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Solutions to Reduce Cardiovascular Events in Patients with Atrial Fibrillation

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Abstract

AF is the most common sustained cardiac rhythm disorder and an established risk factor for ischemic stroke. Ischemic strokes which occur in patients with AF are particularly severe and disabling. In addition, stroke recurrence is more common in patients with AF compared with those without it. Previous cerebrovascular events, age, hypertension, diabetes, and heart failure are risk factors for stroke in patients with AF.

Various risk stratification schemes have been developed to quantify the risk for stroke in patients with AF. Currently, the most frequently used schemes to assess stroke risk in patients with AF are $CHADS_2$, the ACC/AHA/ESC and American College of Chest Physicians (ACCP) schemes.

Current risk scores are largely derived from risk factors identified from clinical trials and many potential risk factors have not been properly considered. Consequently, the stroke risk in many patients could be underestimated, and these patients could receive a suboptimal antithrombotic prophylaxis.

There is substantial evidence for the benefit of vitamin K antagonists (VKA) in preventing stroke and reducing mortality. Novel oral anticoagulants are available for stroke prevention in patients with AF which overcome some of the difficulties associated with VKA. The introduction of novel oral anticoagulants in clinical practice and the advances in identifying patients at risk of stroke together may overcome many of the difficulties in providing effective stroke prevention for patients with AF.

Introduction

Atrial fibrillation (AF) is an independent risk factor for stroke. Risk stratification for ischemic stroke in patients with AF is based on scores which incorporate several risk factors as previous cerebrovascular events, age, hypertension, diabetes, and heart failure. There are a number of risk factors for stroke that are not recognized by traditional risk scores, such as female gender, atherosclerotic vascular disease, valvular dysfunction and myocardial infarction. Consequently, the stroke risk in many patients could be underestimated, and these patients could receive suboptimal antithrombotic prophylaxis. At least two refinements of current risk scores are in development.

Antithrombotic therapy is tailored according to the level of risk, with vitamin K antagonists (VKA) reserved to medium-high risk patients. VKA are effective in preventing stroke and reducing mortality. Newer oral anticoagulants (direct thrombin inhibitors and direct Factor Xa) inhibitors are currently available for stroke prevention in patients overcoming some of the difficulties associated with VKAs.

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In this review, we report on recent advances to optimize the risk scores and on the clinical development on the new oral anticoagulants. Improved risk scores and new oral agents together may overcome the current difficulties in providing effective stroke prevention in patients with AF.

Epidemiology of Atrial Fibrillation

AF is the most common sustained cardiac rhythm disorder. The prevalence of AF is probably underestimated due to under-diagnosis of asymptomatic cases.[1] AF is relatively uncommon before the age of 60 years, but affects nearly 10% of individuals over the age of 80 years.[2] After adjustment for age and predisposing conditions, men have a 1.5-fold greater risk of developing AF than women.[3] Hypertension, diabetes mellitus, hyperthyroidism, alcohol abuse and obesity are additional risk factors for AF.[4] In addition, after adjusting for cardiovascular risk factors, heart failure, valvular heart disease and myocardial infarction increase the risk of AF.[5] Emerging risk factors for AF include reduced vascular compliance, atherosclerosis, insulin resistance, environmental factors, inflammation, increased level of natriuretic peptides and genetic predisposition.[5]

The prevalence of AF is dramatically increasing. This is partly due to increase in the longevity of the general population.[1]

AF and Ischemic Stroke and Impact of AF on Stroke Severity and Risk of Recurrence

AF is the most important independent risk factor for ischemic stroke. AF is associated with an approximate five-fold increased risk of stroke.[6] Indeed, one in every four-five ischemic strokes occurs in patients with AF. Multivariate analysis revealed age, hypertension, diabetes mellitus, prior stroke or TIA, myocardial infarction and congestive heart failure as significant additional risk factors for stroke in patients with AF.[7]

AF-related ischemic strokes are generally more severe and more disabling than strokes suffered by patients without AF. This might be due to several reasons: older age, larger size of the cerebral infarct, more common hemorrhagic transformations and more severe initial neurological impairment .[8-12] Among stroke survivors, those with AF are more likely to suffer a recurrent stroke than those without AF.[13]

Several clinical and observational studies found that the incidence of ischemic stroke in patients with paroxysmal AF was similar to that in patients with permanent AF.[14-17]

