Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)
ISSN 1673-1581 (Print); ISSN 1862-1783 (Online)
www.zju.edu.cn/jzus; www.springerlink.com
E-mail: jzus@zju.edu.cn

Viewpoint:

Clinical considerations of anticoagulation therapy for patients with atrial fibrillation*

Shu ZHANG
(*Arrhythmias Center and Clinical EP Lab., Cardiovascular Institute and Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100037, China*)
E-mail: zsfuwai@vip.163.com
Received June 26, 2012; Revision accepted July 9, 2012
Crosschecked July 17, 2012

doi:10.1631/jzus.B1201007
Document code: A **CLC number:** R541.7+5

Atrial fibrillation (AF) increases the risk of stroke. New anticoagulation agents have recently provided alternative and promising approaches. This paper reviews the current state of anticoagulation therapy in AF patients, focusing on various clinical scenarios and on comparisons, where possible, between western and eastern populations.

Key words: Anticoagulation therapy, Atrial fibrillation, Warfarin, Dabigatran, Riveroxaban, Apixaban

1 Introduction

The fact that atrial fibrillation (AF) increases the risk of stroke has long been known (Wolf *et al.*, 1991). Although effective (Hart *et al.*, 2007), anticoagulation with warfarin has its intrinsic limitations, which hinder its clinical application. Recently, new anticoagulation agents have provided alternative and promising approaches (Connolly *et al.*, 2009; Granger *et al.*, 2011; Patel *et al.*, 2011). However, the debate on how to deal with anticoagulation therapy peri-surgery or during interventional procedures continues. This article reviews the current state of anticoagulation therapy in AF patients, focusing on various clinical scenarios and on comparisons, where possible, between western and eastern populations.

2 Population of AF patients

AF is a very common form of arrhythmia and the incidence is increasing in this ageing world. In the USA, the prevalence of AF is 0.95% in adults aged 20 years or older, and increases from 0.1% among adults younger than 55 years, to 3.8% among people aged 60 years or older, and to 9.0% in people aged 80 years or older. The number of AF patients is projected to reach more than 5.6 million by the year 2050 (Go *et al.*, 2001). Another study estimates that there was an AF incidence of 0.368% and a prevalence of 2.5% in the general population in the USA in 2000, and projects AF patients to reach 12.1 million by the year 2050 in the USA (Miyasaka *et al.*, 2006).

China has a somewhat lower prevalence of AF (Zhang, 2009). A survey of Chinese adults aged ≥35 years showed that the age-adjusted prevalence of AF was 0.74% in men and 0.72% in women. The prevalence among people aged ≥60 years was 1.83% in men and 1.92% in women. Another large epidemiological survey of AF among people aged 30 to 85 years revealed a crude rate of prevalence of AF of 0.77%, falling to 0.61% after being standardized.

3 Necessity of anticoagulation therapy

Beside causing symptoms and affecting cardiac function, AF is a strong independent risk factor for stroke (Wolf *et al.*, 1991). The age-adjusted incidence of stroke showed a near five-fold excess in the presence of non-rheumatic AF. AF is not as benign a form of arrhythmia as once assumed. The poor outcome of

* Project (No. 200902001) supported by the Research on Monitoring, Prevention, Early-Warning, Diagnosis, and Therapy of Cardiovascular Diseases Part II: Community Based Approach for Atrial Fibrillation and Sudden Cardiac Death, China

AF has been proved in studies: AF increases death rates by 31% to 140%, especially in women (Krahn *et al.*, 1995; Benjamin *et al.*, 1998; Stewart *et al.*, 2002; Vidaillet *et al.*, 2002), and has already become a heavy burden on the social economy.

4 Who needs anticoagulation therapy?

AF is a strong risk factor for stroke but not all AF patients have the same risk of stroke. Several grading systems have been put forward to stratify the risk. The well-known $CHADS_2$ scoring system involves assigning 1 point each for the presence of congestive heart failure, hypertension, age of 75 years or older, and diabetes mellitus, and assigning 2 points each for a history of stroke or transient ischemic attack (TIA) (Table 1). Based on this scheme, the stroke rate increases from 1.9% for a score of 0 to 2.8% for 1, 4.0% for 2, 5.9% for 3, 8.5% for 4, 12.5% for 5, and up to 18.2% for 6 (Gage *et al.*, 2001). The focused updated 2011 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/Heart Rhythm Society (HRS) guidelines for the management of patients with AF (Fuster *et al.*, 2011) did not include changes to its risk stratification. Moderate-risk factors include age greater than or equal to 75 years, hypertension, heart failure, left ventricular (LV) ejection fraction 35% or less, and diabetes mellitus. High risk factors include a previous stroke, TIA or embolism, mitral stenosis, and a prosthetic heart valve. Patients with any high risk factor or more than one moderate risk factor should accept anticoagulation therapy, and it might be considered for those with one moderate risk factor.

