Clinical Reviews

Journal Watch

J Wileman

Journals were reviewed between August and December 2010. The journals reviewed include: The lancet, Lancet Neurology, New England Journal of Medicine, British Medical Journal, Heart, Gut, Thorax, Circulation, Journal of the American Medical Association (JAMA), American Journal of Medicine, Archives of Internal Medicine, and Annals of Internal Medicine. The articles chosen are those which have particular relevance to Acute Physicians.

CT coronary angiography and exercise ECG in a population with chest pain and low-to-intermediate pre-test likelihood of coronary artery disease

Maffei E, *et al. Heart.* 2010 Dec 12;96(24):1973-79

This trial adds to existing data on patients with intermediate-to-high risk chest pain, demonstrating that CT-coronary angiography provides excellent diagnostic accuracy in the low-to-intermediate risk patients with chest pain that are typically seen through the AMU. In line with NICE guidelines, it emphasizes that exercise ECG testing is largely inappropriate in these patients. Concerns exist regarding radiation exposure, particularly in younger women, but with newer hardware and software this is expected to come down to more acceptable levels soon.

177 consecutive patients (88 men, 89 women, mean age 53.5 +/- 7.6 years) with chest pain and low-to-intermediate pre-test probabilities of Coronary Artery Disease (CAD) were retrospectively enrolled. All patients underwent exercise ECG, CT-Coroanary Angiography (CT-CA) and Invasive Coronary Angiography (ICA). A lumen diameter of >/= 50% was considered a significant stenosis on CT-CA, but a parallel analysis was also performed for a value of 70% stenosis or more,

ICA found an absence of significant stenosis in 85.3% of patients. CT-CA had a sensitivity, specificity, positive and negative predictive value of 100%, 98.7%, 92.9%, and 100% respectively, when compared to ICA. Exercise ECG had a sensitivity, specificity, positive and negative predictive value of 46.2%, 16.6%, 8.7%, and 64.1%. Agreement between exercise ECG and CT-CA was only 20.9%. With a higher cut-off of 70% stenosis or more, CT-CA scored similarly, whilst the negative predictive value of exercise ECG did moderately improve to 82.1%, although sensitivity remained low at 41.7%.

Implementation and outcome of thrombolysis with alteplase 3-4.5 hours after an acute stroke: an updated analysis from SITS-ISTR

Ahmed N, *et al. The Lancet Neurology*. 2010; 9(9):866-74

The SITS-ISTR observational study in October 2008 demonstrated the safety and safety of extending the thrombolysis window to 4.5 hours. This updated analysis demonstrates that the number of patients being thrombolysed in this time window has increased dramatically, with comparable outcomes to those thrombolysed earlier. Acute Physicians should be aware of this change in practice, but should continue to ensure that patients are treated as quickly as possible to achieve the best outcomes.

23,942 patients have been included in the SITS-ISTR registry between December 2002 and February 2010. Since publication of the observational study in October 2008, three times more patients have been treated between 3-4.5 hours (7% vs. 22%). The admission to treatment time is unchanged since then at a median of 65 minutes. 352 (2%) of the 21,204 treated within 3 hours had symptomatic intra-cerebral haemorrhage at 3 months, compared to 52 (2%) in the 3-4.5 hour group. 12% of each group had died by at 3-month follow-up. 57% of those treated within 3 hours were functionally independent at 3 months, compared to 60% of the 3-4.5 hour group.

Vertebroplasty versus conservative treatment in acute osteoporotic vertebral compression fractures: an open-labelled randomized trial

Klazen CAH, *et al. The Lancet.* 2010 Sept 25;376 (9746):1085-92

In patients with acute osteoporotic vertebral compression fractures and persistent pain, percutaneous vertebroplasty is

Dr Joe Wileman
SpR in Acute Medicine
Queen Alexandra Hospital
Cosham
Portsmouth
PO6 3LY
Email: joewileman@doctors. org.uk

effective and safe with immediate and sustained pain relief. Acute Physicians should consider referring patients for this if their pain is not controlled with conservative measures.

Between October 2005 and June 2008 researchers in Belgium randomized 202 patients to vertebroplasty or conservative treatment. Inclusion criteria were: age over 50, vertebral compression fracture on X-Ray, a minimum of 15% height loss, a level of T5 or lower, bone oedema on MRI, a history of ongoing back pain of six weeks duration or less. The primary outcome was pain relief at 1 and 12 months using the Visual Analogue Score (VAS). Of the 101 patients treated with vertebroplasty pain control was significantly improved. At 1 month the men VAS score was reduced by –5.2 in the vertebroplasty group, and by only –2.7 in the conservative group. At 1 year, the reduction from baseline was –5.7 in the vertebroplasty group and only –3.7 in the conservatively managed group. No complications or adverse events occurred in the vertebroplasty group.

Dabigatran compared with warfarin in patients with atrial fibrillation and previous TIA or stroke: a subgroup analysis of the RE-LY trial

Diener H-C, *et al. Lancet Neurology*. 2010 Dec;9(12):1157-63

The oral Thrombin inhibitor, Dabigatran, has been demonstrated to be non-inferior to warfarin for the primary prevention of stroke in AF in the RE-LY study. This sub-group analysis shows that in patients with AF and a previous TIA or stroke, Dabigatran is as effective as warfarin at lower dose and with less bleeding complications, and that at a higher dose is more effective than warfarin, with equivalent bleeding rates. This, together with its greater predictability and lack of need for laboratory monitoring, make it an attractive option for AF thrombo-prophylaxis. The cost implications of widespread use are likely to mean that initially only selected patients will receive this treatment, however.