Antithrombotic Prophylaxis to Reduce the Risk of Stroke: Evidence from Clinical Trials

Dose-adjusted VKA to maintain an international normalized ratio [INR] between 2.0 and 3.0 are effective for stroke prevention in patients with AF. A meta-analysis of six randomized trials showed that VKA provided about 65% risk reduction of ischemic stroke in comparison to placebo.[18] A similar risk reduction is seen in patients who receive VKA for secondary prophylaxis.[19, 20] Aspirin 325 mg per day provides a 22% reduction in the incidence of stroke versus placebo.[18] A meta-analysis of five randomized trials that compared dose-adjusted warfarin to ASA 325 mg per day showed that warfarin provided a 36% risk reduction for all strokes and a 46% risk reduction for ischemic strokes versus aspirin.[18] VKAs prevent more severe and disabling strokes as compared to aspirin.[21]

In the ACTIVE-W trial, warfarin was also significantly more effective than aspirin plus clopidogrel for stroke prevention in patients at high risk of stroke.[22] However, among patients with AF for whom VKA therapy was considered unsuitable, the combination of clopidogrel and aspirin was associated with a reduction in the primary outcome of stroke, myocardial infarction, non-cerebral systemic embolism or death from vascular causes compared with aspirin alone. The difference was primarily due to a reduction in the rate of stroke. Major bleeding was significantly more common in patients assigned to the combination of clopidogrel and aspirin.[23]

VKA are associated with an increased risk of

bleeding, particularly intracranial hemorrhage and gastrointestinal bleeding, with respect to aspirin or no treatment (0.3%, 0.2% and 0.1% per year respectively).[18,19] VKA use accounts for a significant proportion of iatrogenic emergency room admissions. About 4% of admissions to Stroke Unit for intracranial hemorrhages are due to warfarin treatment within therapeutic range.[24]

Stroke risk rises sharply when the INR falls below 2.0 and the risk of intracranial bleeding increases sharply when the INR increases beyond 3.0.[25]

Identifying Patients at Risk of Stroke to Guide Antithrombotic Prophylaxis

The risk for stroke varies widely among patients with AF. Various risk stratification schemes have been developed [7, 21-31] in attempts to evaluate and quantify individual risk. Currently, the most frequently implemented schemes for assessing stroke risk in patients with AF are $CHADS_2$,[26] the ACC/AHA/ESC [25] and American College of Chest Physicians (ACCP) [30, 31] schemes.

In $CHADS_2$, a cumulative score (range 0–6) is calculated according to the presence of defined risk factors. Different risk factors are given different weightings: two points are assigned for a previous stroke or TIA and one point is assigned for each of the following: age older than 75 years, hypertension, diabetes mellitus and recent cardiac failure. Scores of 0, 1 and ≥2 denote low, moderate and moderate-to-high risk of stroke, respectively.[26, 27]

In contrast, the ACC/AHA/ESC [25] and ACCP [30, 31] schemes do not use a scoring system. Instead, they each categorize patients as being at low, moderate or high risk of stroke according specific combinations of risk factors.

The ACCP scheme does not take into consideration whether the patient has previously experienced a stroke or TIA, making this scheme less applicable to evaluating stroke risk for secondary stroke prevention (Table 1).

The current guidelines for antithrombotic prophylaxis [25,31] recommend that patients with AF at low risk of stroke receive daily aspirin, those at high risk of stroke (or 'moderate-to-high' risk according to $CHADS_2$) receive VKA therapy (unless contraindicated), and either aspirin or a VKAs is recommended for patients classified as being at moderate risk of stroke. $CHADS_2$ is more likely than other schemes to classify a patient as being at moderate risk of stroke,[32, 33] which may lead to uncertainty among physicians with regard to the choice of antithrombotic therapy for these patients (guidelines recommend either aspirin or VKA).

