LETTERS TO THE EDITOR

Anticoagulation and atrial fibrillation

EDITOR,—We would like to congratulate McNulty and colleagues on their excellent clinical audit of antithrombotic therapy in atrial fibrillation.¹ Their approach to the methods of audit has been impeccable, completing the audit cycle by instigating a process of reaudit after the results from the original data set had been intensively presented to hospital colleagues, itself leading to a highly effective intervention.

We would, however, appreciate this opportunity to provide a brief update in a few aspects of the current knowledge of stroke prevention in atrial fibrillation. The Lip and Lowe algorithm used for risk stratification was first published in 1996² and a refinement has since been proposed (box 1),³ which has

been adapted for use in local and national guidelines.

The essential changes relate to the contribution of echocardiography and paroxysmal atrial fibrillation. In the Atrial Fibrillation Investigators overview on echocardiographic risk factors for thromboembolism, left atrial size *per se* does not appear to be an independent risk factor on multivariate analysis and is no longer used in the risk stratification schema⁴; indeed, left atrial dilatation rarely occurs independent of "other" pathology, such as hypertension or heart failure which themselves constitute high risk features.⁴ In this analysis, moderate or severe left ventricular dysfunction on two dimensional echocardiography was the only significant abnormality which appeared to be an independent risk factor for thromboembolic stroke in non-valvular atrial fibrillation.⁴ Other studies using echocardiography for risk stratification have rarely found that the investigation significantly contributed to antithrombotic therapy management decisions, as many patients already had clinical risk factors allowing effective risk stratification.^{5,6}

Regarding other possible risk factors, hormone replacement therapy use may also increase risk while alcohol consumption may be protective.⁷ McNulty and colleagues do not specifically address the problem of paroxysmal atrial fibrillation,¹ but it should be emphasised that such patients carry the same stroke and thromboembolic risk as sustained atrial fibrillation, especially in the presence of clinical risk factors.⁸ In general, our recommendation is to use warfarin in patients with paroxysmal atrial fibrillation unless they can be classified as having "low" atrial fibrillation or there are contraindications to the use of anticoagulation, where aspirin should be used instead.

The safety and tolerability of long term anticoagulation titrated to conventional levels (international normalised ratio (INR) 2-3) is less clear in the very elderly (age older than 75 years), which is the age group encompassing perhaps half of the atrial fibrillation associated stroke patients. The elderly are also prone to more co-morbidity, polypharmacy, cognitive problems and frailty; indeed, biological age in some ways is more important than chronological age, and the decision must be based on the risk-benefit ratio, as with many things in clinical medicine. There have also been suggestions that an INR range of 1.6-2.5 can provide substantial, if partial efficacy (estimated to be nearly 90% of the highest intensities), and could be used for elderly patients to minimise haemorrhagic complications, although this has not been verified by any prospective study.⁹ Given the uncertainty about the safety of INRs >2.5 for patients with atrial fibrillation over the age 75, a target INR of 2.0 (range 1.6-2.5) may be a reasonable compromise between toxicity and efficacy for this age group, pending further data about the safety of higher intensities. Further information from our ongoing Medical Research Council funded BAFTA (Birmingham Atrial Fibrillation Treatment Assessment) study in elderly patients aged >75 years, with non-valvular atrial fibrillation in primary care, would provide further information.

McNulty and colleagues extrapolate from their data the potential savings both in hospital admission days and financial cost,¹ which may be achievable by a nationwide consensus approach to the problem. We wholeheartedly support this, and agree with their call for

improved stroke prevention in atrial fibrillation, especially as there is now evidence the benefits and risks of anticoagulation seen in the clinical trials can realistically be translated into everyday clinical practice.¹⁰

D S G CONWAY

G Y H LIP

Haemostasis Thrombosis and Vascular Biology Unit,
University Department of Medicine,
City Hospital, Birmingham B18 7QH, UK
G.Y.H.LIP@bham.ac.uk

Box 1: Risk stratification and anticoagulation in non-valvular atrial fibrillation

ASSESS RISK AND REASSESS
REGULARLY:

(1) *High risk (annual risk of CVA = 8%-12%)*

- All patients with previous transient ischaemic attack or CVA.
- All patients aged 75 or over with diabetes and/or hypertension.
- All patients with clinical evidence of valve disease, heart failure, thyroid disease, and/or impaired left ventricular function on echocardiography*.

