

Tak-Yeung Chan
Ka-Ying Miu

Department of Medicine and Geriatrics,
Kwong Wah Hospital, Kowloon, Hong
Kong, P.R.O.C.

Key Words

anticoagulants;
Chinese;
hemorrhage

Hemorrhagic Complications of Anticoagulant Therapy in Chinese Patients

Background. Oral anticoagulants have an expanding role in cardiovascular and thrombotic disorders. Few data are available describing their safety among Chinese patients. We aim to evaluate the incidence of major and minor bleeding complications among Chinese patients receiving long term anti coagulants in community practice.

Methods. A retrospective cohort study was undertaken in a regional hospital. All patients who were initiated on warfarin from January 1, 1998 to December 31, 1998 were enrolled. Out-patient medical charts were reviewed for demographic data, clinical characteristics and adequacy of anticoagulation. Major and minor bleeding complications were documented.

Results. A total of 131 patients were identified. The mean age was 67.8 (SD 11.9) years and 52.6% were women. The mean duration of follow-up was 2.2 years (SD 1.1). Major indications for warfarin were: non-valvular atrial fibrillation (60%), venous thrombosis (17%) and rheumatic heart disease (16%). The subjects spent 50% of their total time within target international normalized ratio range. The average annual rates for major and minor bleeding events were 1.8% (95% confidence interval 0.6 to 4.1%) and 18.5% (95% confidence interval 13.9 to 24.2%), respectively. The cumulative incidences of first major and minor bleeding events at 1, 2 and 3 years were 3%, 4%, 5% and 15%, 24% and 37%, respectively. Intensity of anticoagulation was the only predictive factor identified to be associated with bleeding complications.

Conclusions. Among Chinese patients receiving long-term warfarin, major hemorrhage occurred at an acceptable range in clinical practice, while considerable minor bleeding was observed. Utilization of oral anticoagulants in Chinese patients appears safe and should be advocated in situations with appropriate indications.

The benefit of anticoagulation in primary and secondary prevention in patients with non-valvular atrial fibrillation has been well established.¹⁻⁵ Several observational studies have also shown that the efficacy of anticoagulation demonstrated in clinical trials could be translated into actual clinical practice without exposing patients to excessive risks of bleeding.⁶ However most of the clinical trials on warfarin effectiveness were conducted among Caucasians. One of the major drawbacks about anticoagulation is the risk of bleeding, notably major bleeding like intracerebral hemorrhage. Chinese population had been shown to have higher incidence of hemorrhagic stroke versus their Western counterparts, although the pathogenesis remained indefinite.⁷ It is also well recognized that the

benefit of anticoagulation can easily be offset by a modest increase in major hemorrhage. It thus remains uncertain whether the efficacy of warfarin derived from Western data could be extrapolated in a population with a high background risk of bleeding. The purpose of this study was to determine the incidence of major and minor bleeding complications among Chinese patients receiving long-term oral anticoagulant in community practice.

METHODS

A retrospective study was undertaken in the Department of Medicine and Geriatrics, Kwong Wah Hospital,

Received: May 19, 2003.

Accepted: November 19, 2003.

Correspondence to: Tak-Yeung Chan, MD, Department of Medicine and Geriatrics, Kwong Wah Hospital, 25, Waterloo Road, Kowloon, Hong Kong, SAR, P.R.O.C.
Fax: +852-2871-5166; E-mail: mty_chan@yahoo.com

which is a community hospital in Hong Kong. Chart review was undertaken among outpatients receiving long-term oral anti coagulants in the Warfarin Clinic. All newly referred patients who were initiated on warfarin from January 1, 1998 to December 31, 1998 were enrolled. Eligible patients were identified from the database in the Medical Record Office. Patients who were already taking anti-coagulants prior to their first visits were excluded. The observation period ended on June 30, 2001 or sooner if the treatment was terminated. Warfarin was normally initiated in hospital. Patients also received dietary advice from dietitians during their stay in hospital. Regular blood-taking and follow-up was carried out every 4 to 12 weeks, with a median of 8 weeks.

