Table 1

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Shapiro <i>et al</i> , 2005, USA	1278 patients in an urban academic medical center: 18 years or older, admitted to the hospital with a suspected infection-related diagnosis, having had serum lactate level drawn at initial presentation in the ED. Patients stratified according to lactate. Low (L) <2.5 mmol/L, medium (M) 2.5–3.99 mmol/L, high (H) ≥4 mmol/L.	Prospective cohort study. Level IIb evidence.	Death at 28 days	L = 43/877 (4.9%) (95% CI 3.5%–6.3%), M = 24/267 (9.0%) (95% CI 5.6%–12.4%), H = 38/134 (28.4%) (95% CI 21%–36%) Lactate ≥2.5 Sn = 59% (95% CI 50%–68%), Sp = 71% (95% CI 69%–74%), lactate ≥4, Sn = 36% (95% CI 27%–45%), Sp = 92% (95% CI 90%–93%)	Patients without lactate drawn at presentation were not included. Only patients admitted to the hospital were included. No patient demographics or measures of illness severity provided.
			Sensitivity (Sn) and specificity (Sp) for death at 28 days		
			Death within 3 days	L = 13/877 (1.5%) (95% CI 0.7%–2.3%), M = 12/267 (4.5%) (95% CI 2.0%–7.0%), H = 30/134 (22.4%) (95% CI 15%–29%) Lactate ≥2.5 Sn = 76% (95% CI 65%–88%), Sp = 71% (95% CI 68%–73%), lactate ≥4, Sn = 55% (95% CI 41%–68%), Sp = 91% (95% CI 90%–93%)	
			Sensitivity (Sn) and specificity (Sp) for death within 3 days		

ED, emergency department

Negative D-dimer may allow safe early cardioversion of atrial fibrillation

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A short cut review was carried out to establish whether a negative D-dimer will accurately rule out an atrial thrombus in a patient presenting with atrial fibrillation. Ten papers seemed relevant to the clinical question. The author, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses of these papers are tabulated. The clinical bottom line is that a negative D-dimer suggests that it is safe to cardiovert a patient with recent onset of atrial fibrillation.

Three part question

In [patients with atrial fibrillation being considered for electrical or pharmacologic cardioversion] does [measurement of D-dimer] allow [exclusion of atrial thrombus]?

Clinical scenario

A 45-year-old man presents to the emergency department with a 48 hour history of palpitations, postural light-headedness and exertional dyspnoea. ECG demonstrates atrial fibrillation (AF) at a rate of 130 beats/minute. There are no apparent reversible causes following history, examination, chest radiography, urinalysis and haematological and biochemical screening. You feel that pharmacologic or electrical cardioversion to sinus rhythm rather than rate control would be most beneficial to the patient, but as you are aware of the possibility of atrial thrombus and systemic embolism you opt for rate control and refer for anticoagulation. You wonder if measuring D-dimer, a product of clot breakdown, would have allowed accurate

exclusion of atrial thrombus, thus enabling the safe acute administration of flecainide.

Search strategy

All via the Ovid interface: Medline 1950–2007 February Week 4 CINAHL 1982 – 2007 March Week 1 Embase 1980 – 2007 Week 9 Cochrane Central Register of Controlled Trials (CCRCT) <1st Quarter 2007> ACP Journal Club 1991 to January/February 2007 Cochrane Database of Systematic Reviews (CDSR) <1st Quarter 2007> Database of Abstracts of Reviews of Effects (DARE) <1st Quarter 2007> [exp Atrial Fibrillation/OR exp Atrial Flutter/OR (atrial fibrillation OR AF OR atrial flutter OR (cardiac adj thromb\$) OR (intracardiac adj thromb\$) OR ((atrial OR atrium) adj3 thromb\$)).mp. OR] AND [exp Fibrin Fibrinogen Degradation Products/OR D-dimer\$.mp.].

Search outcome

Altogether 110 papers were identified using Medline, 2 using CINAHL, 141 using Embase, 12 in CCRCT, 4 in ACP Journal Club, 1 in CDSR and 0 in DARE. Ten were relevant to the three-part question (table 2).