Oral Rivaroxaban for symptomatic Venous Thromboembolism

Bauersachs R, *et al.* NEJM.org. 2010 Dec 4 (online 1st)

This study demonstrates that the oral Factor Xa inhibitor Rivaroxaban is as effective and safe as a combination of Enoxaparin and Warfarin for the treatment of Deep Venous Thrombosis (DVT). The removal of the need for initial parenteral enoxaparin and laboratory monitoring could dramatically simplify the treatment of DVTs and reduce the burden on DVT services. Whether this is cost effective remains to be established, however.

In this randomized, open-label study 3449 patients with acute DVT were randomized to either Rivaroxaban, or Enoxaparin together with a Vitamin K antagonist. The primary efficacy outcome was recurrent Venous Thromboembolism (VTE), and the primary safety outcome was 'major' bleeding and clinically significant 'non-major' bleeding. Rivaroxaban was shown to be non-inferior both in terms of efficacy (with an event rate of 2.1%, compared to 3.0% in the enoxaparin / Vitamin K antagonist group) and in terms of safety (with an event rate of 8.1% in both groups).

Double-dose versus standard-dose Clopidogrel and high-dose versus low-dose Aspirin in individuals undergoing Percutaneous Coronary Intervention for Acute Coronary Syndromes (CURRENT-OASIS 7): a randomized factorial trial

Mehta SR, *et al. The Lancet*. 2010 Oct; 376 (9748): 1233-43

In patients admitted with Acute Coronary Syndromes who are expected to go for early Percutaneous Coronary Intervention (PCI), 7 days of double-dose clopidogrel significantly reduced Cardio-Vascular events and the risk of subsequent stent thrombosis. Double dose aspirin offered no additional benefit. Admitting physicians should consider double-dose clopidogrel for all such patients.

In this randomized factorial trial, 25.086 patients were recruited from 597 centres in 39 countires. All had Acute Coronary Syndromes and were intended for an early PCI strategy. They were randomly assigned to either double-dose clopidogrel (600mg on day 1, then 150mg on days 2-7) or standard-dose clopidogrel (300mg on day 1, then 75mg on days 2-7) for 7 days. They were also randomly assigned to double-dose Aspirin (300-325mg daily) or standard dose Aspirin (75-100mg daily) for 7 days. The primary outcome measures were Cardio-Vascular deaths, Myocardial Infarction and Stroke at 30 days. Double-dose Clopidogrel significantly reduced the primary outcome from 392 events (4.5%) to 330 events (3.9%). It also reduced the incidence of stent thrombosis from 1.3% to 0.9%. The incidence of major bleeding increased from 1.1% to 1.6%. Double-dose Aspirin resulted in no difference in either the primary outcomes or the bleeding rates.

Clopidogrel with or without Omeprazole in coronary artery disease

Deepak L, *et al. NEJM*. 2010 Nov;363:1909-17

Concerns have been raised about Proton Pump Inhibitors (PPI), especially omeprazole, reducing the effect of clopidogrel and increasing cardiac events in patients with coronary artery disease. This trial appears to reassure physicians that this does not appear to be the case, although the median follow-up period was quite short at 106 days.

3873 patients on dual anti-platelet treatment (clopidogrel and aspirin) were randomly assigned to either omeprazole or placebo. The primary gastrointestinal end point was a composite of overt or occult bleeding, symptomatic gastro-duodenal ulcers or erosions, obstruction, or perforation. The primary cardiovascular end point was a composite of death from cardiovascular causes, nonfatal myocardial infarction, revascularization,

or stroke. The gastrointestinal event rate was reduced from 2.9 with placebo, to 1.1% with omeprazole. The cardiovascular event rate was similar in both group, 4.9% with omeprazole, and 5.7% with placebo, The trial was terminated prematurely when the sponsor lost financing.

Tricyclic antidepressants and headaches: Systematic review and meta-analysis

Jackson J, *et al. BMJ.* 2010 Oct;341:c5222

This study confirms that Tricyclic antidepressants are effective at treating both tension-type headaches and migraine, are more effective than Selective Serotonin Re-uptake Inhibitors (SSRIs), and become more effective over time. They produce more adverse effects than SSRIs, but these do not effect drop-out rates. Acute Physicians frequently see and treat such patients and should continue to use Tricyclics for this purpose. This study did not compare Tricyclics to therapies other than SSRIs, however.

37 studies were included in this meta-analysis. Studies included were of patients treated with Tricyclics only for a minimum of 4 weeks. Tricyclics were shown to significantly reduce the number of days with tension-type headache and the number of headache attacks from migraine, when compared to placebo (average standardised mean difference -1.29, 95% confidence interval -2.18 to -0.39 and -0.70, -0.93 to -0.48. Tricyclics were also more likely to reduce the intensity of headaches by at least 50% than either placebo (tension- type: relative risk 1.41, 95% confidence interval 1.02 to 1.89; migraine: 1.80, 1.24 to 2.62) or selective serotonin reuptake inhibitors (1.73, 1.34 to 2.22 and 1.72, 1.15 to 2.55). Tricyclics were more likely to cause adverse effects than placebo (1.53, 95% confidence interval 1.11 to 2.12) and selective serotonin reuptake inhibitors (2.22, 1.52 to 3.32), including dry mouth ($P<0.0005$ for both), drowsiness ($P<0.0005$ for both), and weight gain ($P<0.001$ for both), but did not increase dropout rates (placebo: 1.22, 0.83 to 1.80, selective serotonin reuptake inhibitors: 1.16, 0.81 to 2.97).