(2) *Moderate risk (annual risk of CVA = 4%)*

- All patients aged under 65 with clinical risk factors: diabetes, hypertension, peripheral arterial disease, ischaemic heart disease.
- All patients aged over 65 who are not in high risk group.

(3) *Low risk (annual risk of CVA = 1%)*

- All patients under 65 with no history of embolism, hypertension, diabetes, or other clinical risk factors.

TREATMENT

- *High risk:* give warfarin (target INR 2.0-3.0) if no contraindications and possible in practice.
- *Moderate risk:* either warfarin or aspirin 75-300 mg. In view of insufficient clear cut evidence, treatment may be decided on individual cases. Referral and echocardiography may help.
- *Low risk:* give aspirin 75-300 mg daily.

*Echocardiography: not needed for routine risk assessment but refines clinical risk stratification in case of impaired left ventricular function and valve disease. A large atrium *per se* is not an independent risk factor on multivariate analysis.

CVA = cerebrovascular accident.

- 1 McNulty SJ, Hutchinson D, Hardy KJ. Implementation of antithrombotic management in atrial fibrillation. *Postgrad Med J* 2000;76:783-6.
- 2 Lip GYH, Lowe GDO. Antithrombotic treatment for atrial fibrillation. *BMJ* 1996;312:45-9.
- 3 Lip GYH. Thromboprophylaxis for atrial fibrillation. *Lancet* 1999;353:4-6.
- 4 Atrial Fibrillation Investigators. Echocardiographic predictors of stroke in patients with atrial fibrillation. *Arch Intern Med* 1998;158:1316-20.
- 5 Cantley P, McKinstry B, Macaulay D, *et al*. Atrial fibrillation in general practice: how useful is echocardiography in selection of suitable patients for anticoagulation? *Br J Gen Pract* 1999;49:219-20.
- 6 Sudlow M, Thomson R, Thwaites B, *et al*. Prevalence of atrial fibrillation and eligibility for anticoagulants in the community. *Lancet* 1998;352:1167-71.
- 7 Hart RG, Pearce LA, McBride R, *et al*. Factors associated with ischaemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I-III clinical trials. The Stroke Prevention in Atrial Fibrillation (SPAF) investigators. *Stroke* 1999;30:1223-9.
- 8 Hart RG, Pearce LA, Rothbart RM, *et al*. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke Prevention in Atrial Fibrillation Investigators. *J Am Coll Cardiol* 2000;35:183-7.
- 9 Hart RG, Benavente O. Primary prevention of stroke in patients with atrial fibrillation. *Proc R Coll Physicians Edinb* 1999;29(3)suppl 6:20-6.
- 10 Kalra L, Yu G, Perez I, *et al*. Prospective cohort study to determine if trial efficacy of anticoagulation for stroke prevention in atrial fibrillation translates into clinical effectiveness. *BMJ* 2000;320:1236-9.

Improvement in antithrombotic management in atrial fibrillation also requires effective INR control

EDITOR,—McNulty *et al* report improved management of atrial fibrillation in a busy district general hospital by increasing the percentage of patients at high risk of stroke who receive oral anticoagulation.¹ They suggest that, based on the results of large randomised prospective studies reported in the late 1980s and early 1990s, a similar improvement in management of all hospital patients with atrial fibrillation in the UK would avoid approximately 1400 strokes annually.

The present recommended international normalised ratio (INR) therapeutic range of 2-3 for atrial fibrillation patients on oral anticoagulation is aimed at reducing the risk of thromboembolic disease while minimising the risk of major bleeds.² However, maintaining orally anticoagulated patients in the desired therapeutic INR range in clinical practice appears to be much more difficult than INR control in carefully selected, well motivated, and closely monitored study subjects.³ For example, in a study of consecutive hospital admissions of over 300 patients to six academic hospitals in the USA, only approximately a third of patients had an INR between 2 and 3 at the time of admission.⁴ The reasons for poor anticoagulant control are numerous but the major underlying cause remains poor patient compliance.