Table 1 $CHADS_2$ score for risk of stroke in non-valvular AF*

Letter	Risk factor	Score
C	Congestive heart failure	1
H	Hypertension	1
A	Age ≥75 years	1
D	Diabetes mellitus	1
S	Stroke or transient ischemic attack	2

* Low risk ($CHADS_2$ 0 or 1), moderate risk ($CHADS_2$ 2 or 3) and high risk ($CHADS_2$ 4, 5, or 6). Adapted from Gage *et al.* (2001)

A novel risk stratification model, CHA_2DS_2-VASc, has been proposed recently, which challenges the $CHADS_2$ stratification and puts the largest proportion (61.9%) of subjects into the intermediate-risk stratum (Lip *et al.*, 2010). This system has new additional risk factors such as age 65–74 years, presence of vascular disease, female sex, and an increased allotment of 2 points for age 75 years or older (Table 2). Lip *et al.* (2010) claimed that this system provided some improvement in predictive value for thromboembolism over the $CHADS_2$ schema, with low event rates in low-risk subjects and the classification of only a small proportion (15.1%) of subjects into the intermediate-risk category. This claim has already been supported by some other studies (Boriani *et al.*, 2011). CHA_2DS_2-VASc has been adopted by the 2010 European Society of Cardiology (ESC) guidelines for the management of AF (Camm *et al.*, 2010), recommending anticoagulation therapy for a CHA_2DS_2-VASc score ≥2, and consideration of therapy for those whose CHA_2DS_2-VASc score is 1.

Table 2 CHA_2DS_2-VASc score for risk of stroke in non-valvular AF*

Letter	Risk factor	Score
C	Congestive heart failure/LV dysfunction	1
H	Hypertension	1
A	Age ≥75 years	2
D	Diabetes mellitus	1
S	Stroke/TIA/TE	2
V	Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
A	Age 65–74 years	1
Sc	Sex category (i.e., female gender)	1

* A score of 0 indicates low risk; 1 indicates moderate risk; ≥2 indicates high risk. LV: left ventricular; TIA: transient ischemic attack; TE: thromboembolism. Adapted from Lip *et al.* (2010)

The bleeding risk accompanying anticoagulation therapy, especially with warfarin, has been a long time concern. A new bleeding risk score termed HAS-BLED has been proposed recently (Table 3) (Pisters *et al.*, 2010) and has been incorporated into ESC guidelines for management of patients with AF. It states that a score of ≥3 indicates 'high risk', and that some caution and regular review of the patient are needed following the initiation of antithrombotic therapy, whether with warfarin or aspirin (Camm *et al.*, 2010). Self-monitoring of oral anticoagulation has been proposed to address the inconvenience of outpatient visits and has shown some promise (Heneghan *et al.*, 2012).

Table 3 Clinical characteristics of the HAS-BLED bleeding risk score

Letter	Risk factor	Score
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (>65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2

INR: international normalized ratio. 'Hypertension' is defined as systolic blood pressure >160 mmHg. 'Abnormal kidney function' is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥200 mmol/L. 'Abnormal liver function' is defined as chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., (bilirubin >2)×(upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/ alkaline phosphatase>3)×(upper limit of normal)). 'Bleeding' refers to previous bleeding history and/or predisposition to bleeding, e.g., bleeding diathesis and anaemia. 'Labile INRs' refers to unstable/high INRs or poor time in therapeutic range (e.g., <60%). 'Drugs/alcohol use' refers to concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse. Adapted from Pisters *et al.* (2010) and Camm *et al.*, 2010)

