	2.655 (2.158-3.267)	<0.001
Vascular Disease	59	2,618	2.25 (1.72-2.91)	2.152 (1.641-2.823)	<0.001
Total	1,174	46,058	2.55 (2.41-2.70)	2.251 (2.024-2.504)	<0.001
* The risk of IS was compared with AF female patients with a CHA_2DS_2-VASc Score of 1 (only due to the female sex) using the Cox regression analysis					

Table recreated from Study 1[1]

Study Critique:

This retrospective cohort study had numerous strengths including a large population sizes with both males and females. It looked at the average risk of IS based on the total CHA_2DS_2-VASc score and stratified the IS risk based on individual CHA_2DS_2-VASc risk factors which allowed for comparison of the number of events, person-years, annual stroke rate, and HR. This lends some insight into the degree of risk each CHA_2DS_2-VASc risk factor actually confers. Person-years is the product of the number of years multiplied by the number of individuals in the study population. This study was published in 2015 making it recent, and it recorded data over 15 years giving it some longevity. It is also the first population-based investigation looking at the above clinical question further setting the stage for research to come.

This study had a number of drawbacks due to data that was collected from a database consisting entirely of Taiwanese residents. This population hinders data extrapolation due to possible differences in exposures, genetics, lifestyle difference, and medical treatment that patients in the United States may not experience. Also, patients were excluded due to taking warfarin or other APT 180 days prior or 90 days after the diagnosis of AF, but they were not excluded if they began taking any of these medications after 90 days until the follow-up period. This could potentially underestimate the annual stroke rate reported. Additionally, the frequency, quality, and equality of follow-up was not defined in the study and it did not specify if patients were lost to follow-up. A final major drawback that the study addressed was the inability to identify the exact cause of IS in these AF patients.

Study 2:

Should Atrial Fibrillation Patients With Only 1 NGR CHA_2DS_2-VASc Risk Factor be Anticoagulated?[2]

Study Objective:

To measure whether a single NGR CHA_2DS_2-VASc risk factor confers a significant risk of stroke and whether the use of OAC can reduce this overall risk with minimal hemorrhagic complications.

Study Design:

This retrospective community cohort identified 8,962 patients diagnosed with AF by the cardiology department at the Centre Hospitalier Regional et Universitaire in Tours, France between 2000 and 2010. AF was defined via ECG by, "replacement of consistent P waves by rapid oscillations or fibrillatory waves that vary in amplitude, shape, and timing, associated with an irregular, frequently rapid ventricular response when atrioventricular conduction was intact." Treatment and comorbidity information was extrapolated using hospital reports and the hospital's computerized coding system, respectively.

Of the 8,962 patients diagnosed with AF, 1,806 patients were diagnosed with valvular AF and excluded from the analysis. CHA_2DS_2-VASc scores were calculated using its standard

protocol for the remaining 7,156 patients, and consequently excluded 4,948 patients who had more than 2 NGR stroke risk factors. The final sample size included patients with <2 NGR stroke risk factors (males with a CHA_2DS_2-VASc score of 0 or 1 and females with a score of 1 or 2). This consisted of 2,208 patients; 685 females and 1,523 males with a mean age of 55+/-14. The remaining sample was separated into four groups with an additional corresponding subgroup.

- **Group A:** patients not treated with OAC with 0 NGR stroke risk factors
- **Group B:** patients not treated with OAC with 1 NGR stroke risk factor
- **Group C:** patients treated with OAC with 0 NGR stroke risk factors
- **Group D:** patients treated with OAC with 1 NGR stroke risk factor
- **Subgroups A.2, B.2, C.2, and D.2:** patients treated with APT

See table 6 for inclusion and exclusion criteria and figure 2 for a diagram depicting study groups.