Comments

Cardioversion of AF to sinus rhythm carries a small but definite risk of systemic thromboembolism from atrial thrombus, typically within the left atrial appendage. Although the risk is greatest when the arrhythmia has lasted for over 48 hours, atrial thrombi may occur earlier (Stoddard *et al*, 1995; Manning *et al*, 1995). As the left atrial appendage is not easily visualised on transthoracic echocardiography (TTE), transoesophageal echocardiography (TOE) is necessary to exclude thrombus. However, this test is invasive, carries a small but definite risk of complications, is unpleasant for the patient and not readily available in most centres.

Current European Society of Cardiology guidelines state that patients must either have TOE or anticoagulation for 3–4 weeks prior to attempted cardioversion unless there is an immediate indication (Fuster *et al*, 2001). A quick, non-invasive test such as D-dimer, that is easily applied in the emergency department

Table 2

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Yasaka <i>et al</i> , 1991, Japan	63 patients with mitral stenosis recruited from in-patient and out-patient departments.	Prospective cross-sectional study	D-dimer levels (mean, (standard error) ng/ml)	Controls (n = 10) 88.5 (10.9); Cases without thrombi (n = 45) 147.2 (18.4) (p<0.01 vs controls); Cases with thrombi (n = 18) 646.9 (165.2) (p<0.01 vs controls; p<0.01 vs cases without thrombi).	The gold standard for diagnosis of atrial thrombus was transthoracic echocardiography, which has limited sensitivity.
Hayashi, 1991, Japan	All underwent transthoracic echocardiography and had blood sampled on the same day. 26 patients with mitral stenosis who had undergone cardiac surgery. All had AF. Blood taken several days before surgery. A second group of normal controls was used for comparison (n not stated).	Prospective cross-sectional study	D-dimer for detection of atrial thrombi (calculated using data presented; controls excluded) D-dimer for detection of mobile atrial thrombus (calculated from data presented) D-dimer levels (mean)	Sensitivity 61%; Specificity 93%; PPV 79%; NPV 86%; LR+ 8.7; LR- 0.4. Sensitivity 100%; Specificity 92%; PPV 71%; NPV 100%; LR+ 12.5; LR- (assuming the next patient enrolled would be a false negative) 0.09. Thrombus present: 378ng/ml; Thrombus absent: 93ng/ml; Normal controls: 64ng/ml. p<0.01 for both. D-dimer significantly correlated with the mass of the thrombus (r=0.87, p<0.01). All patients with a D-dimer >200 ng/ml had atrial thrombus.	A limitation of the study in relation to the three-part question is that only 44 of 63 patients had AF. Only one observer reported echocardiograms. Intra-observer and inter-observer variabilities not assessed.
Black <i>et al</i> , 1993, Australia	135 consecutive patients with non-valvular AF. All patients had TOE (95 were undergoing TOE for clinical indications (embolism 40, electrical cardioversion 38, endocarditis 6, miscellaneous 11); 40 were clinically stable out-patients undergoing TOE for research purposes). Echocardiograms reported by two independent radiographers; discrepancies resolved by consensus. Blood sampling immediately before echocardiography	Prospective cross-sectional study	D-dimer (ng/ml) and presence or absence of spontaneous echo contrast (SEC, which suggests blood stasis or low-velocity blood flow)	SEC absent: 101+/-32; SEC present 111+/-54 (no significant difference). Note: The 3 patients with atrial thrombus were excluded for this analysis.	Japanese language. Abstract only available for review. Sensitivity, specificity and predictive values not reported. Indications for surgery and baseline characteristics not available for comparison. Small numbers D-dimer only measured in the 40 clinically stable out-patients (not in the 95 patients with clinical indications for TOE).
Sakai <i>et al</i> , 1994, Japan	40 patients with AF and 21 control subjects in sinus rhythm. All underwent TOE and had blood tested for D-dimer.	Prospective cross-sectional study	Presence of left atrial thrombus D-dimer levels	Present in the appendage of 8 patients and in the atrium of 6 patients. Significantly raised in cases with left atrial thrombus compared with controls in sinus rhythm (no values given). D-dimer higher in the high-grade SEC group compared with the lower SEC group	D-dimer not correlated with the presence or absence of actual atrial thrombus, only with SEC (implying potential for atrial thrombus). Japanese language, therefore only abstract available for review. No means or P values stated in the abstract. Sensitivity, specificity, PPV, NPV, LR's not calculated.
Kimura <i>et al</i> , 1995, Japan	83 patients who underwent TOE and had blood taken for coagulation marker testing immediately beforehand.	Prospective cross-sectional study	D-dimer according to grade of SEC (divided into four groups)		Japanese language. Only abstract available for review. Results are difficult to interpret given the limited information available. No comparison between D-dimer and actual atrial thrombus was made. No statistical analyses reported in the abstract.