5 Which anticoagulation agent to use?

Traditionally, vitamin K antagonists (VKAs) (e.g., warfarin) were the only available therapeutic option for oral anticoagulation. A series of clinical studies have established warfarin's role in anticoagulation therapy for patients with AF. Earlier meta-analysis, including First Atrial Fibrillation Aspirin and Anticoagulation (AFASAK1), European Atrial Fibrillation Trial (EAFT), Prevention of Arterial Thromboembolism in Atrial Fibrillation (PATAF), Second Stroke Prevention in Atrial Fibrillation Study (SPAF2), AFASAK2, and SPAF3, showed that patients receiving warfarin were significantly less likely to experience a stroke (2.4 vs. 4.5 events per 100 patient-years; hazard ratio 0.55). Thus treating 1000 patients with AF for one year with oral anticoagulant rather than aspirin would prevent 23 ischemic strokes while causing 9 additional major bleeds. All-cause survival did not differ but it appeared to improve for warfarin patients three years after therapy was started (van Walraven *et al.*, 2002). A recent meta-analysis pooled 29 randomized trials and included 28044 participants with non-valvular AF (mean age, 71 years; mean follow-up, 1.5 years) (Hart *et al.*, 2007). Compared with the control, adjusted-dose warfarin (6 trials, 2900 participants) and antiplatelet agents (8 trials, 4876 participants) reduced stroke by 64% and 22%, respectively. Adjusted-dose warfarin was substantially more efficacious than antiplatelet therapy (relative risk reduction, 39%; 12 trials, 12963 participants). Absolute increases in major extracranial hemorrhage were small (≤0.3% year).

New oral anticoagulation agents have been shining in clinical trials recently. Dabigatran is a new oral direct thrombin inhibitor. In Connolly *et al.* (2009)'s study including 18113 patients who had AF and a risk of stroke, dabigatran, given at a dose of 110 mg, was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin (1.53% vs. 1.69%), as well as lower rates of major hemorrhage (2.71% vs. 3.36%, P=0.003). Dabigatran administered at a dose of 150 mg, compared with warfarin, was associated with lower rates of stroke and systemic embolism (1.11% vs. 1.69%, P<0.001) but similar rates of major hemorrhage (3.11% vs. 3.36%, P=0.31). The mortality rate was 4.13% per year in the warfarin group, compared with 3.75% per year with 110 mg of dabigatran (P=0.13) and 3.64% per year with 150 mg of dabigatran (P=0.051). Interestingly, the Food and Drug Administration (FDA) approved a higher but not a lower dose of dabigatran (Beasley *et al.*, 2011).

Rivaroxaban, an oral factor Xa inhibitor, was tested in a clinical trial (Patel *et al.*, 2011) consisting of 14264 patients with non-valvular AF who were at increased risk of stroke. The primary end point of stroke or systemic embolism in the rivaroxaban (at a daily dose of 20 mg) group was 2.1% per year, similar to that of the warfarin group of 2.4% (P=0.12) in the intention-to-treat analysis. Major and non-major clinically relevant bleedings were not different in the rivaroxaban group and the warfarin group (14.9% per year vs. 14.5%, P=0.44), although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.

In a study of 18201 patients with AF and at least one additional risk factor for stroke, apixaban (at a dose of 5 mg twice daily) showed a better outcome

with respect to the primary endpoint of ischemic or hemorrhagic stroke or systemic embolism than did a warfarin group (1.27% vs. 1.60%, P=0.01). The rate of major bleeding was lower in the apixaban group than in the warfarin group (2.13% per year vs. 3.09%, P<0.001), and the rates of death from any cause were 3.52% and 3.94%, respectively (P=0.047). The rate of hemorrhagic stroke was also lower in the apixaban group (Granger *et al.*, 2011).

Compared with previous meta-analyses, there has been a significant improvement in the proportion of time spent in therapeutic anticoagulation, with a resultant decline in observed stroke rates (Agarwal *et al.*, 2012).

Most of the clinical trials of new oral anticoagulation agents were carried out in western countries, where they are expected to replace warfarin in the future. A new era of anticoagulation appears to be emerging for patients with AF (Mega, 2011). However, warfarin will continue to be the major anticoagulation agent in developing countries for some time.

