patient and tumour characteristics as well as preferences. In the few instances where evidence is very strong and confidence high, performance standards and practice incentives might be introduced. Unfortunately, for most situations related to detection and treatment of prostate cancer, more definitive recommendations will require completion of randomised trials.

Competing interests: None declared.

- 1 Wilt TJ, Shamlivan T, Taylor B, MacDonald R, Tacklind J, Rutks I, et al. Comparative effectiveness of therapies for clinically localized prostate cancer. *Comparative Effectiveness Review* 2008. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

- 2 Thompson I, Thrasher JB, Aus G, Burnett AL, Canby-Hagena ED, Cookson MS, et al. Guideline for the management of clinically localized prostate cancer: 2007 update. *J Urol* 2007;177:2106-31.
- 3 Heidenreich A, Aus G, Bolla M, Joniau S, Matveev VB, Schmid HP, et al. EAU guidelines on prostate cancer. *Eur Urol* 2008;53:68-80.
- 4 Thompson IM, Ankerst DP, Chi C, Goodman PJ, Tangen CM, Lucia MS, et al. Assessing prostate cancer risk: results from the prostate cancer prevention trial. *J Nat Cancer Inst* 2006;98:529-34.
- 5 Welch HG, Schwartz LM, Woloshin S. Prostate-specific antigen levels in the United States: implications of various definitions for abnormal. *J Nat Cancer Inst* 2005;97:1132-7.
- 6 Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PAC, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999;282:1458-65.
- 7 Lu-Yao G, Barry MJ, Zietman A, O'Leary M, Walker-Corkery B, Shih W, et al. Disease trajectory of untreated localized prostate cancer in elderly men: a population-based study [abstract]. Genitourinary cancer symposium. San Francisco, CA. February 2008.

CHANGE PAGE

Don't add aspirin for associated stable vascular disease in a patient with atrial fibrillation receiving anticoagulation

Gregory Y H Lip

University Department of
Medicine, City Hospital,
Birmingham B18 7QH
g.y.h.lip@bham.ac.uk

BMJ 2008;336:614-5
doi:10.1136/bmj.39351.706586.AD

The clinical problem

Atrial fibrillation is the commonest cardiac arrhythmia, with increasing prevalence and incidence.¹ Adjusted dose oral anticoagulation (such as with warfarin) is the most effective treatment for stroke prevention in high risk patients with atrial fibrillation.²

However, common practice is to add aspirin (or other antiplatelet treatment) to warfarin in atrial fibrillation if there is associated chronic stable coronary or peripheral artery disease.² This is despite relatively little evidence that adding aspirin to warfarin reduces stroke or other vascular events in patients with atrial fibrillation.

I propose here that we should not add aspirin for associated stable vascular disease in a patient with atrial fibrillation receiving anticoagulation, given the lack of evidence for benefit and the potential for harm.

The evidence for change

Randomised clinical trials in patients with atrial fibrillation using combinations of anticoagulation and aspirin either compared fixed dose (or low intensity, international normalised ratio (INR) <1.5) anti-coagulation plus aspirin with adjusted dose warfarin² or compared adjusted dose anticoagulation (INR 2.0-3.0) plus aspirin with adjusted dose anticoagulation.

The first trial type found that fixed dose anti-coagulation plus aspirin was no better than adjusted dose warfarin.² In the second category, one trial was stopped early owing to poor recruitment but showed a substantially higher bleeding rate in the anti-coagulation plus aspirin arm than in the anti-coagulation alone arm.³ A retrospective analysis of the combined dataset of two large recent randomised

clinical trials⁴ of warfarin versus ximelagatran (an oral direct thrombin inhibitor) in moderate to high risk patients with atrial fibrillation compared aspirin users with non-users. This analysis found no additive effect of taking aspirin (with either of the anticoagulation treatments) in preventing stroke or reducing vascular events (including death or myocardial infarction).⁴ Specifically, the rate of myocardial infarction with aspirin and warfarin was not significantly different from that with warfarin alone (0.6% and 1.0% a year respectively). However, aspirin use resulted in a substantial higher bleeding risk compared with warfarin alone (major bleeding 3.9% and 2.3% a year respectively; $P < 0.01$).

