Papers

Is hyperglycaemia an independent predictor of poor outcome after acute stroke? Results of a long term follow up study

Christopher J Weir, Gordon D Murray, Alexander G Dyker, Kennedy R Lees

Abstract

Objective: To determine whether raised plasma glucose concentration independently influences outcome after acute stroke or is a stress response reflecting increased stroke severity.
Design: Long term follow up study of patients admitted to an acute stroke unit.
Setting: Western Infirmary, Glasgow.
Subjects: 811 patients with acute stroke confirmed by computed tomography. Analysis was restricted to the 750 non-diabetic patients.
Main outcome measures: Survival time and placement three months after stroke.
Results: 645 patients (86%) had ischaemic stroke and 105 patients (14%) haemorrhagic stroke. Cox's proportional hazards modelling with stratification according to Oxfordshire Community Stroke Project categories identified increased age (relative hazard 1.36 per decade; 95% confidence interval 1.21 to 1.53), haemorrhagic stroke (relative hazard 1.67; 1.22 to 2.28), time to resolution of symptoms >72 hours (relative hazard 2.15; 1.15 to 4.05), and hyperglycaemia (relative hazard 1.87; 1.43 to 2.45) as predictors of mortality. The effect of glucose concentration on survival was greatest in the first month.
Conclusions: Plasma glucose concentration above 8 mmol/l after acute stroke predicts a poor prognosis after correcting for age, stroke severity, and stroke subtype. Raised plasma glucose concentration is therefore unlikely to be solely a stress response and should arguably be treated actively. A randomised trial is warranted.

Introduction

Diabetic patients have worse survival and recovery prospects after acute stroke than non-diabetic patients. In addition, hyperglycaemia in the acute phase of stroke has been established as a predictor of poor outcome in non-diabetic patients. There is dispute, however, whether a raised plasma glucose concentration is independently associated with a poor prognosis. Several studies have suggested that hyperglycaemia in non-diabetic patients after acute stroke is a stress response[1-8] reflecting more severe neurological damage. Others have suggested that hyperglycaemia influences outcome independently of stroke severity.[9-11] If the second was true we should need to investigate whether reversing hyperglycaemia in the acute phase of stroke influenced its adverse effect on survival.

We studied the effect of hyperglycaemia on stroke mortality and morbidity by assessing its effect on outcome after adjusting for known prognostic factors. We describe our findings in a cohort of unselected patients admitted to our acute stroke unit.

Patients and methods

The acute stroke unit serves a catchment population of 220 000. All patients who present within 72 hours of the onset of an acute neurological deficit with no known alternative to a vascular cause are admitted irrespective of age or the severity of the deficit. All patients have clinical data and results of investigations recorded prospectively. A diagnosis of ischaemic or haemorrhagic stroke is established by computed tomography. Magnetic resonance imaging is considered as an additional diagnostic tool, particularly in patients with suspected posterior circulation events. The aim is to complete all investigations within 72 hours of admission. All patients have their stroke subtype categorised on the basis of clinical features according to the Oxfordshire Community Stroke Project classification.[12] This classification divides patients into four groups: total anterior circulation syndrome, partial anterior circulation syndrome, posterior circulation syndrome, and lacunar syndrome.

Biochemical data are obtained routinely from all patients on the day of admission and early next morning. Plasma glucose concentration is measured on both occasions, giving one random and one fasting measurement. In this study we used the random glucose measurement for each patient if it was taken; if not we used the fasting measurement. Glucose concentration was recorded both as a continuous variable and as a binary variable (≤ 8 mmol/l, normoglycaemic; >8 mmol/l, hyperglycaemic). The upper limit of normal for a fasting plasma glucose concentration is 6.5 mmol/l. As not all glucose measurements in our study were taken fasting, 8 mmol/l was used as the cut point for hyperglycaemia. Other potential prognostic variables considered were age, stroke type (ischaemic

Acute Stroke Unit, University Department of Medicine and Therapeutics, Western Infirmary, Glasgow G11 6NT
Christopher J Weir, *MRC training fellow*
Alexander G Dyker, *lecturer in stroke medicine*
Kennedy R Lees, *clinical director, acute stroke unit*

Robertson Centre for Biostatistics, University of Glasgow, Glasgow G12 8QQ
Gordon D Murray, *reader in medical statistics*

Correspondence to: Mr Weir.