Adequacy of anticoagulation is measured by international normalized ratio (INR). All blood samples were processed in the Haematology Laboratory in the Department of Pathology of our hospital. The reagent used for determination of prothrombin time ratio was *Thromborel*[®] S supplied by Dade Behring Inc., (Newark, DE.) The corresponding INR was then calculated according to the international sensitivity index (ISI) provided by individual reagent package insert. Several batches of similar reagent were used between 1998 and 2002. The ISI were 1.01, 1.10, 1.01 and 1.05 for years 1998-9, 2000, 2001 and 2002, respectively. The measurement of patients' prothrombin time was continued for 60 seconds before stopping to achieve a corresponding INR of 4.5, and the finding was reported as ≥ 4.5 .

All eligible new cases during the above period were reviewed. Medical charts were assessed for baseline demographics and comorbidity, primary indication, dosage and duration of warfarin therapy, number of medications being taken initially, echocardiogram findings, bleeding complications and thromboembolic events. The indications were divided into 5 categories: non-valvular atrial fibrillation, venous thrombosis (deep vein thrombosis and pulmonary embolism), rheumatic heart disease, prosthetic heart valves, and others. Distinction between primary and secondary prevention was also recorded.

The INR of each outpatient visit after hospital discharge or initial stabilization (4 weeks post treatment) was documented. The first measurement of INR in each hospital admission was also included in the computation. Adequacy of anticoagulation of each patient was ex-

pressed in terms of the proportion of INR that remained within the target INR range. The target INR range is defined in accordance to the recommendations by the American College of Chest Physicians Consensus Conference.⁸ In general, the target INR range is 2 to 3 for most indications except those with prosthetic heart valve, which is 2.5 to 3.5. The time interval between successive INR measurements of individual subject was not adjusted. The approximate "total time" spent by the whole group within the target INR range was calculated by summing the product of "target INR percentage" of each subject and treatment duration and dividing by the total amount of treatment time. The time spent above or below target INR range was also calculated using similar methods. It was a routine practice of our laboratory to report any INR > 4.5 as > 4.5 only irrespective of their absolute value. Thus, the mean INR may not be comparable to other reports.

The bleeding complications were classified as major or minor.⁹ Major hemorrhage was defined as fatal hemorrhage, intracranial hemorrhage of any severity (with computer tomography scan or post-mortem documentation), bleeding that required at least 2 units of blood transfusion, an emergency procedure, or both to terminate bleeding or remove a hematoma or that led to admission to intensive care unit.⁴ All other hemorrhages were classified as minor. Thromboembolic complications like ischemic stroke or deep vein thrombosis were deemed present only if they were validated by imaging studies. For those patients with fatal or major bleeding or who died, their inpatient medical charts were also retrieved and reviewed systemically.

For patients who defaulted in follow-up or were transferred to another hospital, their outcomes were traced from hospital admission records through the inter-hospital computer network. Those patients with incomplete data before the end of observation period were excluded.

Statistics

Descriptive statistics were used to summarize the demographic data. Non-parametric tests and t-test were used to compare proportions and means where appropriate. The average annual rate of bleeding events was estimated using Poisson distribution. The cumulative inci-

dence of first bleeding event was described according to Kaplan-Meier method. Cox proportional hazards regression model was used to analyze the factors influencing the occurrence of bleeding. Unless otherwise specified, all data were expressed as mean (SD). All data analysis was performed using Statistical Package for Social Sciences (Windows Version 9.0).

RESULTS

A total of 149 patients whose warfarin treatment was commenced in 1998 were identified. Complete data were available in 131 patients. Eighteen patients were excluded because of the following reasons: default in follow-up (10), transfer to another hospital (5), non-Chinese ethnicity (1) and prior treatment with warfarin (2). The

mean age was 67.8 (range 26-89) (SD 11.9) years. There were 69 women (52.7%).