Various cohort studies (either case series or registry analyses) in which aspirin was added among patients receiving anticoagulation treatment who were having percutaneous coronary intervention and stenting (only a proportion of patients had atrial fibrillation) also suggest an increase in bleeding risk by adding antiplatelet treatment to warfarin.⁵⁻⁸ In one registry analysis of 10 093 patients with atrial fibrillation, the use of antiplatelet treatment was associated with a threefold increase in intracranial haemorrhage (relative risk 3.0; 95% confidence interval 1.6 to 5.5).⁹

Barriers to change

The perception that aspirin plus warfarin is needed in patients with atrial fibrillation and vascular disease is based on the fact that antiplatelet treatment works on the platelet-rich thrombus ("white clot") associated with vascular disease, whereas warfarin is effective for the fibrin-rich thrombus ("red clot") associated with atrial fibrillation.

Change Page aims to alert clinicians to the immediate need for a change in practice to make it consistent with current evidence. The change must be implementable and must offer therapeutic or diagnostic advantage for a reasonably common clinical problem. Compelling and robust evidence must underpin the proposal for change.

This principle applies particularly in patients with atrial fibrillation who present with acute coronary syndrome or are having percutaneous coronary intervention or stenting, for which aspirin plus clopidogrel is recommended for up to 12 months.¹⁰ If such patients with atrial fibrillation are at high risk of stroke they may be prescribed warfarin also, although sound evidence for its efficacy is still lacking and bleeding risk on such triple therapy is not inconsequential.^{5-8 10} Also, in patients in atrial fibrillation with prosthetic heart valves, some may do better with warfarin plus aspirin.¹¹ In patients with atrial fibrillation who have such “unstable” vascular disease or valvular disease, the real, long term benefit to risk ratio of combination therapy is not known and should be left to the physician’s discretion.

However, for stable coronary artery disease, warfarin can be a useful antithrombotic drug,^{12 13} and adding aspirin may substantially increase bleeding risk without much benefit. None the less, the lack of benefit of added aspirin may not apply to all antiplatelet agents. For example, one randomised trial (n=1209) compared triflusal (an antiplatelet drug that is a cyclo-oxygenase inhibitor, not available in the United Kingdom) to acenocoumarol (an anticoagulant) or combination therapy, in intermediate risk and high risk patient groups. In both groups the primary outcome was lower with triflusal plus acenocoumarol than with anticoagulation alone. No difference was found for bleeding complications between the anticoagulant and the combined therapy arms.¹⁴

How should we change our practice?

Clinicians should be aware that in patients with atrial fibrillation and stable vascular disease, adding aspirin to warfarin does not seem to prevent stroke and vascular events and increases bleeding risk. If a patient taking aspirin for atrial fibrillation is diagnosed with vascular disease and requires warfarin, the aspirin should be stopped once warfarin is started and therapeutic range (INR 2.0-3.0) achieved. Aspirin plus clopidogrel (without warfarin) is not an alternative in patients with atrial fibrillation at high risk of stroke.¹⁵ The message to stop prescribing aspirin alongside warfarin in such patients needs much greater emphasis in prescribing guidelines.

SOURCES AND SELECTION CRITERIA

I performed a comprehensive literature search by using electronic bibliographic databases (Medline, Embase, DARE (Database of Abstracts of Reviews of Effects), Cochrane database), scanning reference lists from included articles, and hand searching abstracts from national and international cardiovascular meetings. For the search, I used the terms “atrial fibrillation” plus “anticoagulation” plus “aspirin”. I reviewed bibliographies of all selected articles and review articles for other relevant articles. Finally, I hand searched the supplements of major journals to identify relevant abstracts that had not been published as peer reviewed articles.