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Table 1 Comparison of diabetic and non-diabetic patients. Except where stated otherwise figures are numbers (percentages) of patients

	Diabetic (n=61)	Non-diabetic (n=750)
Median age (years)	69	70
Male sex	34 (56)	371 (49)
Median plasma glucose (mmol/l)†	11.1	6.5
Hyperglycaemia ‡	42 (69)	162 (22)
Smoker ‡	11 (18)	326 (43)
Median diastolic blood pressure (mm Hg)	90	90
Median systolic blood pressure (mm Hg)§	170	160
Haemorrhagic stroke	4 (7)	105 (14)
Symptoms resolved within 72 hours	7 (11)	92 (12)
Oxford classification:		
Total anterior circulation syndrome	12 (20)	173 (23)
Partial anterior circulation syndrome	22 (36)	259 (35)
Posterior circulation syndrome	4 (7)	78 (10)
Lacunar syndrome	21 (34)	217 (29)
Other	2 (3)	23 (3)

† P<0.0001 (Mann-Whitney test).
‡ P<0.0001 (χ^2 test).
§ P<0.05 (Mann-Whitney test).

or haemorrhagic), admission blood pressure (systolic and diastolic), smoking status (never smoker, former smoker, or current smoker), time to resolution of symptoms ($\leq$72 hours or $>$72 hours), and Oxfordshire Community Stroke Project category.

The patients in this study presented to our acute stroke unit between June 1990 and December 1993. Patients with previously diagnosed diabetes were included, but the data from these patients were analysed separately, as there is evidence that hyperglycaemia affects outcome differently in diabetic patients.[9]

Survival and placement follow up were by record linkage[13] to the Scottish deaths register and to a national database of hospital discharge records. The method of record linkage was validated in an epidemiological study of hypertension[14] and has been used for monitoring end points and adverse events in a large clinical trial.[15] Record linkage provides reliable patient follow up; however, admissions to private hospitals or institutions outside Scotland are not detected. Outcome placement was coded as alive at home, alive in care, or dead. This placement information was recorded two, three, six, and 12 months after admission.

Statistics

Baseline variables in diabetic and non-diabetic patients were compared by χ^2 tests for discrete variables and Mann-Whitney tests for continuous variables. Differences in the distributions of potential prognostic variables between placement categories at three months were assessed by χ^2 test for discrete variables and Kruskal-Wallis analysis of variance for continuous variables. The main analysis used Cox's proportional hazards regression model[16] to estimate the effect of hyperglycaemia on survival after stroke. A separate baseline survival function was fitted for each Oxfordshire Community Stroke Project category, as including the Oxford classification as an explanatory variable was unlikely to fulfil the proportional hazards assumption.

The effect of plasma glucose concentration was determined after entering other significant prognostic variables (selected from age, stroke type, time to resolution of symptoms, smoking status, and systolic and diastolic blood pressure). The assumption of proportional hazards was checked for all variables included in the model. The effect of hyperglycaemia on outcome was further explored by coding outcome at three months as good (alive at home) or poor (alive in care or dead) and then performing a stepwise logistic regression analysis.[17] We tested whether hyperglycaemia was independently associated with this outcome after adjusting as necessary for age, time to resolution of symptoms, stroke subtype, Oxford classification category, smoking status, and systolic and diastolic blood pressure. In the proportional hazards and logistic regression analysis a quadratic relation between blood pressure and outcome was permitted.

