Table 2

Author, country, date	Patient group	Study type	Outcomes	Key results	Study weaknesses
West KM & Kalbfleisch JM 1971 USA	4262 subjects (including 50 known diabetics) in 10 countries	Prospective diagnostic study	+ve urine clinitest. DM diagnosed by blood glucose 2 h after glucose load	Sensitivity 35.3% (fasting) 38.9% (2–4 h after food) 67.0% (after 1 g/kg oral glucose) Specificity 99.7% (fasting) 97.6% (2–4 h after food) 94.4% (after oral glucose)	Diagnostic blood glucose lower than current WHO criteria False negative rate not extrapolated to whole population in sensitivity calculation Statistical significance/ 95% C.I. not assessed Subject selection not discussed
Davidson JK <i>et al</i> , 1978, USA	1952 patients aged 16–76 not known to have DM presenting to medical clinic	Prospective diagnostic study	+ve urine clinitest. DM diagnosed in 20 of 25 +ve patients by fasting glucose or OGTT. 25 normoglycosuric patients underwent OGTT	Sensitivity 74% Specificity 86% ($p < 0.05$)	Diagnostic blood glucose lower than current WHO criteria False negative rate not extrapolated to whole population in sensitivity calculation
Anderson DKG <i>et al</i> , 1992, Sweden	3201 patients aged 35–79 not known to have DM presenting to GP	Prospective diagnostic study	+ve re dia urine test. DM diagnosed by fasting glucose or OGTT. All patients 3 year follow up	Sensitivity 18.1% Specificity 99.1%	3 year follow up may overestimate false negatives Statistical significance/ 95% C.I. not assessed
Davies MJ <i>et al</i> , 1993, UK	442 consecutive patients aged 40–65 not known to be diabetic in larger postal study	Prospective diagnostic study	+ve urine test. All had OGTT	Sensitivity 44% Specificity 98%	Statistical significance/ 95% C.I. not assessed for sensitivity Selection criteria not clear
Friderichsen B & Maunsbach M, 1997, Denmark	1530 patients aged 45–76 responding to postal survey of 3041.	Prospective diagnostic study	+ve urine glukotest R. DM diagnosed by fasting blood glucose	Sensitivity 20.80% (95% C.I. 8.14–52.81%) Specificity 99.14% (95% 98.54–99.59%)	

NIDDM.mp.] AND [exp urine/OR urin\$.mp.] AND [exp test strip/OR exp glucosuria/OR stix.mp. OR glucostix.mp. OR stick.mp.] AND [screen\$.mp. OR diagnos\$] LIMIT to human and English Language

The Cochrane Library Issue 4 2005. Diabetes mellitus [MeSH] AND (Reagent strips [MeSH] OR reagent kits, diagnostic [MeSH] 20 hits

Outcome

178 papers found, of which 173 either did not answer the three part question or were review articles with no original data. The remaining five are shown below.

Comments

If the sensitivity of the first two studies are recalculated, extrapolating the documented prevalence of diabetes in each group to the patients who were considered true negative with no further tests, then the resultant sensitivities are 34.1% and 50.4% respectively. This is a reflection of the chances of finding glycosuria in a diabetic rather than the quality of urine dipsticks. Specificities are high, however low sensitivities preclude their use as a screening tool.

► CLINICAL BOTTOM LINE

Urine dipsticks are of insufficient sensitivity to be used as a screening tool in an asymptomatic population.

West KM, Kalbfleisch JM. Sensitivity and specificity of five screening tests for diabetes in ten countries. *Diabetes* 1971;**20**(5):289–96.

Davidson JK, Reuben D, Sternberg JC, *et al*. Diabetes screening using a quantitative urine glucose method. *Diabetes* 1978;**27**(8):810–6.

Andersson DK, Lundblad E, Svardudd K. A model for early diagnosis of type 2 diabetes mellitus in primary health care. *Diabetic Medicine* 1993;**10**(2):167–73.