The indications for anticoagulation are shown in Table 1. Excluding those with venous thrombosis, 81% of patients took warfarin for primary prevention of thromboembolism, while 19% took it for secondary prevention. Atrial fibrillation was present in 82% of patients, hypertension in 33%, prior stroke or transient ischemic event in 18%, heart failure in 18% and diabetes mellitus in 19%. Besides warfarin, the average number of drugs being taken at the beginning was 2.5 (SD 1.9). Echocardiogram was performed in 94% of the patients in whom risks of cardioembolism was present.

The mean follow-up period was 26.2 months (range 1.4 to 42.5 months; SD 13.5). With 131 patients enrolled, a total of 286.2 patient-years were thus available for analysis. Seventy-nine patients (60%) were still taking warfarin by the end of observation period. Twenty-four patients (18%) completed their treatment course, while 28 patients (22%) terminated their treatment for other reasons (details shown in Table 2). The mean daily dose of warfarin prescribed was 2.5 mg (SD 0.9). The mean and median INR of all subjects were 2.1 (SD 0.3) and 2.1, respectively. The INR for the patients in the study group was in the target range for an average of 50% of the time (range 0-99%), below for 41% of the time and above for 9% of the time. This estimation has been adjusted for different target INR ranges in different indications. There was no significant difference in the time spent within therapeutic range for different indications.

Major bleeding occurred in 5 patients (3 men and 2 women) during the study period. The mean age was 72.8 (66-78), and bleeding occurred from 265 to 906 days after initiation of treatment. One patient died from intracerebral hemorrhage and another died from massive hemoptysis. The relevant clinical notes in these bleeding episodes are summarized in Table 3. The average annual rate of major bleeding events was 1.8% (95% confidence interval 0.6 to 4.1%). The cumulative incidences of first major bleeding event at 1, 2 and 3 years were 3%, 4% and 5%, respectively (Fig. 1).

A total of 53 episodes of minor bleeding were identified among 36 patients over a mean duration of 26.2 months. The most common sites were gum bleeding (14), superficial bruises (10), hemoptysis (10) and epistaxis (8).

Table 1. Indications for anticoagulation in 131 patients

	Patients (%)
Non-rheumatic atrial fibrillation	78 (60.0)
Venous thrombosis	
Deep vein thrombosis(DVT)	18 (13.7)
Pulmonary embolism	3 (2.3)
DVT and pulmonary embolism	1 (0.8)
Rheumatic heart disease	21 (16.0)
Prosthetic valves replacement	4 (3.1)
Dilated cardiomyopathy	4 (3.1)
Others	
Nephrotic syndrome	1 (0.8)
Apical aneurysm	1 (0.8)

Table 2. Reasons for termination of warfarin therapy in 52 patients

	Patients	Percentage
Treatment completed	24	46.2
Deep vein thrombosis	17	
Pulmonary embolism	3	
Self-limiting AF	2	
Nephrotic syndrome	1	
Dilated cardiomyopathy	1	
Deterioration of medical conditions	9	17.3
Died	7	13.5
Bleeding	5	9.6
Non-compliance	3	5.8
Patients' request	2	3.8
Uncertain	2	3.8

Table 3. Clinical information of 5 major bleeding events

Patient	Indication	Site of bleeding	Drop of Hb	INR during bleeding	Intervention	Outcome
F/74	NVAF	GIB	4g/dL in 4 weeks	> 4.5	Transfusion 2U PC, 6U FFP	Alive
M/64	NVAF	GIB, gastric ulcer	3g/dL in 1 week	1.3	Transfusion 2U of PC	Alive
F/77	NVAF	ICH	Not significant	4.3	FFP	Died
M/70	NVAF	Hemoptysis	4g/dL in 4 weeks	4.5	FFP	Died
M/78	NVAF	Groin hematoma	6 g/dL in 1 week	4.5	Transfusion 2U PC FFP	Alive

NVAF = non-valvular atrial fibrillation, GIB = gastrointestinal bleeding, ICH = intracerebral hemorrhage, Hb = hemoglobin FFP = fresh frozen plasma, PC = packed cells.