Results

A total of 811 patients with computed tomography confirmed acute stroke and plasma glucose data were studied. In 624 (77%) cases the plasma glucose concentration was measured on admission, and in 187 (23%) cases it was measured early next morning. The mean times to measurement of glucose concentration were 3.6 hours after admission to the unit and 14.4 hours after stroke onset. Sixty one (8%) patients were diabetic, seven (1%) being insulin dependent. Table 1 compares the characteristics of the diabetic and non-diabetic patients. As expected, the median plasma glucose concentration and proportion of patients with hyperglycaemia were higher in the diabetic group. Our main analysis was restricted to the 750 non-diabetic patients. Fifteen patients were lost to follow up for placement (owing to failure of hospital discharge record linkage) but not for survival. The mean follow up time was 1.65 years.

Table 2 shows the numbers of patients in each outcome category over time. Table 3 shows the distribution of patient variables across the three placement categories. Table 4 gives the results of proportional hazards modelling.

Hyperglycaemia led to higher mortality, even after adjusting for other prognostic variables. Increased systolic and diastolic blood pressure levels were not significant linear or quadratic predictors of poor survival and were not included in the final proportional hazards model. Similarly, smoking status did not predict survival and was excluded from the model. The assumption of proportional hazards held for all variables except plasma glucose concentration (continuous). This variable was therefore removed from the model and plasma glucose concentration considered as a binary variable. Figure 1 shows the Kaplan-Meier survival curves for patients in each Oxford classification category with and without hyperglycaemia.

Table 2 Numbers (percentages) of patients in each outcome category over time

	2 Months	3 Months	6 Months	12 Months
Alive at home	410 (56)	441 (60)	453 (62)	444 (60)
Alive in care	173 (24)	129 (18)	91 (12)	68 (9)
Dead	152 (21)	165 (22)	191 (26)	223 (30)