Table 6. Study 2 Inclusion and Exclusion Criteria

Inclusions Criteria	Exclusion Criteria
1. Patients diagnosed with nonvalvular AF at the cardiology department at the Centre Hospitalier Regional et Universitaire between 2000 and 2010 2. Males with NGR risk factor of 0 or 1 3. Females with NGR risk factor 1 or 2	1. Patients diagnosed with valvular AF 2. Diagnosis and follow-up at any hospital other than Centre Hospitalier Regional et Universitaire 3. Patients diagnosed with NVAF at Centre Hospitalier Regional et Universitaire before 2000 and after 2010 4. Antithrombotic treatment at discharge were unknown 5. Patients with mitral stenosis 6. Patients with any valvular prosthesis in whom OAC was indicated 7. Males with 2 or more NGR risk factors 8. Females with 3 or more NGR risk factors

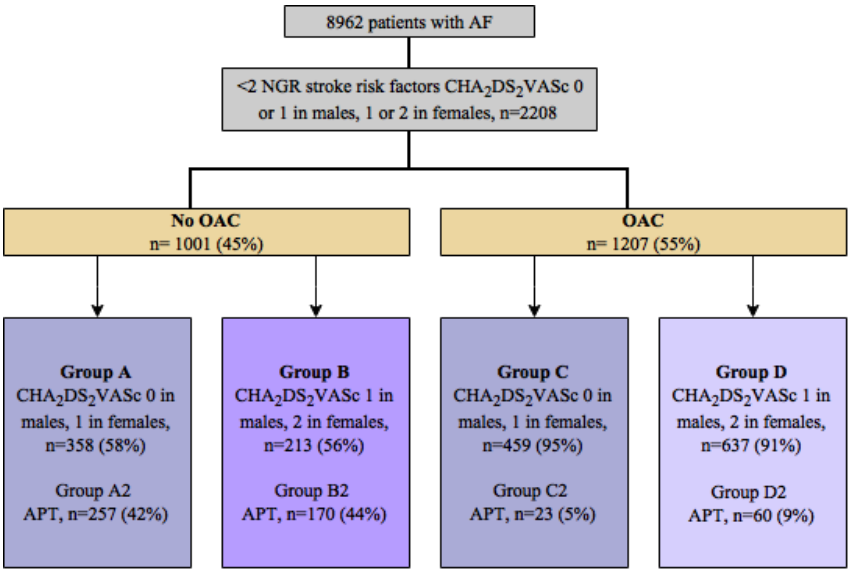

Figure 2. Flowchart of Study Groups

Outcomes recorded included events of interest and deaths from all causes when they occurred and/or followed up at the University of Hospital Tours institution, which is the only public institution in Tours, France and includes four hospitals covering all medical and surgical specialties.

Event rates were measured and compared in nonanticoagulated patients with 0 NGR risk factors (Group A) versus 1 NGR risk factor (Group B). They used event rates for Group B and those measured in anticoagulated patients with 1 NGR risk factor (Group D), and calculated the NCB of OAC therapy. NCB was calculated using two methodologies: the Singer et al and alternative Connolly et al formulas Table 7.

Table 7. Study 2: Net Clinical Benefit Methodologies

Singer et al formula:	NCB = [(IS rate on no treatment) – (IS rate on antithrombotic treatment)] – [1.5 (ICH rate without treatment) – (ICH rate on antithrombotic treatment)]
Connolly et al formula:	NCB = (w1 x ΔRIS) + (w2 x ΔRICH) + w3 x ΔRmajor bleeding + w4 x ΔRMI
Key	• NCB = Net Clinical Benefit • IS = Ischemic Stroke • ICH= Intracerebral Hemorrhage • ΔR = Rate not treated – rate treated • Major Bleeding = Major extracranial bleeding • MI = Myocardial infarction • Weights w1=1, w2=3.08, w3 = 0.67, and w4 = 0.95

Statistical analysis between groups and categorical variables included the X^2, Student t test, and nonparametric Kruskal-Wallis test. The Kruskal-Wallis test is a rank-based nonparametric test used to determine if there are statistically significant differences between independent variable on a continuous or ordinal dependent variable.[15] X^2 tests for goodness of fit and it is used to decide if there is a difference between experimental and theoretical values.[16] A HR of predictive factors and a 95% CI for incidence of events was found using the Cox proportional hazards regression model. Statistical analysis was performed using the Statview 5.0 software.