Limitations of Risk Stratification Scores

Current risk scores are largely derived from risk factors identified from trial cohorts and many potential risk factors have not been considered.[34] The

Table 1 Stroke risk stratification in atrial fibrillation: three prominent schemes

$CHADS_2$	ACC/AHA/ESC Guidelines (2006)	ACCP Practice Guidelines (2008)
Congestive heart failure: 1 point	High risk	High risk
Hypertension: 1 point	Prior thromboembolism	Prior thromboembolism
Age >75 years: 1 point	≥2 moderate risk features	≥2 moderate risk features
Diabetes: 1 point	Moderate risk	Intermediate risk
Stroke/TIA: 2 points	Age ≥75 years	Age ≥75 years
	Heart failure	Heart failure
	Hypertension	Hypertension
Low risk=0 points	Diabetes	Diabetes
Moderate risk: 1 point	Left ventricular ejection fraction ≤35% or fractional shortening <25%	Moderately to severely impaired left ventricular systolic function
High risk: ≥2 points	Low risk	Low risk
	No moderate- or high-risk features	No intermediate- or high-risk features

majority of patients with AF have at least one additional clinical condition that further increases their risk of stroke. Indeed, there are a number of risk factors for stroke that are not recognized by $CHADS_2$ as female gender, atherosclerotic vascular disease, valvular dysfunction and myocardial infarction. Consequently, many patients' stroke risk could be underestimated, and they could receive suboptimal antithrombotic prophylaxis. In addition, several independent analyses have shown that assignment of stroke risk varies widely depending on the scheme used,[32, 35] which may contribute to inconsistent implementation of guideline recommendations for anticoagulation. Disagreement between risk scores comes in the critical range for decision-making; they all identify very low and very high risk pretty well, but diverge in the moderate classification.

An additional limitation of current risk stratification schemes is that they were all developed and validated in patients not receiving anticoagulants. Consequently, these schemes identify which patients are above a certain threshold of risk and would benefit from anticoagulation, but not those patients who remain at risk despite anticoagulation.[32] A recent study found that carotid/vertebral atherosclerosis and hyperlipidemia are associated with an increased risk for ischemic events in patients with AF on adequate warfarin treatment .[36]

Stroke prevention in patients with AF might therefore be improved with more accurate schemes for stratifying stroke risk. It's equally likely that treating everyone who is not low risk would just as good as try to predict risk. However, being able to communicate risk to the patient might improve adherence to medical recommendations. As the incidence of ischemic stroke is similar in patients with paroxysmal AF and those with permanent AF,[15-17,37] antithrombotic therapy should not be guided by the clinical subtype of AF, but rather by the presence of additional risk factors for stroke.

Advances in Evaluating Stroke Risk: Building on $CHADS_2$

$CHA2DS_2$-VASc was recently developed with the aim of more accurately predicting stroke risk for patients with AF by taking into account some of the additional risk factors not recognized by $CHADS_2$.[38] Like $CHADS_2$, a cumulative scoring system is used (see Table 2). However, the scoring for age is stratified and relatively younger age (≥65 years) is recognized as a risk factor whereas $CHADS_2$ only recognizes patients over the age of 75 years. In addition, female gender and vascular disease are included in the evaluation of stroke risk, whereas these risk factors are not recognized by $CHADS_2$. CHA_2DS_2-VASc was validated in the Euro Heart Survey; prediction of stroke risk was improved compared with $CHADS_2$ and only a small proportion of patients were categorized as being at 'intermediate risk' of stroke.

Another scheme for evaluation stroke risk in patients with AF has been developed by Rietbrock et al. [39] As in $CHADS_2$, a cumulative score is calculated (see Table 2). However, this new scheme differs from $CHADS_2$ as follows: a greater weighting is placed on a previous stroke or TIA (six points compared with two points in $CHADS_2$), female gender is recognized, and the points assigned for age are

Table 2 Comparison of new stroke risk evaluation schemes with $CHADS_2$

	Points Assigned for Presence of each Risk Factor		
Risk Factor	**$CHADS_2$ (Gage et al. 2001, 2004)**	**Rietbrock scheme (Rietbrock et al. 2008)**	**$CHA2DS_2$-VASc (Lip et al. 2009)**
Age	>75 years: +1	40–64 years: +1 65–69 years: +2 70–74 years: +3 75–79 years: +4 80–84 years: +5 85–115 years: +6	≥75 years: +2 65–74 years: +1
Diabetes mellitus	+1	+1	+1
Previous stroke/TIA	+2	+6	+2
Heart failure	+1	–	+1
Hypertension	+1	–	+1
Female gender	–	+1	+1
Vascular disease	–	–	+1
Cumulative score	range 0–6	range 0–14	range 0–9

awarded on a sliding scale, with points assigned to patients ≥40 years of age, whereas in $CHADS_2$ points for age are only assigned to those who are >75 years old. This scheme was evaluated in the UK General Practice Research Database (>51,000 patients with AF) and showed a modest improvement in the accuracy for predicting stroke over $CHADS_2$ (C-statistic: 0.68 for $CHADS_2$, 0.72 for the Rietbrock scheme).