Fifteen patients were lost to follow up for placement

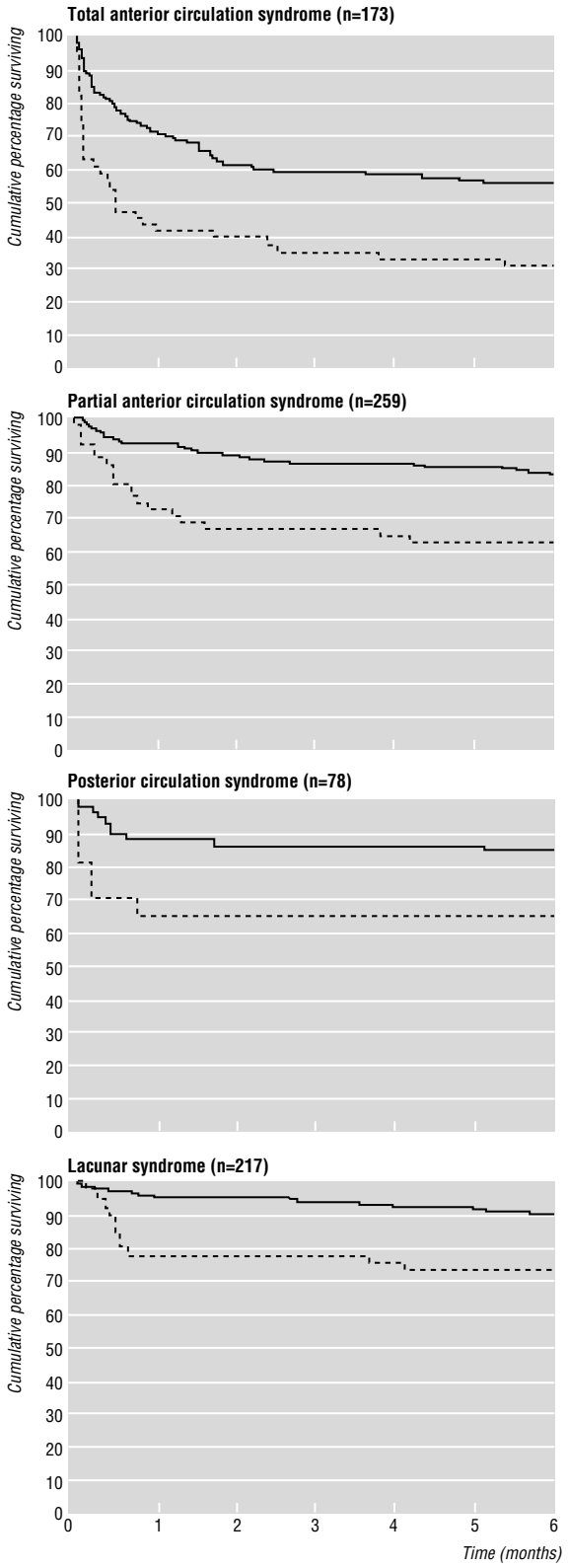

Fig 1 Kaplan-Meier survival curves for hyperglycaemic (broken line) and normoglycaemic (solid line) patients with each Oxford classification category of stroke

Hyperglycaemia also predicted poor outcome at three months. This variable significantly (P = 0.0003) improved prediction of outcome at three months (alive at home versus in care or dead) by logistic regression after adjusting for age, time to resolution of symptoms, stroke subtype, and Oxford classification category. Levels of systolic and diastolic blood pressure were not included in the logistic regression model, as they were neither linear nor quadratic predictors of outcome. Smoking status did not predict outcome and was excluded from the model.

Table 3 Distribution of variables with three month placement. Except where stated otherwise figures are numbers (percentages) of patients

	Alive at home (n=441)	Alive in care (n=129)	Dead (n=165)
Median age (years)†	68	75	72
Male sex‡	239 (54)	51 (40)	78 (47)
Median plasma glucose† (mmol/l)	6.2	6.7	7.3
Hyperglycaemia§	68 (15)	27 (21)	66 (40)
Smoker	206 (47)	50 (39)	63 (38)
Median diastolic blood pressure (mm Hg)	90	90	90
Median systolic blood pressure (mm Hg)	160	164	160
Haemorrhagic stroke§	36 (8)	21 (16)	45 (27)
Symptoms resolved within 72 hours§	82 (19)	4 (3)	5 (3)
Oxford classification§:			
Total anterior circulation syndrome	47 (11)	44 (35)	80 (50)
Partial anterior circulation syndrome	167 (39)	38 (31)	46 (29)
Posterior circulation syndrome	60 (14)	2 (2)	15 (9)
Lacunar syndrome	154 (36)	40 (32)	19 (12)

† Kruskal-Wallis analysis of variance for differences between outcome groups: P<0.001.
‡ χ^2 Test for differences between outcome groups: P<0.01.
§ χ^2 Test for differences between outcome groups: P<0.0001.

Table 4 Proportional hazards modelling of mortality

	Relative hazard	95% Confidence interval	P value
Hyperglycaemia	1.87	1.43 to 2.45	<0.0001
Increasing age (per decade)	1.36	1.21 to 1.53	<0.0001
Symptoms remaining after 72 hours	2.15	1.15 to 4.05	0.015
Haemorrhagic stroke	1.67	1.22 to 2.28	0.001

Discussion

Our results show that hyperglycaemia predicts higher mortality and morbidity after acute stroke independently of other adverse prognostic factors, such as older age, type and severity of stroke, and non-reversibility of the neurological deficit. The effect of hyperglycaemia on mortality is large. The estimated relative hazard of 1.87 was greater than that for haemorrhagic versus ischaemic stroke and equivalent to adding more than 20 years to a patient's age.