Study Results:

Follow-up was over a period of 1,028 +/- 1,189 days for all groups. Groups A and B included 1001 patients who were not treated with OAC and their subgroups A.2 and B.2 that received APT. Outcomes measured included; MI, all strokes, IS, stroke/systemic thromboembolism, bleeding, major Bleeding Academic Research Consortium (BARC) bleeding event, ICH, and the composite endpoint of death/stroke/systemic embolism. The yearly rate of stroke/systemic embolism measured in nonanticoagulated patients with 1 NGR stroke risk factor (Group B, CHA_2DS_2-VASc score of 1 in males and 2 in females) was 2.09% (95% CI, 1.37-

3.18). The corresponding HR is 2.82 (95% CI 1.32-6.04) compared to nonanticoagulated patients with 0 NGR stroke risk factors (Group A, CHA_2DS_2-VASc score of 0 in males and 1 in females).

For nonanticoagulated patients with 1 NGR stroke risk factor (group B), the yearly rate of death was 3.78% and the composite endpoint of death/stroke/systemic embolism was 5.59%. For nonanticoagulated patients with 0 NGR stroke risk factors (group A), the yearly rate of death was 0.87% and the composite endpoint of death/stroke/systemic embolism was 1.42%. For nonanticoagulated patients with 0 or 1 CHA_2DS_2-VASc score, the yearly rate of event for major BARC bleeding was 0.65% and ICH was 0.43%. For the events measured in nonanticoagulated patients with 1 NGR (Group B) compared to patients with 0 NGR stroke risk factor (group A), there was nonsignificant increase in the HR.

Groups C and D included 1,207 patients that were treated with OAC and their subgroups C.2 and D.2 that also received APT. Outcomes measured included; IS, ICH, major extracranial bleeding, and MI. The comparison of yearly event rates seen in anticoagulated patients with 1 NGR stroke risk factor (Group D) versus nonanticoagulated patients with 1 NGR stroke risk factor (Group B) can be seen in table 8.

For all patients with 1 NGR stroke risk factor (Group B+D), the study compared the treatment of OAC to those who didn't receive OAC by measuring the yearly event rates of IS and ICH. Data was extrapolated and used to calculate the NCB with two different methodologies. In other words, the benefit of reducing IS in patients with 1 NGR stroke risk factor was weighed against OAC's potential risk of causing an ICH. The data suggest a positive NCB in favor of using OAC, specifically a vitamin K antagonist (VKA), versus no OAC in patients with 1 NGR stroke risk factor. This was consistent across both the Singer and Connolly methodologies (Table 9). However, for patients with 1 NGR stroke risk factor and APT use with no OAC (Group B.2), there was a negative NCB calculated in comparison to those who used no APT or OAC (Group B.1).

Table 8. Event Rates for Different Outcomes Measured

	n	Person-Years	Events	Event Rate %/yr. (95% CI)	HR (95% CI)	P value
Ischemic Stroke						
OAC Therapy(D.1)	637	1976	18	0.91 (0.58-1.44)	0.84 (0.34-2.11)	0.72
No OAC therapy (B.1)	213	554	6	1.08 (0.50-2.34)	Reference	
Intracranial Hemorrhage						
OAC Therapy (D.1)	637	2021	9	0.45 (0.23-0.84)	0.83 (0.23-3.07)	0.82
No OAC therapy(B.1)	213	562	3	0.53 (0.18-1.56)	Reference	
Major Extracranial Bleeding Event						
OAC Therapy (D.1)	637	1824	10	0.55 (0.30-1.01)	0.90 (0.25-3.24)	0.86
No OAC therapy(B.1)	213	490	3	0.61 (0.21-1.78)	Reference	
Myocardial Infarction						
OAC Therapy (D.1)	637	2014	13	0.65 (0.38-1.10)	0.40 (0.17-0.92)	0.04
No OAC therapy(B.1)	213	553	9	1.63 (0.86-3.06)	Reference	

Table adapted from Study 2[2]