Table 4. Univariate results of variables tested as predictors of major and minor bleeding in 131 patients

	Hazard ratio	95% confidence interval	<i>p</i> value
Age	0.99	0.96 to 1.02	0.463
Treated hypertension	0.86	0.40 to 1.87	0.707
Female sex	1.16	0.62 to 2.16	0.639
Prior stroke	0.82	0.36 to 1.85	0.626
Intensity of INR*	1.04	1.02 to 1.07	0.0009
Number of concomitant illnesses	1.02	0.76 to 1.37	0.888
Number of drugs	1.14	0.98 to 1.34	0.092
Use of aspirin	1.38	0.61 to 3.13	0.439

* Percentage of time with INR > 3.0.

Other patients were complicated by rectal bleeding (5), gross hematuria (3), upper gastrointestinal bleeding (1), traumatic hemarthrosis (1) and menorrhagia (1). Further investigations were performed in 7 patients and local pathologies including cystitis, hemorrhoids and uterine fibroid were identified in 3 of them. Minor bleeding led to warfarin termination in four patients. The mean and median INR when bleeding occurred were 3.0 (SD 1.0) and 2.9, respectively. The average annual rate of minor bleed-

ing events was 18.5% (95% confidence interval 13.9% to 24.2%). The cumulative incidences of first ever minor bleeding at 1, 2 and 3 years were 15%, 24% and 37%, respectively (Fig. 2).

Using Cox proportional hazard regression analysis, we did not find any association between age, gender, hypertension, prior stroke, number of concomitant medical illnesses, number of medications taken and use of aspirin with the first major or minor bleeding event (Table 4).

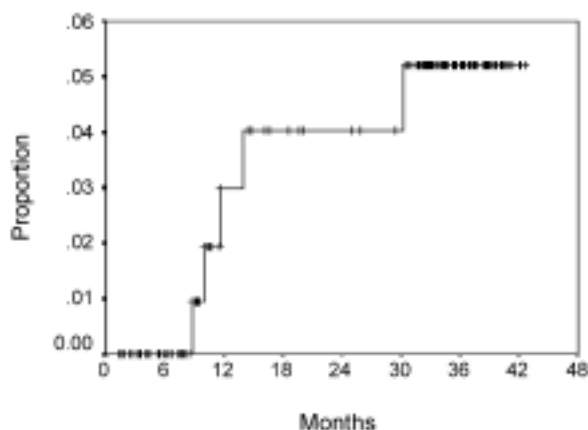


Fig. 1. Kaplan-Meier estimated cumulative incidence of first major hemorrhage in 131 patients during warfarin therapy.

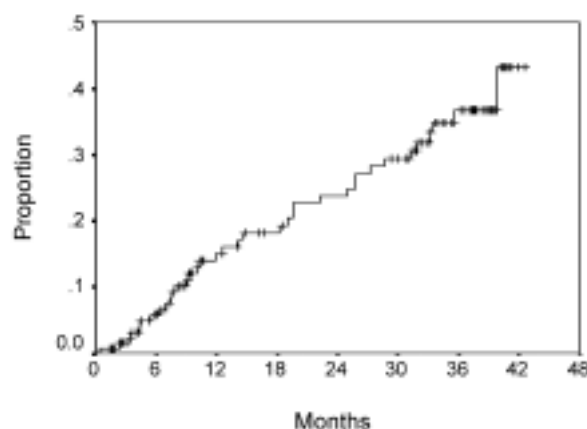


Fig. 2. Kaplan-Meier estimated cumulative incidence of first minor hemorrhage in 131 patients during warfarin therapy.