Davies MJ, Williams DR, Metcalfe J, *et al*. Community screening for non-insulin-dependent diabetes mellitus: self-testing for post-prandial glycosuria. *Quarterly Journal of Medicine* 1993;**86**(10):677–84.

Friderichsen B, Maunsbach M. Glycosuric tests should not be employed in population screenings for NIDDM. *J Public Health Med* 1997;**19**(1):55–60.

Clopidogrel plus aspirin or aspirin alone in unstable angina

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A short cut review was carried out to establish whether clopidogrel and aspirin is better than aspirin alone in improving cardiovascular outcome in patients with unstable angina. 676 papers were found using the reported searches, of which two presented the best evidence to answer the clinical question. The author, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses of these best papers are tabulated. It is concluded that clopidogrel together with aspirin gives a better cardiovascular outcome than aspirin alone in patients with unstable angina.

Clinical scenario

A 55 year old man, known to have angina, presents to the Emergency Department with new-onset typical ischaemic rest pain that is not relieved by his nitrate spray at home. His ECG shows ST depression in V3–V6. He is haemodynamically stable. You treat him with oxygen, aspirin, nitrates, beta-blockers and heparin, after which he becomes pain free. You also give him clopidogrel 300 mg because you have heard that patients with unstable angina and non ST-elevation MI have a better cardiovascular outcome when treated with a

combination of clopidogrel and aspirin versus aspirin alone. You wonder whether there is any evidence to support this.

Three part question

In [patients suspected to have unstable angina] is [the use of clopidogrel plus aspirin better than aspirin alone] at [improving cardiovascular outcome]

Search strategy

Medline 1966–11/2005 using the OVID interface: [{unstable angina.mp. OR exp Angina, Unstable/ OR acute coronary syndrome.mp. OR non-ST elevation MI.mp. OR non-ST elevation infarction.mp. OR non-ST elevation myocardial infarction.mp OR ACS.mp.} AND {exp Platelet Aggregation Inhibitors/ OR exp Ticlopidine/ OR exp Adenosine Diphosphate/ OR clopidogrel.mp. OR adenosine 5'-diphosphate antagonist.mp. OR plavix.mp. OR Thienopyridines.mp.} AND {aspirin.mp. OR exp ASPIRIN/ OR ASA.mp. OR exp Aminosalicic Acids/}] LIMIT to Human AND English

The Cochrane Library Issue 4 2005: [Angina, Unstable {MeSH explode all trees} AND clopidogrel {All fields} OR Platelet Aggregation Inhibitors/TU {MeSH this term only, therapeutic use} OR adenosine NEXT diphosphate {All fields} OR Ticlopidine {MeSH explode all trees} AND Aspirin {MeSH explode all trees} OR Aminosalicic Acids/TU {MeSH explode all trees, therapeutic use}] (47 papers)

Embase 1980–2005 week 47: [{exp unstable angina pectoris/ OR unstable angina.mp. OR acute coronary syndrome.mp. OR non-ST elevation MI.mp. OR non-ST elevation infarction.mp. OR non-ST elevation myocardial infarction.mp.

OR ACS.mp. OR non-STEMI.mp.} AND {platelet aggregation inhibitor\$.mp. OR exp Ticlopidine/ OR exp Adenosine Diphosphate/ OR adenosine 5'-diphosphate antagonist.mp. OR plavix.mp. OR exp clopidogrel/ OR Thienopyridines.mp} AND { aspirin.mp. OR exp Acetylsalicic Acid/ OR exp Aminosalicic Acid Derivative/}] LIMIT to Human AND English and Clinical Queries "treatment – high specificity" (190 papers)

Search outcome

676/47/190 papers were identified. The CURE trial is the only RCT relevant to the question. It is also the only article in a systematic review which looked at the clinical and cost effectiveness of using clopidogrel in combination with aspirin in ACS.