The results suggest that hyperglycaemia is not solely a stress response to neurological insult, as it predicts outcome after taking other prognostic factors into account. Indeed, the relative risk conferred by hyperglycaemia is greatest in patients with lacunar stroke. Previous studies which concluded that hyperglycaemia was a stress response, based on a correlation between stroke severity and plasma glucose concentration,[6 7] did not consider whether hyperglycaemia independently predicted outcome after adjusting for stroke severity. Van Kooten *et al* showed that noradrenaline concentrations were associated with stroke severity but could not find significant relations between catecholamine and plasma glucose concentration or between glucose concentration and stroke severity.[10] They concluded that raised plasma glucose concentration in non-diabetic stroke patients could not be explained by a stress response. Jorgensen *et al* showed a correlation between glucose concentration

Key messages

- A plasma glucose concentration above 8 mmol/l after acute stroke predicts poorer chances of survival and independence
- This effect of raised glucose concentration persists after adjusting for factors known to affect the outcome of stroke—namely, age, stroke type, and stroke severity
- A clinical trial of active control of plasma glucose concentration is warranted

and stroke severity but found that glucose concentration independently predicted outcome after adjusting for stroke severity.[9]

We sought to correct for the blood pressure on admission in our modelling of survival, as raised blood pressure after admission for stroke may be due to both the mental stress of hospitalisation[18 19] and the physical stress of the neurological damage. However, neither systolic nor diastolic blood pressure was associated with outcome. In addition, diastolic blood pressure was not significantly correlated with plasma glucose concentration (Spearman's rank correlation coefficient (r_s) 0.053; P = 0.0819) and systolic blood pressure was only weakly correlated with plasma glucose concentration ($r_s = 0.131$; P = 0.0003). This further indicates that raised plasma glucose concentration is not due to a stress response after acute stroke.

Duration of hyperglycaemia

Probably in many hyperglycaemic patients in our study the raised plasma glucose concentration was of long standing. Other workers investigated this by measuring haemoglobin A_{1c} concentration and inferred that raised values indicated a long prestroke history of hyperglycaemia.[2 3 9-11] Haemoglobin A_{1c} concentration is not routinely monitored in our unit, so we could not estimate the prevalence of previously undiagnosed diabetes.

The mechanism by which hyperglycaemia might influence stroke outcome is uncertain. Both acute and chronic hyperglycaemia are associated with increased oedema and infarct size[20] and with reduced cerebral blood flow and cerebrovascular reserve.[21] Ischaemia leads to a slowing of the oxidative glucose metabolism and an increase in anaerobic glycolysis. The concentration of lactic acid increases locally as a result. Hence intracellular pH is lowered and cells die or become dysfunctional.[22] Hyperglycaemia exacerbates these changes.[23 24] Experimental evidence suggests that hyperglycaemia may increase lactate production in two ways—either directly in severely ischaemic brains by increasing available glucose, or indirectly in the case of incomplete cerebral ischaemia by inhibiting mitochondrial respiration and glucose oxidation.[24] Such increased lactate production in the ischaemic penumbra may lead to poorer outcome. The above mechanisms may also cause a worse outcome in hyperglycaemic primary intracerebral haemorrhage, the excess lactate production occurring in the area of ischaemia around the site of the haemorrhage.

Our results suggest that a randomised trial of glucose control is warranted in patients with stroke complicated by hyperglycaemia. Randomisation should be soon enough after stroke onset to allow treatment during the "window of opportunity" for pharmacological intervention. Recent studies suggest that this time window lasts for up to three[25] or even 12[26] hours after stroke onset.