Table 2 Continued

Author, date and country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Heppell <i>et al</i> , 1997, UK	109 patients with non-rheumatic atrial fibrillation on their presenting ECG, recruited from in-patient and out-patient departments.	Prospective case-control study	D-dimer levels (thrombus present vs. thrombus absent)	Higher if thrombus present. Median (interquartile range) 479 (334–738) ng/ml vs 298 (175–502) ng/ml, $p=0.004$.	TOE interpreted by two observers. Differences were resolved by consensus but, if consensus could not be reached, the feature was deemed not present. Interobserver and intraobserver variabilities not reported.
	Excluded if history of rheumatic fever, clinical or echocardiographic evidence of mitral stenosis, a prosthetic heart valve, oral anticoagulation or recent thrombotic event. Blood taken between 0900 and 1000 after 15 minutes of rest in the semi-recumbent position. All patients underwent transoesophageal echocardiography (TOE), interpreted by two observers.				D-dimer levels not dichotomised to enable calculation of sensitivity, specificity and predictive values.
Nakajima <i>et al</i> , 2000, Japan	122 patients with chronic non-rheumatic AF, who underwent TOE and had blood sent for D-dimer at the same time.	Prospective cross-sectional study	Left atrial thrombi on TOE D-dimer levels	28 (23%) had thrombi. Thrombus present: 302 ± 7 –200 ng/ml; Thrombus absent 157 ± 7 –101 ng/ml. $p<0.0001$.	Japanese language. Abstract only available to review. No calculation of sensitivity, specificity or predictive values, which would be more clinically meaningful.
Nakagawa <i>et al</i> , 2001, Japan	91 (of 135 consecutive) patients with non-rheumatic AF referred for TOE (to evaluate thromboembolic risk or source of previous embolism). 44 patients excluded because they did not have AF at the time of TOE. TOE interpreted by two independent observers with discrepancies resolved by a third independent observer. Presence or absence of aortic and left atrial spontaneous echo contrast (SEC) recorded.	Prospective cross-sectional study	D-dimer level and presence of aortic SEC	With aortic SEC: Mean 193.7 (standard error 24.9) ng/ml; Without aortic SEC: Mean 119.2 (standard error 12.8) ng/ml. $p<0.05$.	Approximately two-thirds of patients were taking oral anticoagulants, which may have affected the results.
Sakurai <i>et al</i> , 2003, Japan	113 consecutive patients who underwent transoesophageal and transthoracic echocardiography and also had blood testing for haemostatic markers. 27 patients were in normal sinus rhythm, 28 in atrial flutter and 58 in atrial fibrillation. Patients were deemed to be high or low risk for the development of thromboembolism according to the presence or absence of left atrial spontaneous echocardiographic contrast and left atrial appendage flow velocity, as assessed on echocardiography.	Prospective observational cohort	D-dimer levels according to risk for thromboembolism	Significantly higher in high risk patients (mean 1.9 mcg/ml vs 0.6 mcg/ml , $p=0.03$)	D-dimer levels not dichotomised to enable calculation of sensitivity, specificity and predictive values. Correlation between D-dimer and actual left atrial thrombus not reported.
Somloi <i>et al</i> , 2003, Hungary	75 consecutive patients referred for TOE before cardioversion for AF or flutter >48 hours duration. All patients had D-dimer measured immediately before TOE. TOE results assessed blind.	Prospective observational cohort	D-dimer for detection of atrial thrombus (gold standard TOE)	Area under ROC curve 0.78. At optimal cut-off of 0.6 ug/ml , sensitivity 89%, specificity 75%, PPV 33%, NPV 98%. Thus for every 100 patients, 66 would avoid the need for TOE or anticoagulation at the cost of one false negative.	2 patients excluded because of equivocal TOE results (may have introduced important bias)

AF, atrial fibrillation; NPV, negative predictive value; PPV, positive predictive value; LR+, positive likelihood ratio; LR-, negative likelihood ratio; SEC, spontaneous echo contrast; TOE, transoesophageal echocardiography

and may allow confident institution of appropriate early treatment to restore sinus rhythm, is therefore highly desirable.