Table 5. Clinical factors related to major and minor bleeding in 131 patients

	No bleeding (N = 91)	Bleeding (N = 40)	p value	95% confidence interval
Mean age	67.9	67.4	0.834	-4.99 to 4.04
Number of concomitant illnesses	1.02	1.13	0.593	0.28 to -0.48
Mean INR	2.04	2.21	0.002	0.06 to 0.28
Mean treatment duration (years)	2.07	2.50	0.020	0.07 to 0.81
Treatment time with INR > 3	5.8%	12%	0.001	2.67 to 9.74
Use of aspirin (n = 17)	59%	41%	0.233	
Prior stroke (n = 68)	69%	31%	0.562	

The only predictive factor was the intensity of anticoagulation. We used the percentage of time above target INR range (INR > 3) as the explanatory variable. The hazard ratio was 1.04 (95% confidence interval 1.02 to 1.07). When 2 groups of patients with and without bleeding were compared, we also found that intensity of anticoagulation as measured by treatment time with INR > 3 and mean INR was significantly related to bleeding (Table 5).

Two definite and 1 doubtful case of ischemic stroke occurred in 3 patients who were taking warfarin during the study period. The corresponding INRs were 1.5, 1.9 and 2.0, respectively. A total of 7 patients died during the study period. Two deaths were directly related to anticoagulation treatment as described. Apart from these, all INRs were within therapeutic range and no drop of hemoglobin was documented.

DISCUSSION

To our knowledge, the present study represents the first systemic analysis of various types of bleeding complications among Chinese patients receiving long-term oral anticoagulants. We decided to include only warfarin-naïve patients because it had been shown that bleeding rates varied with treatment time,¹⁰ and interpretation of findings would be difficult if incidental cases were recruited instead of an inception cohort.

In this study, we found that the average annual rates of fatal, major, and major or minor bleeding were 0.7% (95% confidence interval 0.08 to 2.5%), 1.8% (95% confidence interval 0.57% to 4.1%) and 20.3% (95% confidence interval 14.5 to 25.0%), respectively. A systemic review of 25 inception cohorts by Landefeld in

1993 showed that the corresponding bleeding rates for all indications of oral anticoagulants were 0.6% (95% confidence interval 0.4 to 0.7%), 3.0% (95% confidence interval 2.6 to 3.4%) and 9.6% (95% confidence interval 8.8 to 10.3%), respectively.¹¹ The rate of major bleeding events was similar in our group, while that of minor events was higher. It was suggested that most of the studies included in the review by Landefeld originated from experimental trials. Monitoring of patients in clinical trials is usually more intensive than in usual practice. Moreover, characteristics of patients recruited in clinical trials might differ from the patients treated in actual practice. However, in an observational study on patients receiving oral anticoagulants for atrial fibrillation by Kalra *et al.*, the reported annual rates of major and minor events were 1.4% (95 confidence interval 0.2 to 4.6) and 5.4% (95% confidence interval 2.4 to 10.2), respectively.¹² Their study adopted an INR range identical with ours. Although their patients were older and had more ischemic heart disease and hypertension than our cohort, the rate of minor bleeding was lower than our subjects. We believe that the major reason is related to the intensity of monitoring. Subjects in Kalra's study spent an average of 61% of their time within therapeutic range (*vs.* 50% in our study) and underwent monitoring of INR every 28 days or less for 67% of the time. INR checking was less frequent in our group, with a median interval of eight weeks.

Various patient and treatment-related risks factors have been proposed to be associated with bleeding complications in patients taking oral anticoagulants.¹¹ The former include age, history of ischemic cerebrovascular events, treated hypertension and use of aspirin, while the latter include intensity of anticoagulation and duration of therapy. In our study, none of the patients'

related factors were found to be predictive of bleeding complications. Besides duration of therapy, intensity of anticoagulation (proportional of time with INR > 3) was the only risk factor identified to be associated with bleeding complications. Gitter *et al.* also failed to demonstrate any of these patient-related risk factors to be significantly associated with major bleeding events, except for a history of malignant condition.¹³ We believe that the putative risk factors demonstrated previously originated from trials where the intensity of anticoagulation was higher than conventional recommendations. Fihn *et al.* also showed that during the first 3 months of initiation of anticoagulant, more serious bleeding events were observed as compared to later time.¹⁰ We thus think that the cumulative incidence of adverse events is a better indicator of bleeding risks. The cumulative incidences of major complications of our patients at 1, 2 and 3 years were 3%, 4% and 5%, respectively, suggesting the risk of bleeding during first year was 3 times that of subsequent years. It is highly desirable to ensure close monitoring of anticoagulation during the early period of therapy.