KEY POINTS

Adding aspirin to warfarin does not seem to prevent stroke and vascular events in patients with atrial fibrillation and stable vascular disease

Bleeding risks are much higher in patients prescribed both warfarin and aspirin

We should stop prescribing aspirin plus warfarin to prevent stroke and vascular events in stable patients with atrial fibrillation who are receiving anticoagulation treatment

Contributors: GHYL is the sole contributor.

Competing interests: None declared.

Provenance and peer review: Commissioned; externally peer reviewed.

- 1 Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006;114:119-25.
- 2 Lip GY, Boos CJ. Antithrombotic treatment in atrial fibrillation. *Heart* 2006;92:155-61.
- 3 Lechat P, Lardoux H, Mallet A, Sanchez P, Derumeaux G, Lecompte T, et al. Anticoagulant (fluidione)-aspirin combination in patients with high-risk atrial fibrillation. A randomized trial (Fluidione, Fibrillation Auriculaire, Aspirin et Contraste Spontané; FFAACS). *Cerebrovasc Dis* 2001;12:245-52.
- 4 Flaker GC, Gruber M, Connolly SJ, Goldman S, Chaparro S, Vahanian A, et al. Risks and benefits of combining aspirin with anticoagulant therapy in patients with atrial fibrillation: an exploratory analysis of stroke prevention using an oral thrombin inhibitor in atrial fibrillation (SPORTIF) trials. *Am Heart J* 2006;152:967-73.
- 5 Khurram Z, Chou E, Minutello R, Bergman G, Parikh M, Naidu S, et al. Combination therapy with aspirin, clopidogrel and warfarin following coronary stenting is associated with a significant risk of bleeding. *J Invasive Cardiol* 2006;18:162-4.
- 6 Orford JL, Fasseas P, Melby S, Burger K, Steinhilber SR, Holmes DR, et al. Safety and efficacy of aspirin, clopidogrel, and warfarin after coronary stent placement in patients with an indication for anticoagulation. *Am Heart J* 2004;147:463-7.
- 7 Karjalainen PP, Porela P, Ylitalo A, Vikman S, Nyman K, Vaitinen MA, et al. Safety and efficacy of combined antiplatelet-warfarin therapy after coronary stenting. *Eur Heart J* 2007;28:726-32.
- 8 Porter A, Konstantino Y, Iakobishvili Z, Shachar L, Battler A, Hasdai D. Short-term triple therapy with aspirin, warfarin, and a thienopyridine among patients undergoing percutaneous coronary intervention. *Catheter Cardiovasc Interv* 2006;68:56-61.
- 9 Shireman TI, Howard PA, Kresowik TF, Ellerbeck EF. Combined anticoagulant-antiplatelet use and major bleeding events in elderly atrial fibrillation patients. *Stroke* 2004;35:2362-7.
- 10 Lip GY, Karpha M. Anticoagulant and antiplatelet therapy use in patients with atrial fibrillation undergoing percutaneous coronary intervention: the need for consensus and a management guideline. *Chest* 2006;130:1823-7.
- 11 Dentali F, Douketis JD, Lim W, Crowther M. Combined aspirin-oral anticoagulant therapy compared with oral anticoagulant therapy alone among patients at risk for cardiovascular disease: a meta-analysis of randomized trials. *Arch Intern Med* 2007;167:117-24.
- 12 Andreotti F, Testa L, Biondi-Zoccai GG, Crea F. Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes: an updated and comprehensive meta-analysis of 25,307 patients. *Eur Heart J* 2006;27:519-26.
- 13 Lip GY, Varma C. Anticoagulation plus aspirin following acute myocardial infarction: yes or no . . . and if the latter, why not? *Thromb Res* 2006;118:429-32.
- 14 Perez-Gomez F, Alegria E, Berjon J, Iriarte JA, Zumalde J, Salvador A, et al. Comparative effects of antiplatelet, anticoagulant, or combined therapy in patients with valvular and nonvalvular atrial fibrillation: a randomized multicenter study. *J Am Coll Cardiol* 2004;44:1557-66.
- 15 ACTIVE Writing Group on behalf of the ACTIVE Investigators. 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;367:1903-12.