6 Specific populations

Elderly patients with AF, constituting almost half of all AF patients, are at increased risk of stroke. Among patients diagnosed with AF, 45% are older than 75 years, and it is estimated that more than half of patients with AF will be older than 80 years by the year 2050 (Wolf *et al.*, 1991). In the Framingham cohort, the proportion of AF-associated strokes increased progressively with age: from 6.7% for ages 50–59 years to 36.2% for ages 80–89 years (Wolf *et al.*, 1987). Anticoagulant therapy with warfarin reduces the risk of stroke in all patients, including the elderly. Unfortunately, bleeding complications caused by warfarin are particularly frequent in elderly patients, and might be the major reason for anticoagulation under-use in such patients. The cumulative incidence of major haemorrhage is 13.1 per 100 patient-years for patients older than 80 years, vs. only 4.7 per 100 patient-years for those below 80 years. Nevertheless, the risk of major bleeding appears only to increase modestly with increasing thromboembolic risk, resulting in a greater absolute net clinical benefit from anticoagulation for older patients (Sinnaeve *et al.*, 2012). In Canada and in the EU, regulatory agencies recommend the use of dabigatran at 150 mg twice a day (BID) for patients below 80 years of age, and at 110 mg BID for patients aged 80 years or more (Sinnaeve *et al.*, 2012).

Although neither European nor American AF guidelines recommend special INR values for elder patients, one exploratory study showed a low rate of stroke and major bleeding in elderly patients (>75 years) being managed in an anticoagulation clinic for primary stroke prevention with low-intensity anticoagulation (INR 1.5–2.0, median achieved value 1.86) (Pengo *et al.*, 2010). The 2010 Japanese AF guidelines recommend to 'control patients with nonvalvular AF ≥70 years of age who are indicated for warfarin therapy with a target INR of 1.6 to 2.6' (JCS Joint Working Group, 2010). It is not clear whether a lower INR would be more appropriate for Asian patients. Warfarin therapy was associated with a comparable risk of intracerebral haemorrhaging in non-Caucasians, especially Asians (Shen *et al.*, 2007). A study carried out in Chinese patients with nonvavular AF found no difference between the low-intensity anticoagulation treatment (INR 1.6–2.0) and the standard intensity anticoagulation treatment (INR 2.0–2.5) (Zhang, 2009).

Novel oral anticoagulant agents that are easier to use and which might offer similar or better levels of stroke prevention with a similar or reduced risk of bleeding should promote increased use of antithrombotic therapy in the management of elderly AF patients.

7 Specific situations

Whether to and how to interrupt oral anticoagulation therapy during peri-operation and peri-interventional procedures have been the subjects of an ongoing debate. Relevant recommendations from the 2012 American College of Chest Physicians (ACCP) guidelines for perioperative management of antithrombotic therapy (Douketis *et al.*, 2012) include: 'In patients with a mechanical heart valve, AF, or venous thromboembolism (VTE) at high risk for thromboembolism, we suggest bridging anticoagulation instead of no bridging during interruption of VKA therapy; in patients with a mechanical heart valve, AF, or VTE at low risk for thromboembolism, we suggest

no bridging instead of bridging anticoagulation during interruption of VKA therapy; in patients with a mechanical heart valve, AF, or VTE at moderate risk for thromboembolism, the bridging or no-bridging approach chosen is, as in the higher- and lower-risk patients, based on an assessment of individual patient- and surgery-related factors'. The risk stratum is: high, a $CHADS_2$ score of 5 or 6, a recent (within three months) stroke or TIA, and rheumatic valvular heart disease; moderate, a $CHADS_2$ score of 3 or 4; and low, a $CHADS_2$ score of 0 to 2 (assuming no prior stroke or TIA).

For pacemaker implantation, oral anticoagulation can be safely interrupted before implantation under overlapping therapy with low molecular weight heparin. Reducing heparin doses in patients with low thromboembolic risk and renal insufficiency led to a low incidence of major bleeding without increasing thromboembolic events (Hammerstingl and Omran, 2011). Other studies have suggested that patients with moderate to high thromboembolism risk should undergo device implantation without stopping oral anticoagulation (Cano *et al.*, 2012). The perioperative anticoagulation for pacemaker implantation is yet to be established. Temporarily interrupting anticoagulation is associated with increased thromboembolic events, whereas cessation of warfarin with bridging anticoagulation is associated with a higher rate of pocket hematoma and a longer hospital stay. Continuing warfarin with a therapeutic INR appears to be a safe and cost-effective approach when implanting a pacemaker or defibrillator in patients with moderate to high thromboembolic risk (Ahmed *et al.*, 2010). Recent trials suggest that warfarin can be continued when patients are undergoing cardiac device procedures (Brinker, 2012).