Unfortunately, McNulty *et al* fail to provide information on the percentage of

time orally anticoagulated patients in their audit were in therapeutic INR range or on the incidence of thrombotic stroke and major haemorrhage in this patient group. As implementation of antithrombotic management in atrial fibrillation patients in their hospital remains suboptimal, even on follow up audit, INR control in the orally anticoagulated patient group could also be inadequate, thus jeopardising the hoped for reduction in strokes in this high risk atrial fibrillation group. In addition, the increase in patients on oral anticoagulation in the period between the two audits may have adversely affected the delivery of acceptable INR control by increasing demands on time and resources in a presumably already overstretched district general hospital haematology laboratory.

We suggest that, in future, similar audits of management of atrial fibrillation should include information on the quality of INR control in orally anticoagulated patients. If such patients are found to be inadequately maintained in therapeutic INR range, increased resources should be allocated to improve the efficacy of INR control. Possible areas of improvement in anticoagulant control might include the upgrading of laboratory coagulation equipment, better communication between clinicians and the anticoagulation clinic, adequate laboratory, clerical, nursing and medical staffing, ongoing and more effective patient and hospital staff education, computerised dosage systems⁵ and, in selected cases, patient self monitoring and self management.

P T MURPHY
Department of Haematology,
Royal Shrewsbury Hospital,
Shrewsbury SY3 8XQ, UK

M C CASEY
Department of Geriatric Medicine,
Keele University

- 1 McNulty SJ, Hutchinson D, Hardy KJ. Implementation of antithrombotic management in atrial fibrillation. *Postgrad Med J* 2000;76:783-6.
- 2 Lip GYH, Lowe GDO. Antithrombotic treatment for atrial fibrillation. *BMJ* 1996;312:45-9.
- 3 Rose PE. Audit of anticoagulant therapy. *J Clin Pathol* 1996;49:5-9.
- 4 Albers GW, Yim JM, Belew KM, et al. Status of antithrombotic therapy for patients with atrial fibrillation in university hospitals. *Arch Intern Med* 1996;156:2311-6.
- 5 Poller L, Schniack CR, MacCallum PR, et al. Multicentre randomised study of computerised anticoagulant dosage. *Lancet* 1998;352:1505-39.

Implementation of antithrombotic management in atrial fibrillation

EDITOR,—We read the above original article of McNulty *et al* with interest particularly the antithrombotic management algorithm in fig 1.¹ There is no mention of the time when the retrospective study was conducted. As it was submitted in January 2000 we assume that the study was conducted sometime in 1999.

The algorithm originally published in 1996² should be considered outdated in 1999/2000 because: first, in atrial fibrillation an age of 75 years or older is a high risk factor for thromboembolism to qualify for long term anticoagulation.³ Secondly, a large left atrium in patients with atrial fibrillation but without mitral valve disease is not an independent risk factor for thromboembolism.³ Therefore left atrium size of more than 4.5 cm *per se* should not be used to decide for long term anticoagulation in these patients. Thirdly, patients with atrial fibrillation who

are below 65 years of age but with hypertension/ischaemic heart disease/diabetes mellitus are at high risk and should be given warfarin, not aspirin.³ Fourthly, patients with atrial fibrillation at high risk of thromboembolism in whom warfarin and aspirin are contraindicated should be considered for clopidogrel or at least dipyridamole. In patients with atherosclerotic vascular disease, clopidogrel has been shown to be more effective than aspirin in reducing risk of ischaemic stroke, myocardial infarction or vascular death without increasing adverse effect.⁴ Patients intolerant of aspirin should be given modified release dipyridamole or clopidogrel.⁵

We believe that using such improved management protocol for atrial fibrillation either for audit purpose or clinical practice, is likely to further reduce the risk of ischaemic stroke.

S K S LAIRIKYENGBAM
A G DAVIES
P D JONES
Department of Medicine,
Bronglais General Hospital,
Aberystwyth SY23 1ER, UK

- 1 McNulty SJ, Hutchinson D, Hardy KJ. Implementation of antithrombotic management in atrial fibrillation. *Postgrad Med J* 2000;76:783-6.
- 2 Lip GYH, Lowe GDO. Antithrombotic treatment for atrial fibrillation. *BMJ* 1996;312:45-9.
- 3 Final Consensus Statement. Atrial fibrillation in hospital and general practice: the Sir James Mackenzie Consensus Conference. *Proc R Coll Physicians Edinb* 1999;29(3):2-3.
- 4 CAPRIE Steering Committee. A randomised, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic stroke (CAPRIE). *Lancet* 1996;348:1329-39.
- 5 Consensus conference on medical management of stroke. *Proc R Coll Physicians Edinb* 1998;28:367-9.