Table 9. NCB Analysis Stroke Prevention Strategy for AF patients with 1 NGR Stroke Risk Factor (CHA_2DS_2-VASc **1 in males and 2 in females) Treated with OAC**

Singer et al: NCB (%/y) 95% CI	**Connolly et al:** NCB (%/y) 95% CI
0.30 (0.015 to 0.61)	1.42 (1.01 to 1.99)

Table adapted from Study 2[2]

Study Critique:

This was a retrospective study that utilized non-randomized registry data to analyze a large community cohort within Tours, France. Different countries and lifestyles carry different risk factors, therefore the data provided for France may not be completely applicable to the U.S. population. However, the analysis provided comparative and complementary data to that of randomized control trials. Reliability is further compromised due to the observational nature because the authors could not implement stringent protocol to minimize confounding variables. While some variables were adjusted for, certain variables cannot be properly assessed. A major threat to the validity of the study includes the possibility that less severe strokes and ICH were not accounted for if those patients were not hospitalized. Furthermore, the study was not able to account for acuteness or severity of outcomes measured.

Absence of design stratification is inherent to retrospective observational study designs and therefore treatment bias and variable patient management must be taken into consideration. Additionally, the quality of anticoagulation, compliance, and therapeutic range was not available. The longevity of follow-up puts this study at risk for treatment changes that cannot be adequately adjusted for due to lack of knowledge regarding possible changes.

Using data from records not designed for a study can result in poor data quality due to limited availability. Any deaths that may have occurred due to an undiagnosed stroke could not be accounted for due to the lack of mandated postmortem imaging that would be required in a clinical trial. This study also lacked data about strokes that potentially occurred outside of the four institutions included under the University Hospital of Tour, therefore differential losses to follow-up is another bias that must be considered.

Study design is the biggest limitation to the validity of this study, however a retrospective observational cohort is the appropriate study design for this research question due to the ethical sensitivity of studying AF and anticoagulation. However, the observational nature of this study can also be considered a strength because it allows for a realistic representation with variable challenges that providers often face in clinical practice.

Study 3:

IS risk in patients with atrial fibrillation and CHA_2DS_2-VASc score of 1; Systematic review and meta-analysis.[3]

Study Objective:

To help resolve uncertainty about OAC therapy in patients with a CHA_2DS_2-VASc score of 1 by determining the annual IS rate in AF patients and comparing it to pre-determined treatment thresholds.

Study Design:

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The authors searched MEDLINE, Embase, PubMed, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and the Web of Science Core Collection from the beginning of each database until April 15, 2015 using variations of the word "CHA_2DS_2-VASc" as their literary search terms. Inclusion and exclusion criteria for this study are listed in table 10.

For each study meeting the inclusion and exclusion criteria, the authors extracted patient baseline characteristics and outcome information. They calculated summary estimates of IS rate for CHA_2DS_2-VASc scores of 0, 1, and 2 using inverse variance weights, in which studies that are larger and have less random variation are given more weight in the meta-analysis than studies that are smaller and have more random variation.[17] The authors calculated the variance of IS rates using a Poisson rate parameter, which is used to calculate the total number of events in a time period when the events occur randomly but at an average rate,[18] and an adjusted Wald interval, which is a statistical method to calculate CIs.[19] The authors also included a sensitivity analysis in which they removed the study with the highest stroke rate in each CHA_2DS_2-VASc score group to assess its effect on the summary estimate.

Once the summary annual IS rates were estimated for each CHA_2DS_2-VASc group, the authors compared these numbers to pre-determined treatment thresholds for anticoagulant use. These thresholds, determined by Eckman et al, are the "tipping point" at which the benefits of oral anticoagulant use for reducing IS begin to outweigh the risk of hemorrhagic complications.