The incidence of intracerebral hemorrhage in local Chinese was higher than those in European and United States studies.⁷ It thus remains uncertain whether warfarin would intensify the risk of intracerebral hemorrhage in Oriental patients to a greater extent. In our study, only 1 patient developed intracerebral hemorrhage, which was also a fatal event. The corresponding INR when bleeding occurred was 4.2, so it was likely that warfarin overdose was a strong precipitating factor. Another local study by Cheung *et al.* showed that the annual rate of intracerebral hemorrhage was as high as 3.2%.¹⁴ There was no difference in patients' age between their study and ours. However, all patients in Cheung's study had history of cerebrovascular disease, while most of our subjects belonged to the low risk groups, like primary prevention in non-valvular atrial fibrillation and venous thrombosis. Although history of ischemic stroke was not shown to be a risk factor for major bleeding in our study, we urge taking precaution when anticoagulation is initiated in Chinese patients with prior cerebrovascular disease.

For measurement of bleeding complications to be reliable, adequacy of anticoagulation should be ensured

and that is best reflected by the time spent within therapeutic INR range. Our patients spent 50% of their time within the recommended target INR range. Our practice appeared suboptimal when compared to western studies, which reported that their patients spent 61% to 66% of the total time within the target INR range.^{6,15} However, there was a wide variation in the definition of therapeutic range in these randomized clinical trials. The target INR range varied from 2.0-4.5 in the Stroke Prevention for Atrial Fibrillation (SPAF) study to 1.5-2.7 in the Boston Area Anticoagulation Trial for Atrial Fibrillation (BAATAF) study.^{2,16}

While half of their time was spent within therapeutic range, our patients spent 90% of the remaining time below the recommended range. A Japanese group suggested that optimal INR for secondary prevention in non-valvular atrial fibrillation, especially for elderly, could be lowered to 1.6-2.2 without compromising the efficacy of warfarin.¹⁷ Such finding is consistent with the hypothesis by Hart *et al.* suggesting that if we keep the INR between 1.6 and 2.5, we could confer substantial, though partial (90%), efficacy of the higher target intensities.¹⁸ In fact, if the lower range of our target INR is reduced to 1.6 with the upper limit 3.0 kept unchanged, the time spent within this range would increase to 73% of the total time.

A total of 3 cases (one of which was doubtful) of ischemic stroke were encountered during the study period. The estimated annual event rate for stroke was about 1%, which was in keeping with findings from other clinical trials.¹⁵ It appeared that our patients did not receive suboptimal protection from anticoagulation despite only half of their time being spent within recommended therapeutic range.

Among 149 eligible patients, we excluded 18 patients who either defaulted in follow-up or were transferred to another hospital. We recognize that major events could have occurred soon after their last follow-up. We also managed to ascertain that none of them were admitted to public hospital within 3 months after last attendance. Although it was possible that these patients could be admitted elsewhere or died rapidly in Emergency Department, we do not think gross underestimation of major bleeding events was likely.

A bias in patient selection implies that our results

may not be generalized to all patients eligible for anticoagulation. Patient who cannot return to follow-up due to institutionalization were excluded from treatment. These patients could be deprived of an effective means to reduce thromboembolic risks. On the other hand, they represent a high-risk group who are more susceptible to potential hazards of this treatment. In this study, we have only included patients who took warfarin as recommended by attending physician. It remains uncertain what proportion of potential suitable patients were denied of treatment and their outcome if recommended guidelines were followed. Prospective study is required to determine the actual benefits and hazards of oral anticoagulants among all appropriate patients with recommended indications.