Preliminary data has demonstrated that peripheral D-dimer estimation correlates with atrial coagulation activity (Li-Saw-Hee *et al*, 1999). Two studies (Kimura *et al*, 1995; Nakagawa *et al*, 2001) have demonstrated higher D-dimer levels in the presence of low atrial flow, a risk factor for developing atrial thrombus, although another study (Black *et al*, 1993) did report conflicting results. Several studies (Hayashi *et al*, 1991; Yasaka *et al*, 1991; Sakai *et al*, 1994; Heppell *et al*, 1997; Somloi *et al*, 2003) have demonstrated significantly raised D-dimer levels in the presence of atrial thrombus.

Studies that have investigated the clinical utility of D-dimer for exclusion of atrial thrombus in AF have yielded promising results. Using data from the study by Yasaka *et al* (1991), D-dimer excluded atrial thrombus with a negative predictive value (NPV) of 86% in a population with a high prevalence of atrial thrombi (40%). It is possible that the test would perform better in the Emergency Department population. Further, D-dimer had a sensitivity of 100% for the detection of mobile thrombi, which represent a higher embolic risk.

The high NPV of 98% reported by Somloi *et al* (2003) means that, in a population with a 12.3% pre-test probability of atrial thrombus, the post-test probability following a negative test is 2%. If 100 patients were treated according to D-dimer results, one false negative diagnosis would be expected, but early cardioversion would be possible for a further 68 patients without atrial thrombus.

This compares favourably with TOE for detection of atrial thrombus, which has been reported to have a sensitivity of 93.3% and a NPV of 98.9%. As such, for every 100 patients treated according to TOE results, 1 false negative would be expected (Hwang *et al*, 1993). Further, although warfarin has been shown to effectively reduce atrial thrombus, 14% of patients may have residual thrombus following 4 weeks of treatment (Collins *et al*, 1995).

The evidence therefore suggests that D-dimer has great potential for clinical use in the emergency department to exclude atrial thrombus prior to attempted electrical or pharmacological cardioversion. Further evidence from large studies would be desirable before implementation.

It is important to stress, however, that the coagulation system is activated following electric, but not pharmacologic cardioversion (Giansante *et al*, 2000). The risk of atrial thrombus formation and systemic embolism therefore persists even after reversion to sinus rhythm following electric cardioversion. As such, successful electric cardioversion following a negative D-dimer result would not avoid the need for anticoagulation with warfarin. European Society of Cardiology guidelines state that patients should be anticoagulated for 3–4 weeks post-procedure (Fuster *et al*, 2001).

► CLINICAL BOTTOM LINE

D-dimer is promising as an early marker of mural thrombus in atrial fibrillation and may be no less effective than either transoesophageal echocardiography or anticoagulation for 4 weeks. The evidence suggests that a negative result enables safe early cardioversion, although further evidence from large studies would be desirable.

Level of evidence

Level 2 – Studies considered were neither 1 or 3.

BET editor's comment

The authors identified a number of studies that were relevant to the three-part question but were in Japanese language. Although no translator was available, it was felt that excluding

these studies by limiting the search strategy to English language would ignore some important evidence. The abstracts have therefore been tabulated, although it should be recognised that there are significant limitations to appraising only the abstract of a study.

Li-Saw-Hee FL, Blann AD, Goldsmith I, *et al*. Indexes of hypercoagulability measured in peripheral blood reflect levels in intracardiac blood in patients with atrial fibrillation secondary to mitral stenosis *Am J Cardiol* 1999;**83**:1206–9.

Hwang JJ, Chen JJ, Lin SC, *et al*. Diagnostic accuracy of transoesophageal echocardiography for detecting left atrial thrombi in patients with rheumatic heart disease having undergone mitral valve operations *Am J Cardiol* 1993;**72**(9):677–781.