Drs McNulty, Hutchinson, and Hardy respond:

We read the three letters above with much interest and would like to address the issues raised by each, in turn. We appreciate the update on current knowledge of stroke prevention provided by Conway and Lip, which we have followed as it appears in the literature. Obviously we were unable to use these revised guidelines as our original audit predated the publication of this revision.¹ When the audit was conceived we did debate whether to include paroxysmal atrial fibrillation (PAF) as well as sustained atrial fibrillation in our study but at that time the "jury was still out" as to whether PAF carried the same risk—so we chose to audit sustained atrial fibrillation only; again we appreciate the update on PAF.²

In response to Lairikyengbam *et al*—as stated our paper was submitted in January 2000. The auditing process took over a year to complete, as it takes time to accumulate 370 patients with atrial fibrillation, retrieve and extensively review case notes, and analyse the data. It should also be noted that there was a gap of six months between the two audits reported to allow for an education programme. Therefore when the revised guidelines were published in July 1999³ the audit was completed.

Finally, the response from Murphy and Casey seems to raise two questions and a possible word of warning. The questions regard whether our patients had therapeutic INR control and what was the incidence of major adverse events in our group—unfortunately audit (and reaudit, in the case of our report⁴) consists of snapshots of current management. In the case of lifelong

intervention with warfarin therapy, audit would be an inappropriate tool to measure their two concerns and perhaps a prospective study would be a more useful way of answering their questions. We note a recent report by Gupta *et al* studying elderly patients with atrial fibrillation on warfarin.⁵ The last five prothrombin readings were analysed, and it was found that only 9% of these patients were not adequately warfarinised; only four major bleeds occurred over 263 treatment years in this particular treatment group. They also raise concerns regarding the increased resources needed to deliver the current published recommended guidelines. We agree that treating more patients with warfarin would increase demands on haematology laboratory resources; however, we (like most people involved in this field) believe that this is offset by the potential reduction in the demands made upon stroke and general inpatient beds, physiotherapy, occupational therapy, and all the other resources which are consumed after a stroke.

- 1 Lip GYH. Thromboprophylaxis for atrial fibrillation. *Lancet* 1999;353:4-6.
- 2 Hart RG, Pearce LA, Rothbart RM, et al. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke Prevention in Atrial Fibrillation Investigators. *J Am Coll Cardiol* 2000;35:183-7.
- 3 Final Consensus Statement. Atrial fibrillation in Hospital and General Practice: the Sir James Mackenzie Consensus Conference. *Proc R Coll Physicians Edinb* 1999;29(3):2-3.
- 4 McNulty SJ, Hutchinson D, Hardy KJ. Implementation of antithrombotic management in atrial fibrillation. *Postgrad Med J* 2000;76:783-6.
- 5 Gupta A, Thomas P. Are atrial fibrillation patients receiving appropriate stroke prophylaxis? *Br J Cardiol* 2001;8:38-42.

DIARY

Techniques and Applications of Molecular Biology: A Course for Medical Practitioners

9-12 July 2001, University of Warwick, Coventry

This is a four day residential course for those in the medical profession wishing to improve their understanding of the principles and applications of genetic engineering techniques. *Further information:* Dr Charlotte West, Department of Biological Sciences, University of Warwick, Coventry CV4 7AL (tel 024 7652 3540, fax 024 7652 3701, email Charlotte.West@warwick.ac.uk).

Ninth Annual Pediatric Update

20-21 July 2001, Lucile Packard Children's Hospital, Palo Alto, California

This conference is presented by the Department of Pediatrics at Stanford University School of Medicine and Lucile Packard Children's Hospital. It is designed for paediatricians, family physicians, nurses, and allied health professionals and will highlight the most recent advances and issues in paediatrics. *Further information:* Lucile Packard Children's Hospital CME Office at +1 650 497 8554 or email lpchcme@medcenter.stanford.edu.