In addition the accuracy of $CHADS_2$ for predicting stroke risk might be improved by also taking into account AF burden (e.g. presence and duration of AF in addition to $CHADS_2$ variables) since AF increases the risk of stroke in an independent manner .[40,41]

Antithrombotic Prophylaxis: Unmet Needs

The Euro Heart Survey showed that VKA are not being used in accordance with the current guidelines and not in accordance with stroke risk.[42-44] Only 61% of patients with AF were treated in accordance with the guidelines: 28% were undertreated, which was associated with a higher risk of thromboembolism and stroke; 11% were overtreated, which was associated with a trend towards a higher risk of bleeding.[44]

The NABOR (National Anticoagulation Benchmark Outcomes Report) program, a performance improvement program designed to benchmark anticoagulation prophylaxis, treatment, and outcomes among participating hospitals, confirmed that VKA are under-prescribed to eligible patients with AF and conversely are prescribed to a high proportion of patients at low risk who do not require anticoagulation.[45] Real-world data from registries and observational studies have also shown that patients with paroxysmal AF are much less likely to receive VKA prophylaxis than those with persistent or permanent AF.[37, 43, 45]

Only 11% of patients admitted to the Stroke Unit of the University of Perugia for an ischemic stroke and known AF had received VKA prior to admission and only 40% of them were in the therapeutic range.[11] A retrospective cohort study (ISAM) showed that 11–36% of patients (depending on country) are outside of the target INR range for >50% of the time,[46] which leaves them either at increased risk of stroke (INR <2.0) or increased risk of bleeding (INR >3.0).

There is much concern with regard to the management of patients at moderate to high risk of stroke who are in need of anticoagulation but are deemed ineligible for VKAs for one reason or another. In the absence of alternative oral anticoagulants to VKAs, the only available option is the administration of antiplatelet agents (aspirin alone or aspirin plus clopidogrel combined), which is significantly less effective than VKAs (as discussed above) or no prophylaxis. Such patients are likely to receive only ASA (i.e. to be greatly undertreated and remain at risk of stroke). Major bleeding occurred in 251 patients receiving clopidogrel (2.0% per year) and in 162 patients receiving placebo (1.3% per year) (relative risk, 1.57; 95% CI, 1.29 to 1.92; P<0.001).

New Oral Anticoagulants In the Development of Stroke Prevention in AF

The ideal profile of a new oral anticoagulant includes the following: a predictable pharmacological profile, so that INR monitoring and dose modifications are not required, rapid onset and offset of actions as well as fixed oral dosing that would be most convenient for patients and could potentially improve adherence to the prescribed regimen.

Oral Direct Thrombin Inhibitors

Ximelagatran was the first of these latest novels, and The SPORTIF trials [47, 48] showed that it was at least as effective as warfarin for the prevention of stroke, with no difference seen in the rate of total bleeding. Ximelagatran was withdrawn from the market in 2006 due to liver toxicity. Nevertheless, this drug provided the proof of concept for direct thrombin inhibition and showed that oral anticoagulation without regular INR monitoring could be safe and effective.

Dabigatran is a second-generation of direct thrombin inhibitors. In the landmark phase III RE-LY trial, dabigatran was the first oral anticoagulant to show its superiority to warfarin for stroke prevention in AF.[49] Dabigatran 110 mg twice daily (bid) resulted in a rate of stroke and systemic em-

bolism similar to that observed in warfarin-treated patients (1.53% per year vs. 1.69% per year, p<0.001 for non-inferiority) but with a lower rate of major hemorrhage (2.71 per year vs. 3.36 per year, p=0.003). Dabigatran 150 mg bid resulted in a lower rate of stroke and systemic embolism than warfarin (1.11% per year vs. 1.69% per year, p<0.001 for superiority) and its rate of major hemorrhage was comparable to that observed in warfarin-treated patients (3.11% per year vs. 3.36% per year, p=0.31).

Dabigatran was also associated with higher rates of treatment discontinuation than warfarin, and dabigatran-treated patients had somewhat signals for more myocardial infarction, major GI bleeding and dyspepsia.