Table 10. Study 3 Inclusion and Exclusion Criteria

Inclusions Criteria	Exclusion Criteria
1. Mention of nonvalvular AF and CHA_2DS_2-VASc and stroke 2. Event rate for at least 1 stratum of the CHA_2DS_2-VASc score between 0 and 2 or the necessary data to produce event rate (events and patient years)	1. Excluded if the study exclusively recruited patients with a specific comorbidity other than AF 2. Excluded if primary data were not available/analyzed (e.g., reviews, editorials, or letters to the editor) 3. Excluded if IS was not a measured outcome 4. Excluded studies not including groups without anticoagulation and duplicate cohorts

Study Results:

The estimated summary annual IS rate for a CHA_2DS_2-VASc score of 1 was 1.61% (2517 events per 166017 patient-years) with a 95% CI of 0-3.23%. The estimated rate for a CHA_2DS_2-VASc score of 0 was 0.68% (761 events per 109,197 patient-years) with a 95% CI of

0.12-1.23%, and the estimated rate for a CHA_2DS_2-VASc score of 2 was 2.49% (4319 events per 133,298 patient-years) with a 95% CI of 1.16-3.83%. These results are summarized in table 11.

The summary IS rate treatment thresholds determined by Eckman et al include a stroke rate of 0.9% for novel oral anticoagulants and 1.7% for warfarin. Therefore, according to this study, patients with a CHA_2DS_2-VASc score of 0 are below the threshold for any anticoagulant therapy, patients with a CHA_2DS_2-VASc score of 1 meet the threshold for novel oral anticoagulant therapy but not treatment with warfarin, and patients with a CHA_2DS_2-VASc score of 2 meet the threshold for both novel oral anticoagulant and warfarin treatment. These results are summarized in figure 3.

Based on these results, in addition to the heterogeneity of the study and the potential difference in risk factor significance, the authors promote an individualized, rather than rule-based approach to anticoagulant treatment. They suggest that NOACs may have a positive NCB for patients with a CHA_2DS_2-VASc score of 1, but they posit that the final decision should be made based on clinical judgment, the patient's individual characteristics, and the patient's values and preferences.

Table 11. Estimated Summary Annual IS Rate for CHA_2DS_2-VASc Scores of 0, 1, and 2

CHA_2DS_2-VASc Score	Estimated Summary Annual IS Rate	Events	95% CI
0	0.68%	(761 events per 109,197 patient-years)	0.12 - 1.23%
1	1.61%	(2,517 events per 166,017 patient-years)	0 - 3.23%
2	2.49%	(4,319 events per 133,298 patient-years)	1.16 - 3.83%

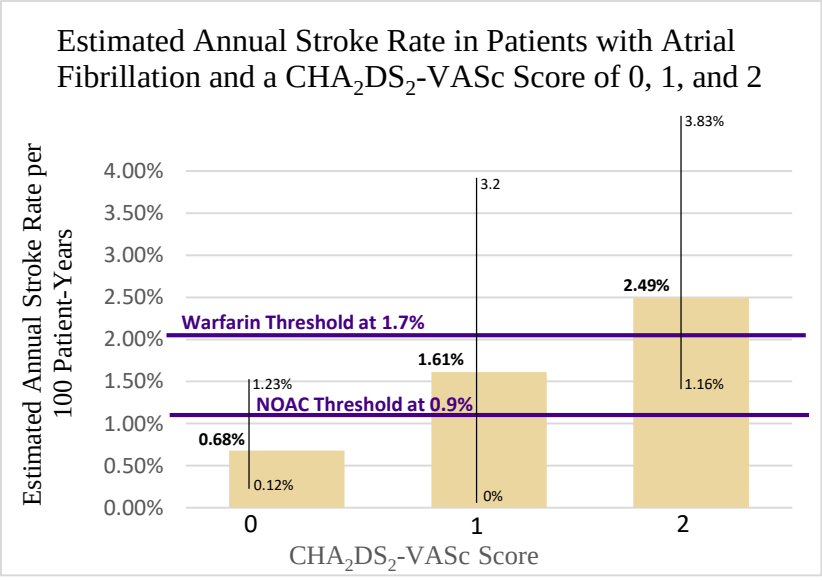

Figure 3.

Study Critique:

Strengths of this study include its recent publication date, its use of the CHA_2DS_2-VASc score, the similarity of outcomes measured among studies, its large study size, the similar weights of the studies included, and the variety of countries in which the individual studies were conducted. This study is also the first meta-analysis to look at annual IS rates based on the CHA_2DS_2-VASc score, thus paving the way for future studies.