Hayashi I, Miyauchi T, Sakamoto K, *et al*. [Laboratory diagnosis of left atrial thrombi in patients with mitral stenosis] [Japanese] [Abstr] *J Cardiol* 1993;**23**(2):177–183.

Fuster V, Ryden LE, Asinger RW, *et al*. ACC/AHA/ESC Guidelines for the management of patients with atrial fibrillation: Executive summary. *Circulation* 2001;**104**:2118–50.

Giansante C, Fiotti N, Altamura N, *et al*. Coagulation indicators in patients with paroxysmal atrial fibrillation: Effects of electric and pharmacologic cardioversion *Am Heart J* 2000;**140**(3):423–9.

Stoddard MF, Dawkins PR, Prince CR, *et al*. Left atrial appendage thrombus is not uncommon in patients with acute atrial fibrillation and a recent embolic event: a transoesophageal echocardiographic study. *J Am Coll Cardiol* 1995;**25**:452–9.

Manning WJ, Silverman DI, Waksmonski CA, *et al*. Prevalence of residual left atrial thrombi among patients with acute thromboembolism and newly recognized atrial fibrillation *Arch Intern Med* 1995;**155**:2193–8.

Collins LJ, Silverman DI, Douglas PS, *et al*. Reduced thromboembolic complications with 4 weeks of precardioversion anticoagulation are related to atrial thrombus resolution *Circulation* 1995;**92**:160–3.

Sakurai K, Hirai T, Nakagawa K, *et al*. Left atrial appendage function and abnormal hypercoagulability in patients with atrial flutter *Chest* 2003;**124**:1670–5.

Yasaka M, Miyatake K, Mitani M, *et al*. Intracardiac mobile thrombus and D-dimer fragment of fibrin in patients with mitral stenosis *Br Heart J* 1991;**66**(1):22–5.

Hayashi I. [Laboratory diagnosis of left atrial thrombi in patients with mitral stenosis] [Japanese] [Abstr] *Fukuoka Igaku Zasshi - Fukuoka Acta Medica* 1991;**82**(11):550–61.

Black IW, Chesterman CN, Hopkins AP, *et al*. Haematologic correlates of left atrial spontaneous echo contrast and thromboembolism in nonvalvular atrial fibrillation *J Am Coll Cardiol* 1993;**21**(2):451–7.

Sakai M, Hamamatsu A, Kuboki K, *et al*. [Examinations to detect left atrial thrombus and blood coagulation test analyses in aged patients with atrial fibrillation] [Japanese] [Abstr] *Nippon Ronen Igakkai Zasshi - Japanese Journal of Geriatrics* 1994;**31**(6):447–55.

Kimura T, Yoshida S, Sato K, *et al*. [Relationship between left atrial spontaneous contrast echo and coagulofibrinolytic findings] [Japanese] [Abstr] *Rinsho Byori - Japanese Journal of Clinical Pathology* 1995;**43**(3):275–280.

Heppell RM, Berkin KE, McLenachan JM, *et al*. Haemostatic and haemodynamic abnormalities associated with left atrial thrombosis in non-rheumatic atrial fibrillation *Heart* 1997;**77**:407–11.

Nakajima K. [The relationship between left atrial thrombus and haematological markers in patients with chronic non-rheumatic atrial fibrillation] [Japanese] [Abstr] *Nippon Ronen Igakkai Zasshi - Japanese Journal of Geriatrics* 2000;**37**(11):903–7.

Nakagawa K, Hirai T, Shinokawa N, *et al*. Aortic spontaneous echocardiographic contrast and hemostatic markers in patients with nonrheumatic atrial fibrillation *Chest* 2002;**121**:500–5.

Somloi M, Tomcsanyi J, Nagy E, *et al*. D-dimer determination as a screening tool to exclude atrial thrombi in atrial fibrillation *Am J Cardiol* 2003;**92**:85–7.

Does clopidogrel increase morbidity and mortality after minor head injury

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A short cut review was carried out to establish whether patients who are on clopidogrel and suffer a minor head injury have an increase in morbidity and/or mortality. Four papers had some data relevant to the clinical question. The author, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses of these papers are tabulated. The clinical bottom line is that there is