Oral Direct Factor Xa Inhibitors

The oral direct factor Xa inhibitor rivaroxaban was compared to warfarin in the ROCKET-AF study.[50] This trial was a phase III, randomized, double-blind, event-driven non-inferiority trial with over 14,000 patients comparing rivaroxaban with warfarin in nonvalvular AF (at least two documented episodes) and a history of stroke, TIA, or non-CNS embolism or at least two independent risk factors for future stroke. Enrolment of patients without stroke, TIA, or systemic embolism and only two risk factors was capped at 10% of the overall study population; all subsequently enrolled patients were required to have at least three stroke risk factors or a history of stroke, TIA, or systemic embolism. A total of 86% of the population had a $CHADS_2$ score of 3 or higher. Patients were randomized to rivaroxaban 20 mg once daily (or 15 mg once daily in patients with moderate renal impairment), or dose-adjusted warfarin titrated to a target INR of 2.5. The per-protocol, as treated primary analysis was designed to determine whether rivaroxaban was noninferior to warfarin for the primary end point of stroke or systemic embolism; if the non-inferiority criteria were satisfied, superiority was analyzed in the intent-to-treat population. Rivaroxaban was similar to warfarin for the primary efficacy endpoint of prevention of stroke and systemic embolism (event rate 1.71 versus 2.16 per 100 patient years for rivaroxaban versus warfarin; hazard ratio [HR] 0.79, 95% confidence interval [CI] 0.66–0.96, P, 0.001 for non-inferiority). The stricter intention-to-treat analysis also showed rivaroxaban to be similar to warfarin but did not reach statistical significance for superiority: event rate 2.12 versus 2.42 per 100 patient years for rivaroxaban versus warfarin; HR 0.88, 95% CI 0.74–1.03, P = 0.117 for superiority. This superiority was only demonstrated in the per-protocol analysis of patients who continued to receive treatment for the 40-month trial period: event rate 1.70 versus 2.15 per 100 patient years for rivaroxaban versus warfarin; HR 0.79, 95% CI 0.65–0.95, P = 0.015 for superiority. Major and non-major clinically relevant bleeding was similar between the rivaroxaban and warfarin groups. The rivaroxaban group had significantly less fatal bleeding (0.2 versus 0.5 per 100 patient years, HR 0.50, 95% CI 0.31–0.79, P = 0.003), intracranial hemorrhage (0.5 versus 0.7 per 100 patient years; P = 0.02). The number of patients experiencing a serious adverse event was similar for the two groups (rivaroxaban 37.3% versus warfarin 38.2%).

The AVERROES study was designed to evaluate the use of apixaban for stroke prophylaxis by comparing it to aspirin in patients unsuitable for warfarin.[51] The study enrolled 5,600 patients with AF who could not take warfarin and compared apixaban 5 mg twice daily (2.5 mg twice daily for patients aged over 80 years, weighing less than 60 kg or with renal impairment) with aspirin 81–324 mg/day. The study was stopped because of an acceptable safety profile and benefit in favor of apixaban. After a year, patients taking apixaban were found to have a 55% reduction in the primary endpoint of stroke or systemic embolism (1.6% versus 3.7% per year, HR 0.45, 95% CI 0.32–0.62, P, 0.001). The rate of major bleeding was similar in both groups: 1.4% per year for apixaban and 1.2% per year for aspirin (HR 1.13, 95% CI 0.74–1.75, P = 0.57). Aspirin was the less well-tolerated therapy.

The ARISTOTLE trial compared apixaban to warfarin in patients with AF.[52] It was a randomized phase III, double-blind, international trial comparing apixaban 5 mg twice/day versus warfarin titrated to an INR between 2 and 3 in over 18,000 patients. The primary outcome was stroke (either ischemic or hemorrhagic) or systemic embolism, and the trial was designed to test for non-inferiority. Secondary objectives included an analysis for superiority with respect to the primary outcome and to the rates of major bleeding and all-causes of mortality. The follow-up period was 1.8 years.