Trans-septal puncture and AF ablation can be performed safely in patients with ongoing oral anticoagulation therapy (Hakalahti *et al.*, 2011). The 2012 HRS/European Heart Rhythm Association (EHRA)/European Cardiac Arrhythmia Society (ECAS) Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation states that 'Performance of catheter ablation of AF on a patient who is therapeutically anticoagulated with warfarin should be considered.' and 'Discontinuation of systemic anticoagulation therapy post ablation is not recommended in patients who are at high risk of stroke as estimated by currently recommended schemes ($CHADS_2$ or CHA_2DS_2-VASc)' (Calkins *et al.*, 2012). There is highly consistent evidence from observational studies that a continued warfarin strategy during radio frequency catheter ablation of AF reduces the risk of thromboembolic complications without increasing the risk of bleeding (Santangeli *et al.*, 2012; Verma and Tsang, 2012), which appears at present to be a problem. It is assumed that patients taking dabigatran are unlikely to require bridge therapy because of a predictable anticoagulant effect and a rapid onset of action. However, there is evidence that in patients undergoing AF ablation, periprocedural dabigatran use significantly increases the risk of bleeding or thromboembolic complications compared with uninterrupted warfarin therapy (Quintela *et al.*, 2012).

Cost effective analyses of anticoagulation therapy for AF and alternative approaches for the prevention of strokes in AF patients, such as left atrial appendage occlusion, are also interesting current topics, but they are beyond the scope of this review.

References

Agarwal, S., Hachamovitch, R., Menon, V., 2012. Current trial-associated outcomes with warfarin in prevention of stroke in patients with nonvalvular atrial fibrillation: a meta-analysis. *Arch. Intern. Med.*, **172**(8):623-631. [doi:10.1001/archinternmed.2012.121]

Ahmed, I., Gertner, E., Nelson, W.B., House, C.M., Dahiya, R., Anderson, C.P., Benditt, D.G., Zhu, D.W., 2010. Continuing warfarin therapy is superior to interrupting warfarin with or without bridging anticoagulation therapy in patients undergoing pacemaker and defibrillator implantation. *Heart Rhythm*, **7**(6):745-749. [doi:10.1016/j.hrthm.2010.02.018]

Beasley, B.N., Unger, E.F., Temple, R., 2011. Anticoagulant options—why the FDA approved a higher but not a lower dose of dabigatran. *N. Engl. J. Med.*, **364**(19):1788-1790. [doi:10.1056/NEJMp1103050]

Benjamin, E.J., Wolf, P.A., D′Agostino, R.B., Silbershatz, H., Kannel, W.B., Levy, D., 1998. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*, **98**(10):946-952. [doi:10.1161/01.CIR.98.10.946]

Boriani, G., Botto, G.L., Padeletti, L., Santini, M., Capucci, A., Gulizia, M., Ricci, R., Biffi, M., de Santo, T., Corbucci, G., *et al.*, 2011. Improving stroke risk stratification using the $CHADS_2$ and CHA_2DS_2-VASc risk scores in patients with paroxysmal atrial fibrillation by continuous arrhythmia burden monitoring. *Stroke*, **42**(6):1768-1770. [doi:10.1161/STROKEAHA.110.609297]

Brinker, J., 2012. Device surgery in the anticoagulated patient: the Goldilocks principle. *Heart Rhythm*, **9**(3):368-369. [doi:10.1016/j.hrthm.2011.11.018]

Calkins, H., Kuck, K.H., Cappato, R., Brugada, J., Camm, A.J., Chen, S.A., Crijns, H.J., Damiano, R.J.Jr., Davies, D.W., DiMarco, J., *et al.*, 2012. 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation. Developed in partnership with the European Heart Rhythm Association (EHRA), a registered branch of the European Society of Cardiology (ESC) and the European Cardiac Arrhythmia Society (ECAS); and in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), the Asia Pacific Heart Rhythm Society (APHRS), and the Society of Thoracic Surgeons (STS). Endorsed by the governing bodies of the American College of Cardiology Foundation, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, the Asia Pacific Heart Rhythm Society, and the Heart Rhythm Society. *Heart Rhythm.*, **9**(4):632-696.e21. [doi:10.1016/j.hrthm.2011.12.016]

Camm, A.J., Kirchhof, P., Lip, G.Y., Schotten, U., Savelieva, I., Ernst, S., van Gelder, I.C., Al-Attar, N., Hindricks, G., Prendergast, B., *et al.*, 2010. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur. Heart J.*, **31**(19): 2369-2429. [doi:10.1093/eurheartj/ehq278]