Comments

To date only one randomised controlled trial has been conducted to compare the effects of clopidogrel and aspirin versus aspirin alone in non-ST elevation acute coronary syndromes. This large trial, which included 12,562 patients, yielded promising results. It appears that clopidogrel decreases the 12 month cardiovascular event rate. Interestingly, there was a significant reduction in the incidence of the second primary outcome by 24 hours after starting therapy and there was evidence of separation of the cumulative hazard rate curves within as early as a few hours. This has significant implications for Emergency Medicine, suggesting that clopidogrel loading should commence as soon as possible following presentation.

Table 3

Author, country, date	Patient group	Study type	Outcomes	Key results	Study weaknesses
CURE Trial Investigators 2001	12,562 patients presenting with chest pain within 24 hrs of onset of symptoms with either ECG changes consistent with ischaemia (but not ST-elevation) or raised serum cardiac enzymes to twice normal upper limit. Randomised to receive either clopidogrel (300 mg loading followed by 75 mg od) (n=6259) or placebo (n=6303) plus aspirin for 3–12 months.	Prospective, multi-centric placebo-controlled randomised trial	First primary composite outcome (CV death, MI or Stroke) Second primary outcome (CV death, MI, Stroke or Refractory ischaemia) All bleeding Major bleeding Minor bleeding Life-threatening bleeding Myocardial infarction Incidence of second primary outcome by 24 hours	9.3% clopidogrel v/s 11.4% placebo (p<0.001) RR 0.80 CI 0.72–0.92 16.5% clopidogrel v/s 18.8% placebo (p<0.001) RR 0.86 CI 0.79–0.94 8.5% clopidogrel v/s 5.0% placebo (p<0.001) RR 1.69 3.7% clopidogrel v/s 2.7% placebo (p<0.001) RR 1.38 5.1% clopidogrel v/s 2.4% placebo (p<0.001) RR 2.12 2.2% clopidogrel v/s 1.8% placebo (p=0.12). 5.2% clopidogrel v/s 6.7% placebo. RR 0.77 (0.67–0.89). 1.4% clopidogrel v/s 2.1% placebo. RR 0.66 (0.51–0.86). 4.1% v/s 5.7% (p<0.04) RR 0.71; CI 0.52–0.97, NNT 63 9.8% v/s 11.4% (p<0.03) RR 0.85 CI 0.74–0.98, NNT 63 15.9% v/s 20.7% (p<0.004) RR 0.73; CI 0.60–0.90, NNT 21	Patients were recruited from centres favouring conservativemanagement of ACS. In the initial study design patients over 60 years of age with no new ECG changes but a history of coronary artery disease were included. After recruiting the first 3000 patients, event rates were low (thus potentially rendering the trial underpowered) and this inclusion criteria was removed. Only patients with ECG changes or raised cardiac enzymes were treated, not all chest pain syndromes Retrospective subgroup analysis
Budaj A. <i>et al</i> , 2002, Poland.	Patients presenting with symptoms within 24 hrs of onset with either 1) ECG changes consistent with ischaemia (but not ST-elevation) or 2) raised serum cardiac enzymes or markers to twice the normal upper limit	Retrospective sub-group analysis of the CURE trial	Low - risk group (TIMI 0-2) primary outcome rates, RR and NNT (for 12 mths, mean 9 mths) Intermediate - risk group (TIMI 3-4) primary outcome rates, RR and NNT (for 12 mths, mean 9 mths) High-risk group (TIMI 5-7) primary outcome rates, RR and NNT (for 12 mths, mean 9 mths)		

Analysis of the data from the CURE trial reveals that the number needed to treat (NNT) with clopidogrel to prevent the first primary outcome is 47. The number needed to harm (NNH) with clopidogrel to cause one major haemorrhage is 99. This means that, for every 100 patients with non-ST elevation acute coronary syndrome treated for 3–12 months, clopidogrel will prevent two cardiovascular deaths, MI's or strokes while causing one major haemorrhage.