The rate of the primary outcome in ARISTOTLE was 1.27% per year in the apixaban group versus 1.60% per year in the warfarin group (hazard ratio with apixaban, 0.79; 95% confidence interval [CI], 0.66 to 0.95; P , 0.001 for non- inferiority; P = 0.01 for superiority). This was primarily driven by a reduction in hemorrhagic stroke, as the rates of ischemic stroke were comparable with warfarin: 0.97% per year in the apixaban group versus 1.05% per year in the warfarin group (hazard ratio, 0.92; 95% CI, 0.74 to 1.13; P = 0.42). Conversely, the rates of hemorrhagic stroke were 0.24% per year in the apixaban group versus 0.47% per year in the warfarin group (hazard ratio, 0.51; 95% CI, 0.35 to 0.75; P, 0.001). Apixaban demonstrated a benefit with regards to all-causes of mortality compared to warfarin: rates of death from any cause were 3.52% in the apixaban group versus 3.94% in the warfarin group (hazard ratio, 0.89; 95% CI, 0.80 to 0.99; P = 0.047). Apixaban was found to be safer than warfarin with regard to major bleeding: 2.13% per year in the apixaban group versus 3.09% per year in the warfarin group (hazard ratio, 0.69; 95%CI, 0.60 to 0.80; P, 0.001). Drug discontinuation occurred less frequently with apixaban compared to warfarin: 25.3% versus 27.5% (P = 0.001). The average time spent in therapeutic INR was 62.2% for the warfarin-treated patients. The reported adverse and serious adverse effects were similar in both groups.

Another randomized phase III trials exploring the use of oral direct Factor Xa inhibitors for stroke prevention in patients with AF is currently ongoing. This study is the ENGAGE AF TIMI 48 (NCT00781391): double-blind, randomized study comparing two different doses of edoxaban (30 mg or 60 mg once a day) with dose-adjusted warfarin.

Conclusions

- AF is a major risk factor for stroke, and its prevalence increases with older age
- Patients with AF vary widely with regard to their stroke risk and currently the choice of antithrombotic prophylaxis depends on an individual patient's magnitude of risk. The role of risk stratification after the advent of newer agents is not entirely clear
- There is room for improvement in risk stratification and several refinements are in development. Better stratification of stroke risk may lead to better adherence to antithrombotic prophylaxis for individual patients

- VKAs are effective but are associated with a number of drawbacks in real-life practice
- Novel oral anticoagulants (including two major classes of agents: direct thrombin inhibitors and selective Factor Xa inhibitors) are available for stroke prevention in patients with AF which overcome some of the difficulties associated with VKAs.
- These advances in identifying patients at risk of stroke together with the introduction of novel oral anticoagulants into clinical practice may overcome many of the current difficulties in providing effective stroke prevention for patients at risk.

Disclosures

No disclosures relevant to this article were made by the authors.

References

1. Steinberg JS. Atrial fibrillation: an emerging epidemic? Heart. 2004 Mar;90(3):239-40.
2. Ryder KM, Benjamin EJ. Epidemiology and significance of atrial fibrillation. Am J Cardiol 1999; 84: 131R-138R.
3. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol. 1998;82(8A):2N-9N.
4. Indik JH, Alpert JS. The patient with atrial fibrillation. Am J Med 2009; 122: 415-418.
5. Kannel WB, Benjamin EJ. Status of the epidemiology of atrial fibrillation. Med Clin North Am. 2008 Jan;92(1):17-40.
6. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991 Aug;22(8):983-8.
7. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation: analysis of pooled data from five randomised controlled trials. Arch Int Med 1994; 154: 1449-1457.
8. Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, D'Agostino RB. Stroke severity in atrial fibrillation. The Framingham Study. Stroke. 1996; 27(10):1760-4.
9. Jørgensen HS, Nakayama H, Reith J, Raaschou HO, Olsen TS. Acute stroke with atrial fibrillation. The Copenhagen Stroke Study. Stroke. 1996;27(10):1765-9.
10. Dulli DA, Stanko H, Levine RL. Atrial fibrillation is associated with severe acute ischemic stroke. Neuroepidemiology. 2003;22(2):118-23.
11. Paciaroni M, Agnelli G, Caso V, Venti M, Milia P, Silvestrelli