Cano, O., Munoz, B., Tejada, D., Osca, J., Sancho-Tello, M.J., Olague, J., Castro, J.E., Salvador, A., 2012. Evaluation of a new standardized protocol for the perioperative management of chronically anticoagulated patients receiving implantable cardiac arrhythmia devices. *Heart Rhythm*, **9**(3):361-367. [doi:10.1016/j.hrthm.2011.10.010]

Connolly, S.J., Ezekowitz, M.D., Yusuf, S., Eikelboom, J., Oldgren, J., Parekh, A., Pogue, J., Reilly, P.A., Themeles, E., Varrone, J., *et al.*, 2009. Dabigatran versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.*, **361**(12): 1139-1151. [doi:10.1056/NEJMoa0905561]

Douketis, J.D., Spyropoulos, A.C., Spencer, F.A., Mayr, M., Jaffer, A.K., Eckman, M.H., Dunn, A.S., Kunz, R., 2012. Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*, **141**(2 Suppl.): e326S-e350S. [doi:10.1378/chest.11-2298]

Fuster, V., Ryden, L.E., Cannom, D.S., Crijns, H.J., Curtis, A.B., Ellenbogen, K.A., Halperin, J.L., Kay, G.N., le Huezey, J.Y., Lowe, J.E., *et al.*, 2011. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *J. Am. Coll. Cardiol.*, **57**(11):e101-e198. [doi:10.1016/j.jacc.2010.09.013]

Gage, B.F., Waterman, A.D., Shannon, W., Boechler, M., Rich, M.W., Radford, M.J., 2001. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*, **285**(22):2864-2870. [doi:10.1001/jama.285.22.2864]

Go, A.S., Hylek, E.M., Phillips, K.A., Chang, Y., Henault, L.E., Selby, J.V., Singer, D.E., 2001. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*, **285**(18): 2370-2375. [doi:10.1001/jama.285.18.2370]

Granger, C.B., Alexander, J.H., McMurray, J.J., Lopes, R.D., Hylek, E.M., Hanna, M., Al-Khalidi, H.R., Ansell, J., Atar, D., Avezum, A., *et al.*, 2011. Apixaban versus warfarin in patients with atrial fibrillation. *N. Engl. J. Med.*, **365**(11):981-992. [doi:10.1056/NEJMoa1107039]

Hakalahti, A., Uusimaa, P., Ylitalo, K., Raatikainen, M.J., 2011. Catheter ablation of atrial fibrillation in patients with therapeutic oral anticoagulation treatment. *Europace*, **13**(5):640-645. [doi:10.1093/europace/eur038]

Hammerstingl, C., Omran, H., 2011. Perioperative bridging of chronic oral anticoagulation in patients undergoing pacemaker implantation—a study in 200 patients. *Europace*, **13**(9):1304-1310. [doi:10.1093/europace/eur107]

Hart, R.G., Pearce, L.A., Aguilar, M.I., 2007. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann. Intern. Med.*, **146**(12):857-867.

Heneghan, C., Ward, A., Perera, R., Bankhead, C., Fuller, A., Stevens, R., Bradford, K., Tyndel, S., Alonso-Coello, P., Ansell, J., *et al.*, 2012. Self-monitoring of oral anticoagulation: systematic review and meta-analysis of individual patient data. *Lancet*, **379**(9813):322-334. [doi:10.1016/S0140-6736(11)61294-4]

JCS Joint Working Group, 2010. Guidelines for pharmacotherapy of atrial fibrillation (JCS 2008): digest version. *Circ. J.*, **74**(11):2479-2500. [doi:10.1253/circj.CJ-88-0001]

Krahn, A.D., Manfreda, J., Tate, R.B., Mathewson, F.A., Cuddy, T.E., 1995. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the manitoba follow-up study. *Am. J. Med.*, **98**(5):476-484. [doi:10.1016/S0002-9343(99)80348-9]

Lip, G.Y., Nieuwlaat, R., Pisters, R., Lane, D.A., Crijns, H.J., 2010. 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*, **137**(2):263-272. [doi:10.1378/chest.09-1584]

Mega, J.L., 2011. A new era for anticoagulation in atrial fibrillation. *N. Engl. J. Med.*, **365**(11):1052-1054. [doi:10.1056/NEJMe1109748]