In conclusion, our study demonstrated that among Chinese patients taking warfarin for all indications, fatal or major bleeding occurred at an acceptable rate despite considerable minor bleeding being observed. The risk of major hemorrhage was highest during the initial period of anticoagulation. We urge clinicians to perform close monitoring of INR during such intervals. Intensity of anticoagulation was the only risk factor identified to be associated with both major and minor bleeding events.

ACKNOWLEDGEMENTS

We are indebted to Dr. Daniel Fong, Senior Medical Statistician, Clinical Trial Center, University of Hong Kong for his statistical assistance and Dr. PK Hui, Consultant Hematologist, Kwong Wah Hospital for his advice on analysis of hematological tests. We also thank Ms. Catherine Chan, Pharmacist, Kwong Wah Hospital for her assistance in enrollment of patients.

REFERENCES

1. Stroke Prevention in Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation Study: final results. *Circulation* 1991;84:527-39.
2. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med* 1990;323:1505-11.
3. Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian Atrial Fibrillation Anticoagulation Study. *J Am Coll Cardiol*. 1991;18:349-55.
4. Ezekowitz MD, Bridgers SL, James KE, Carliner NH, Colling CL, Govnick CC, *et al*. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. *N Engl J Med* 1992;327:1406-12.
5. Patersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. *Lancet* 1989;1:175-9.
6. Evans A, Kalra L. Are the results of randomized controlled trials on anticoagulation in patients with atrial fibrillation generalizable to clinical practice? *Arch Intern Med* 2001;161:1443-7.
7. Kay R, Woo J, Kreel L, Wong HY, Teoh R, Nicholls MG. Stroke subtypes among Chinese living in Hong Kong. *Neurology* 1992;42:985-7.
8. Hirsh J, Dalen JE, Anderson DR, Pollen L, Bussey H, Ansell J, *et al*. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest* 2001;119(suppl):8-21.
9. Landefeld CS, Anderson PA, Goofnough LT, Moir TW, Hom DL, Rosenblatt MW, *et al*. The bleeding severity index: validation and comparison to other methods for classifying bleeding complications of medical therapy. *J Clin Epidemiol* 1989;42:711-8.
10. Fihn SD, McDonnell M, Martin D, Henikoff J, Vermes D, Kent D, *et al*. Risk factors for complications of chronic anticoagulation: a multicenter study. *Ann Intern Med* 1993;118:511-20.
11. Landefeld CS, Beyth RJ. Anticoagulation-related bleeding: clinical epidemiology, prediction and prevention. *Am J Med* 1993;95:315-28.
12. Kalra L, Yu G, Perez I, Lakhani A, Donaldson N. Prospective cohort study to determine if trial efficacy of anticoagulation for stroke prevention in atrial fibrillation translates into clinical effectiveness. *Brit Med J* 2000;320:1236-9.
13. Gitter MJ, Jeger TM, Petterson TM, Gersh BJ, Silverstein MD. Bleeding and thromboembolism during anticoagulation therapy: a population-based study in Rochester, Minnesota. *Mayo Clin Proc* 1995;70:725-33.
14. Cheung RTE, Li LSW, Tsang KL, Leung KP. Stroke prevention in atrial fibrillation among Hong Kong Chinese. *Cerebrovasc Dis* 2001;11:353-4.
15. Analysis of pooled data from five randomized controlled trials: risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. *Arch Intern Med* 1994;154:

- 1449-57.
16. Stroke Prevention in Atrial Fibrillation Investigators. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet* 1994;343:687-91.
 17. Yamaguchi T. Optimal intensity of warfarin therapy for secondary prevention of stroke in patients with nonvalvular atrial fibrillation. *Stroke* 2000;31:817-21.
 18. Hart RG, Sherman DG, Easton JD, Cairns JA. Prevention of stroke in patients with nonvalvular atrial fibrillation. *Neurology* 1998;51:674-81.