G, Parnetti L, Biagini S. Atrial fibrillation in patients with first-ever stroke: frequency, antithrombotic treatment before the event and effect on clinical outcome. J Thromb Haemost. 2005 Jun;3(6):1218-23.
12. Paciaroni M, Agnelli G, Corea F, Ageno W, Alberti A, Lanari A, Caso V, Micheli S, Bertolani L, Venti M, Palmerini F, Biagini S, Comi G, Previdi P, Silvestrelli G. Early hemorrhagic transformation of brain infarction: rate, predictive factors, and influence on clinical outcome: results of a prospective multicenter study. Stroke. 2008 Aug;39(8):2249-56.
13. Marini C, De Santis F, Sacco S, Russo T, Olivieri L, Totaro R, Carolei A. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. Stroke. 2005 Jun;36(6):1115-9.
14. Friberg L, Hammar N, Edvardsson N, Rosenqvist M. The prognosis of patients with atrial fibrillation is improved when sinus rhythm is restored: report from the Stockholm Cohort of Atrial Fibrillation (SCAF). Heart. 2009;95(12):1000-5.
15. Hart RG, Pearce LA, Rothbart RM, McAnulty JH, Asinger RW, Halperin JL. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke Prevention in Atrial Fibrillation Investigators. J Am Coll Cardiol. 2000;35(1):183-7.
16. Nieuwlaat R, Dinh T, Olsson SB, Camm AJ, Capucci A, Tieleman RG, Lip GY, Crijns HJ; Euro Heart Survey Investigators. Should we abandon the common practice of withholding oral anticoagulation in paroxysmal atrial fibrillation? Eur Heart J. 2008;29(7):915-22.
17. Hohnloser SH, Pajitnev D, Pogue J, Healey JS, Pfeffer MA, Yusuf S, Connolly SJ; ACTIVE W Investigators. Incidence of stroke in paroxysmal versus sustained atrial fibrillation in patients taking oral anticoagulation or combined antiplatelet therapy: an ACTIVE W Substudy. J Am Coll Cardiol. 2007;50(22):2156-61.
18. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. Ann Intern Med. 1999;131(7):492-501.
19. Saxena R, Koudstaal PJ. Anticoagulants for preventing stroke in patients with nonrheumatic atrial fibrillation and a history of stroke or transient ischemic attack. Cochrane Database Syst Rev 2003;3:CD000185.
20. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007; 146: 857-867.
21. Hart RG, Halperin JL. Atrial fibrillation and thromboembolism: a decade of progress in stroke prevention. Ann Intern Med. 1999;131(9):688-95.
22. Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, Pfeffer M, Hohnloser S, Yusuf S. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet. 2006;367(9526):1903-12.
23. Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, Chrolavicius S, Yusuf S. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med. 2009; 360(20):2066-78.
24. Paciaroni M, Agnelli G, Ageno W, Caso V, Corea F, Lanari A, Alberti A, Previdi P, Fedele M, Manina G, Vedovati C, Venti M, Billeci AMR, Batta M, Silvestrelli G. Cerebral ischemic and hemorrhagic events in patients with atrial fibrillation on warfarin: a prospective multi-centre study. Abstract presented to the American Academy of Neurology meeting, Toronto 2010.
25. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation. 2006;114(7):e257-354.
26. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001;285(22):2864-70.
27. Gage BF, van Walraven C, Pearce L, Hart RG, Koudstaal PJ, Boode BS, Petersen P. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. Circulation. 2004 Oct 19;110(16):2287-92.
28. Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB, Larson MG, Kannel WB, Benjamin EJ. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. JAMA. 2003; 290(8): 1049-56.
29. van Walraven C, Hart RG, Wells GA, Petersen P, Koudstaal PJ, Gullov AL, Hellemons BS, Koefed BG, Laupacis A. Arch Intern Med. 2003;163(8):936-43.
30. Albers GW, Dalen JE, Laupacis A, Manning WJ, Petersen P, Singer DE. Antithrombotic therapy in atrial fibrillation. Chest. 2001;119(1 Suppl):194S-206S.
31. You JJ, Singer DE, Howard PA, Lane DA, Eckman MH, Fang MC, Hylek EM, Schulman S, Go AS, Hughes M, Spencer FA, Manning WJ, Halperin JL, Lip GY; American College of Chest Physicians. Antithrombotic therapy for atrial fibrillation. Chest. 2012 Feb;141(2 Suppl):e531S-75S.
32. Baruch L, Gage BF, Horrow J, Juul-Möller S, Labovitz A, Persson M, Zabalgoitia M. Can patients at elevated risk of stroke treated with anticoagulants be further risk stratified? Stroke. 2007;38(9):2459-63.
33. Poli D, Antonucci E, Grifoni E, Abbate R, Gensini GF, Prisco D. Stroke risk in atrial fibrillation patients on warfarin. Predictive ability of risk stratification schemes for primary and secondary prevention. Thromb Haemost. 2009;101(2):367-72.
34. Lip GY. Risk factors and stroke risk stratification for atrial fibrillation: limitations and new possibilities. Am Heart J. 2008 Jul;156(1):1-3.
35. Fang MC, Go AS, Chang Y, Borowsky L, Pomernacki NK, Singer DE; ATRIA Study Group. Comparison of risk stratification schemes to predict thromboembolism in people with nonvalvular