Weaknesses of this study include several types of bias, a lack of discussion regarding the quality of the studies included, the presence of wide CIs, and the presence of significant heterogeneity among studies. These weaknesses are discussed in further detail below.

The authors acknowledge the potential bias present in this study. Egger regression tests and funnel plots showed publication bias. In addition, the authors did not search unpublished data during their literature search, thus increasing the likelihood for bias. Six out of 10 of the studies had possible selection bias due to varying patient characteristics, 7 out of 10 of the studies had possible performance bias due to lack of knowledge regarding whether any patients underwent treatment changes during the follow-up period, 6 out of 10 of the studies had possible attrition bias due to lack of information regarding patient loss to follow-up, 5 out of 10 studies had possible detection bias due to the lack of a specific definition of "IS" and the lack of an imaging requirement for diagnosis, and 3 out of 10 studies had funding bias, with an additional 5 out of 10 studies not mentioning sources of funding.

The authors state they assessed the quality of the studies using the Cochrane handbook, but the results of this assessment are not included in the article or data supplement. This information would have been helpful in assessing the validity of this study.

The 95% CIs for the estimated annual stroke rates are wide, meaning there is a wide range of numeric outcomes which could include the actual result. This could dramatically change the outcome and clinical recommendation of the study. For example, the study states that the estimated annual stroke rate for a CHA_2DS_2-VASc score of 1 is 1.61%; however, the CI is a range from 0-3.23%. This means the actual annual stroke rate for patients with a CHA_2DS_2-VASc score of 1 could range between 0 and 3.23%. This matters clinically because the lower end of the CI does not even meet the treatment threshold for NOACs, whereas the upper end of the CI surpasses both the treatment threshold for NOACs and warfarin.

There is significant heterogeneity among the studies used in the meta-analysis, which decreases the validity of the results. The authors acknowledge that substantial variation existed among patients' mean age, ethnicities, comorbidities, use of antithrombotics, and risk factors. I2 statistical calculations are used to assess the heterogeneity among studies used in a meta-analysis. An I^2 value less than 25% indicates homogenous studies, and an I^2 value greater than 75% indicates a high level of heterogeneity. The study's I2 values for patients with a CHA_2DS_2-VASc score of 0 is 98.96%, I2 for a CHA_2DS_2-VASc score of 1 is 99.69%, and I2 for a CHA_2DS_2-VASc score of 2 is 96.94%, each indicating extremely high heterogeneity. Similarly, the chi-squared based Q statistic is significantly higher than the degrees of freedom for each CHA_2DS_2-VASc score, which also indicates significant heterogeneity among studies.

Discussion

Overall, all three studies provided valuable insight to the decision of whether patients with 1 NGR stroke risk factor or an intermediate CHA_2DS_2-VASc score would have a positive NCB from OAC therapy. Study 1 and study 2 recommend OAC therapy in patients with 1 or more NGR stroke risk factors (CHA_2DS_2-VASc score of 1 for males and 2 for females). Study 3 recommends considering OAC therapy in patients with a total CHA_2DS_2-VASc score of 1 or higher, regardless of gender or risk factor, but states that all treatment should be individualized based on patient risk, characteristics, and preference. For study characteristics, see table 12.

Table 12. Study Characteristics

Study	Study Type	Location	Number of Patients in Study	Study Recommendation
Study 1	Retrospective Cohort	Taiwan	20,838 patients	Recommend anticoagulation therapy in patients with 1 or more NGR risk factors for IS (CHA_2DS_2-VASc score of 1 for males and 2 for females)
Study 2	Retrospective Cohort	France	2,208 patients	
Study 3	Systematic Review and Meta-Analysis	Studies Included in the Meta-Analysis: Banerjee et al: Denmark Chao et al: Taiwan Friberg et al: Sweden Hobbs et al: United Kingdom Huang et al: China Komatsu et al: Japan Larsen et al: Denmark Lip et al: Multi-Country Siu et al: China Suzuki et al: Japan	Studies Included in the Meta-Analysis: Banerjee et al: 132,372 Chao et al: 186,570 Friberg et al: 182,678 Hobbs et al: 665 Huang et al: 548 Komatsu et al: 332 Larsen et al: 1,603 Lip et al: 5,599 Siu et al: 9,727 Suzuki et al: 3,588	Recommend considering OAC therapy in patients with a total CHA_2DS_2-VASc score of 1 or higher for males and females.