Miyasaka, Y., Barnes, M.E., Gersh, B.J., Cha, S.S., Bailey, K.R., Abhayaratna, W.P., Seward, J.B., Tsang, T.S., 2006. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*, **114**(2):119-125. [doi:10.1161/CIRCULATIONAHA.105.595140]

Patel, M.R., Mahaffey, K.W., Garg, J., Pan, G., Singer, D.E., Hacke, W., Breithardt, G., Halperin, J.L., Hankey, G.J., Piccini, J.P., *et al.*, 2011. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N. Engl. J. Med.*, **365**(10):883-891. [doi:10.1056/NEJMoa1009638]

Pengo, V., Cucchini, U., Denas, G., Davidson, B.L., Marzot, F., Jose, S.P., Iliceto, S., 2010. Lower versus standard intensity oral anticoagulant therapy (OAT) in elderly warfarin-experienced patients with non-valvular atrial fibrillation. *Thromb. Haemost.*, **103**(2):442-449. [doi:10.1160/TH09-05-0311]

Pisters, R., Lane, D.A., Nieuwlaat, R., de Vos, C.B., Crijns, H.J., Lip, G.Y., 2010. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*, **138**(5):1093-1100. [doi:10.1378/chest.10-0134]

Quintela, S., Villaran, M.C., de Armentia, I.L., Elejalde, E., 2012. Ochratoxin A removal from red wine by several oenological fining agents: bentonite, egg albumin, allergen-free adsorbents, chitin and chitosan. *Food Addit. Contam.: Part A: Chem. Anal. Control Expo. Risk Assess.*, **29**(7):1168-1174. [doi:10.1080/19440049.2012.682166]

Santangeli, P., di Biase, L., Horton, R., Burkhardt, J.D., Sanchez, J., Al-Ahmad, A., Hongo, R., Beheiry, S., Bai, R., Mohanty, P., *et al.*, 2012. Ablation of atrial fibrillation under therapeutic warfarin reduces periprocedural complications: evidence from a meta-analysis. *Circ. Arrhythm. Electrophysiol.*, **5**(2):302-311. [doi:10.1161/CIRCEP.111.964916]

Shen, A.Y., Yao, J.F., Brar, S.S., Jorgensen, M.B., Chen, W., 2007. Racial/ethnic differences in the risk of intracranial hemorrhage among patients with atrial fibrillation. *J. Am. Coll. Cardiol.*, **50**(4):309-315. [doi:10.1016/j.jacc.2007.01.098]

Sinnaeve, P.R., Brueckmann, M., Clemens, A., Oldgren, J., Eikelboom, J., Healey, J.S., 2012. Stroke prevention in elderly patients with atrial fibrillation: challenges for anticoagulation. *J. Intern. Med.*, **271**(1):15-24. [doi:10.1111/j.1365-2796.2011.02464.x]

Stewart, S., Hart, C.L., Hole, D.J., McMurray, J.J., 2002. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am. J. Med.*, **113**(5):359-364. [doi:10.1016/S0002-9343(02)01236-6]

van Walraven, C., Hart, R.G., Singer, D.E., Laupacis, A., Connolly, S., Petersen, P., Koudstaal, P.J., Chang, Y., Hellemons, B., 2002. Oral anticoagulants vs. aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. *JAMA*, **288**(19):2441-2448. [doi:10.1001/jama.288.19.2441]

Verma, A., Tsang, B., 2012. The use of anticoagulation during the periprocedure period of atrial fibrillation ablation. *Curr. Opin. Cardiol.*, **27**(1):55-61. [doi:10.1097/HCO.0b013e32834dc34d]

Vidaillet, H., Granada, J.F., Chyou, P.H., Maassen, K., Ortiz, M., Pulido, J.N., Sharma, P., Smith, P.N., Hayes, J., 2002. A population-based study of mortality among patients with atrial fibrillation or flutter. *Am. J. Med.*, **113**(5):365-370. [doi:10.1016/S0002-9343(02)01253-6]

Wolf, P.A., Abbott, R.D., Kannel, W.B., 1987. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. *Arch. Intern. Med.*, **147**(9):1561-1564. [doi:10.1001/archinte.1987.00370090041008]

Wolf, P.A., Abbott, R.D., Kannel, W.B., 1991. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*, **22**(8):983-988. [doi:10.1161/01.STR.22.8.983]

Zhang, S., 2009. Atrial fibrillation in mainland China: epidemiology and current management. *Heart*, **95**(13):1052-1055. [doi:10.1136/hrt.2008.146589]