atrial fibrillation. J Am Coll Cardiol. 2008;51(8):810-5.
36. Paciaroni M, Agnelli G, Ageno W, Caso V, Corea F, Lanari A, Alberti A, Previdi P, Fedele M, Manina G, Vedovati MC, Venti M, Billeci AMR, Batta M, Galli L, Silvestrelli G. Risk factors for cerebral ischemic events in patients with atrial fibrillation on warfarin for stroke prevention. Atherosclerosis 2010 ; 212: 564-566.
37. Friberg L, Hammar N, Ringh M, Pettersson H, Rosenqvist M. Stroke prophylaxis in atrial fibrillation: who gets it and who does not? Report from the Stockholm Cohort-study on Atrial Fibrillation (SCAF-study). Eur Heart J. 2006;27(16):1954-64.
38. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137(2):263-72.
39. Rietbrock S, Heeley E, Plumb J, van Staa T. Chronic atrial fibrillation: Incidence, prevalence, and prediction of stroke using the Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, and prior Stroke or transient ischemic attack (CHADS2) risk stratification scheme. Am Heart J. 2008 Jul;156(1):57-64.
40. Botto GL, Padeletti L, Santini M, Capucci A, Gulizia M, Zolezzi F, Favale S, Molon G, Ricci R, Biffi M, Russo G, Vimercati M, Corbucci G, Boriani G. Presence and duration of atrial fibrillation detected by continuous monitoring: crucial implications for the risk of thromboembolic events. J Cardiovasc Electrophysiol. 2009;20(3):241-8.
41. Crandall MA, Horne BD, Day JD, Anderson JL, Muhlestein JB, Crandall BG, Weiss JP, Osborne JS, Lappé DL, Bunch TJ. Atrial fibrillation significantly increases total mortality and stroke risk beyond that conveyed by the CHADS2 risk factors. Pacing Clin Electrophysiol. 2009;32(8):981-6.
42. Nieuwlaat R, Capucci A, Camm AJ, Olsson SB, Andresen D, Davies DW, Cobbe S, Breithardt G, Le Heuzey JY, Prins MH, Lévy S, Crijns HJ. Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. Eur Heart J. 2005;26(22):2422-34.
43. Nieuwlaat R, Capucci A, Lip GY, Olsson SB, Prins MH, Nieman FH, López-Sendón J, Vardas PE, Aliot E, Santini M, Crijns HJ; Euro Heart Survey Investigators. Antithrombotic treatment in real-life atrial fibrillation patients: a report from the Euro Heart Survey on Atrial Fibrillation. Eur Heart J. 2006;27(24):3018-26.
44. Nieuwlaat R, Olsson SB, Lip GY, Camm AJ, Breithardt G, Capucci A, Meeder JG, Prins MH, Lévy S, Crijns HJ. Guideline-adherent antithrombotic treatment is associated with improved outcomes compared with undertreatment in high-risk patients with atrial fibrillation. The Euro Heart Survey on Atrial Fibrillation. Am Heart J. 2007;153(6):1006-12.
45. Waldo AL, Becker RC, Tapson VF, Colgan KJ. Hospitalized patients with atrial fibrillation and a high risk of stroke are not being provided with adequate anticoagulation. J Am Coll Cardiol. 2005;46(9):1729-36.
46. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133(6 Suppl):160S-198S.
47. Albers GW, Diener HC, Frison L, Grind M, Nevinson M, Partridge S, Halperin JL, Horrow J, Olsson SB, Petersen P, Vahanian A. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. JAMA. 2005;293(6):690-8.
48. Olsson SB; Executive Steering Committee of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. Lancet. 2003 Nov 22;362(9397):1691-8.
49. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139-51.
50. Patel MR, Mahaffey KW, Garg J, et al. ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvularatrial fibrillation. N EnglJ Med. 2011;365:883–91.
51. Connolly SJ, Eikelboom J, Joyner C, et al. AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. N Engl J Med. 2011;364:806–17.
52. Granger CB, Alexander JH, McMurray JJ, et al. ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–92.