Study 1 utilized the CHA_2DS_2-VASc score by considering NGR stroke risk factors and calculating the annual stroke rate for male AF patients with a CHA_2DS_2-VASc score of 1 and female AF patients with a CHA_2DS_2-VASc score of 2. It compared these stroke rates to male AF patients with a CHA_2DS_2-VASc score of 0 and female AF patients with a CHA_2DS_2-VASc score of 1. The study used IS as its clinical endpoint and did not measure NCB but did recommend the future use of NCB in reference to the prevention of thromboembolism and major bleeding with the use of OAC therapy. The overall annual IS rate that was measured for males with a CHA_2DS_2-VASc score of 1 was 2.75% and for females with a CHA_2DS_2-VASc score of 2 was 2.55%. This was the highest annual stroke compared to Study 2 and Study 3. Overall Study

1 supports prescribing OAC for all AF patients with 1 NGR stroke risk factor due to their high risk of IS. Overall, this study provided useful information regarding annual stroke rates based on each CHA_2DS_2-VASc risk factor as well as providing narrow CIs and statistically significant P values ($p<0.05$).

Study 2 also used the CHA_2DS_2-VASc score to look at NGR stroke risk factors and the risk of IS versus hemorrhagic stroke. The use of OAC in patients with 1 NGR stroke risk factor (CHA_2DS_2-VASc score of 1 for males and 2 for female) has been debated among clinicians. This paper measured outcomes for all patients with 1 NGR risk factor (Groups B and D) and compared the yearly percent rates of events in those who were anticoagulated versus those who were not. Using this information they were able to calculate the overall NCB to help quantify the benefit versus harm that OAC can potentially cause in a less clearly defined intermediate risk group.

Rates of IS, ICH, major extracranial bleeding, and MI that occurred in patients with 1 NGR were measured and compared in three groups: B1, B2, D1. Principle findings showed no OAC with 1 NGR versus 0 NGR had an increased risk of cardiovascular events at follow-up. In addition, the use of VKA showed a positive NCB for preventing stroke and thromboembolic events. The study highlights that the NICE and ESC guidelines recommend OAC for patients with 1 NGR risk factors whereas the ACC/AHA/HRS guidelines recommend OAC for patients with 2 or more total risk factors. Study findings showed AF patients with 1 NGR and OAC use were associated with a positive NCB with VKA versus no antithrombotic therapy or aspirin. Therefore, the authors support the strategy for OAC proposed in the current ESC and NICE guidelines and recommend that the ACC/AHA guidelines reconsider treating just a single NGR risk factor. Thus, the author suggests that physicians should appreciate that even a single NGR risk factor confers real risk of stroke/systemic thromboembolism/death and that OAC would decrease this overall risk, providing a positive NCB.

Study 3 utilized the CHA_2DS_2-VASc score by performing a systematic review and meta-analysis to calculate summary estimates of IS rates for CHA_2DS_2-VASc scores of 0, 1, and 2. This study did not separate male and female CHA_2DS_2-VASc scores and looked at the overall risk of IS based on the total CHA_2DS_2-VASc score rather than looking at only NGR risk factors. The study used IS as its clinical endpoint, and the meta-analysis included only studies that used IS as a measured outcome.

The study looked at NCB in two ways. First, they used published net-benefit thresholds for the use of OAC therapy, determined by Eckman et al. These net-benefit thresholds were determined by a Markov state-transition model and estimate the tipping point at which the benefits of OAC therapy begin to outweigh the risks. Eckman et al defined a stroke rate of 0.9% as the treatment threshold for novel oral anticoagulants and a stroke rate of 1.7% as the treatment threshold for warfarin.