Subgroup analysis of the CURE trial demonstrates that patients who at high clinical risk (as judged by the TIMI risk score) gain particular benefit from clopidogrel therapy, although lower risk patients with non-ST elevation acute coronary syndromes may still stand to benefit. In low-risk patients, 16 patients would need to be treated (NNT) for 3–12 months to prevent one primary outcome, while treating 143 patients for the same period (NNH) would lead to one major haemorrhage. For intermediate-risk patients, NNT is 63 while NNH is 83. For high-risk patients, NNT is 21 while NNH is 100.

As such, if 1,000 patients in each category were treated, 16 low-risk patients would be saved from a primary outcome, while 7 would have a major haemorrhage. For intermediate-risk patients, 16 would be saved while 12 would have a major haemorrhage. For high-risk patients, 48 would be saved while 10 would have a major haemorrhage.

While the benefit of clopidogrel is maintained in all risk groups, the effect was most profound in the high-risk group. A careful risk-benefit consideration should be made before prescribing the drug for prolonged periods in low-risk patients.

► CLINICAL BOTTOM LINE

Clopidogrel should be given to patients with non-ST elevation acute coronary syndromes in the Emergency Department.

CURE investigators CURE Trial. *New England Journal of Medicine* 2001;**345**:494–502.

Budaj A, Yusuf S, Mehta SR, et al. Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) Trial Investigators Benefit of clopidogrel in patients with acute coronary syndromes without ST-segment elevation in various risk groups. *Circulation* 2002;**106**(13):1622–6.

Administration of steroids in acute exacerbations of COPD

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A short cut review was carried out to establish whether post discharge steroids are beneficial in acute exacerbations of COPD. 237 papers were found using the reported search, of which one presented the best evidence to answer the clinical question. The author, date and country of publication, patient group studied, study type, relevant outcomes, results and study weaknesses of this best paper are tabulated. It is concluded that post-discharge steroids are beneficial in the short term.

Table 4

Author, country, date	Patient group	Study type	Outcomes	Key results	Study weaknesses
Wood-Baker RR <i>et al</i> , 2005, Tasmania	All randomised controlled trials comparing oral or parenteral corticosteroids with a placebo in the treatment of acute exacerbations of COPD	Systematic review	Treatment Failure ie Relapse/Return to ED, Re-admission rates	7 studies; 805 patients; Steroids reduced the risk treatment failure: odds ratio 0.48; 95% CI 0.34 to 0.68. NNT 9.	The studies were not designed to look at mortality and therefore the follow up was not for a long period of time. The primary outcome was relapse rates and re-admission rates and mortality was secondary outcome measure
			Death	9 studies; 910 patients; no statistically significant difference, Odds Ratio 0.85; 95% CI 0.45 to 1.59.	
			FEV1 up to 72 hours	7 studies; 652 patients; weighted mean difference 140; 95% CI 80 to 200 ml	
			Arterial blood gas measurements (ABG)	2 studies 155 patients; improvements in pO ₂ at 72 hrs; Standardised Mean Difference 0.35 [0.03, 0.67]	
	A total of 921 participants were included in the nine studies contributing to the meta-analysis		Dyspnoea scores	2 studies showed diff at 72 hrs; 1 no diff. no data from remaining studies	
			Adverse drug effects (ADE)	7 studies; 650 patients; odds ratio 2.29; 95% confidence interval 1.55 to 3.38. Overall one extra adverse effect occurred for every 6 people treated (95% CI 4 to 10). The risk of hyperglycaemia was significantly increased, odds ratio 5.48; 95% confidence interval 1.58 to 18.96.	
			Adverse effect-hyperglycaemia Late FEV1 (litres)	3 studies; 313 patients; odds Ratio 5.48 [1.58, 18.96] 5 studies; 537 patients; Weighted Mean Difference 0.03 [–0.04, 0.10]	