The meta-analysis then compared their estimated annual IS rates for AF patients with the net-benefit thresholds determined by Eckman et al, thus determining the overall NCB of OAC for these patients. Patients with a CHA_2DS_2-VASc score of 0 had an estimated stroke rate of

0.68% and therefore did not meet the threshold for either type of OAC therapy. Patients with a score of 1 had an estimated stroke rate of 1.61% and therefore met the threshold for novel oral anticoagulants but not for warfarin. Patients with a score of 2 had an estimated stroke rate of 2.49% and therefore met the threshold for both types of OAC.

Based on these results, the authors of the meta-analysis recommended that patients with a CHA_2DS_2-VASc score of 0 may not benefit from OAC therapy, patients with a score of 2 should be strongly considered for OAC therapy including novel oral anticoagulants or warfarin, and patients with a score of 1 may have a positive NCB from novel oral anticoagulants but not likely from warfarin. The authors acknowledge there is a high degree of uncertainty due to the variation of risk conferred by specific patient risk factors, and so the final decision regarding whether to use anticoagulation therapy should be made by the clinician based on each individual patient. The authors suggest that patients with a score of 1 should be further stratified based on individual risk factors in order to provide further clarity for anticoagulation guidelines since each risk factor may not confer the same degree of risk.

Each of the studies had different strengths and weaknesses that contribute to their overall value in this review. Overall, one main benefit of each of these studies is that they are some of the initial population based and meta-analysis studies relating to our clinical question, laying the framework for further research to come. Additionally, each of these studies was published recently and so each study represents recent data and clinical practices.

One main strength of Study 1 and Study 3 is their large sample size. Study 2 had a smaller sample size relative to 1 and 3, but still had over 2,000 patients, and so still provided a large data set. Another strength of Study 1 is that it stratified annual stroke risk based on each individual stroke risk factor, which is helpful when weighing the relative significance of each risk factor in the CHA_2DS_2-VASc score. Studies 2 and 3 did not stratify the risk factors and only reported annual stroke rates based on total CHA_2DS_2-VASc scores. This makes it more difficult to apply the results in clinical practice because each stroke risk factor does not confer an equal amount of risk of IS.

Studies 1 and 3 did not have any apparent funding bias, although some of the individual studies used in Study 3 had funding bias. Study 2 had potential funding bias due to receiving financial support from several drug companies. All three studies had possible attrition bias due to lack of information regarding follow-up and possible performance bias due to potential alterations in treatment during the follow-up period.

Study 3 had wide CIs, significant heterogeneity, and lacked discussion regarding the quality of the studies included, all of which potentially limit its reliability. Each of the studies included in the meta-analysis, however, carried similar weight, which adds to its reliability, and the variety of locations in which the studies took place also shows its applicability among many patient populations.

One main limitation of all three studies is that, due to their observational nature, none of the studies were able to adequately control or adjust for specific variables such as defined anticoagulation treatment protocols. Randomized control trials will be needed in the future to

conclusively demonstrate the cause and effect of anticoagulation therapy on IS rate. There is still benefit, however, in the observational nature of these studies because many variables in clinical practice are difficult to control, and reporting nonrandomized, real world retrospective data may provide a realistic perspective and may help guide future research and guidelines.

Conclusion

Based on our review of the current literature, we found that the presence of even 1 NGR stroke risk factor significantly increases a patient's risk of IS. Therefore, we agree with the ESC and NICE guidelines that support considering OAC therapy in AF patients with one NGR risk factor, and we suggest that the ACC/AHA/HRS guidelines follow suit. We also agree with current guidelines that patients with zero NGR stroke risk factors should not be offered OAC therapy and patients with 2 or more NGR stroke risk factors should be offered OAC therapy. More research is needed to determine whether women with sex as their only risk factor would benefit from OAC therapy. As with all guidelines, these are recommendations based on research and evidence; however, they are not concrete rules. Individual patient risk, characteristics, and preference should always be considered when making the decision about whether to use any type of therapy.

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