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1 O'Neill PA, Davies I, Fullerton KJ, Bennett D. Stress hormone and blood glucose response following acute stroke in the elderly. *Stroke* 1991;22:842-7.
2 Murros K, Fogelholm R, Kettunen S, Vuorela AL, Valve J. Blood glucose, glycosylated hemoglobin, and outcome of ischemic brain infarction. *J Neurol Sci* 1992;111:59-64.
3 Murros K, Fogelholm R, Kettunen S, Vuorela AL. Serum cortisol and outcome in ischemic brain infarction. *J Neurol Sci* 1993;116:12-7.
4 Woo J, Lam CWK, Kay R, Wong AHY, Teoh R, Nicholls MG. The influence of hyperglycemia and diabetes mellitus on immediate and 3-month morbidity and mortality after acute stroke. *Arch Neurol* 1990;47:1174-7.
5 Woo E, Chan YW, Yu YL, Huan CY. Admission glucose level in relation to mortality and morbidity outcome in 252 stroke patients. *Stroke* 1988;19:185-91.
6 Candelise L, Landi G, Orazio EN, Boccardi E. Prognostic significance of hyperglycemia in acute stroke. *Arch Neurol* 1985;42:661-3.
7 Melamed E. Reactive hyperglycemia in patients with acute stroke. *J Neurol Sci* 1976;29:267-75.
8 Toni D, Sacchetti ML, Argentino C, Gentile M, Cavalletti C, Frontoni M, *et al.* Does hyperglycemia play a role on the outcome of acute ischemic stroke patients? *J Neurol* 1992;239:382-6.
9 Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Stroke in patients with diabetes: the Copenhagen stroke study. *Stroke* 1994;25:1977-84.
10 van Kooten F, Hoogerbrugge N, Naarding P, Koudstaal PJ. Hyperglycemia in the acute phase of stroke is not caused by stress. *Stroke* 1993;24:1129-32.
11 Kiers L, Davis SM, Larkins R, Hopper J, Tress B, Rossiter SC, *et al.* Stroke topography and outcome in relation to hyperglycaemia and diabetes. *J Neurol Neurosurg Psychiatry* 1992;55:263-70.
12 Bamford JM, Sandercock PAG, Dennis MS, Burn J, Warlow CP. Classification and natural-history of clinically identifiable subtypes of cerebral infarction. *Lancet* 1991;337:1521-6.
13 Kendrick S, Clarke J. The Scottish record linkage system. *Health Bull (Edinb)* 1993;51:1-15.
14 Isles CG, Walker LM, Beevers GD, Brown I, Cameron HL, Clarke J, *et al.* Mortality in patients of the Glasgow blood pressure clinic. *J Hypertens* 1986;4:141-56.
15 West of Scotland Coronary Prevention Study Group. Computerised record linkage: compared with traditional patient follow-up methods in clinical trials and illustrated in a prospective epidemiological study. *J Clin Epidemiol* 1995;48:1441-52.
16 Cox DR. Regression models and life tables. *J R Stat Soc B* 1972;34:187-220.
17 Engelman L. Stepwise logistic regression. In: Dixon WJ, Brown MB, Engelman L, Jennrich RI, eds. *BMDP statistical software manual.* Berkeley: University of California Press, 1990:1013-46.
18 Carlberg B, Asplund K, Hagg E. Course of blood pressure in different subsets of patients after acute stroke. *Cerebrovasc Dis* 1991;1:281-7.
19 Carlberg B, Asplund K, Hagg E. Factors influencing admission blood pressure levels in patients with acute stroke. *Stroke* 1991;22:527-30.
20 Helgason CM. Blood glucose and stroke. *Stroke* 1988;19:1049-53.
21 De Chiara S, Mancini M, Vaccaro O, Riccardi G, Ferrara LA, Gallotta G, *et al.* Cerebrovascular reactivity by transcranial Doppler ultrasonography in insulin-dependent diabetic patients. *Cerebrovasc Dis* 1993;3:111-5.
22 Rehncrona S, Rosen I, Siesjo BK. Brain lactic acidosis and ischemic damage. I: Biochemistry and neurophysiology. *J Cereb Blood Flow Metab* 1981;1:297-311.
23 Chew W, Kucharczyk J, Moseley M, Derugin N, Norman D. Hyperglycemia augments ischemic brain injury: in vivo MR imaging/spectroscopic study with nicardipine in cats with occluded middle cerebral arteries. *Am J Neuroradiol* 1991;12:603-9.
24 Pulsinelli WA, Waldman S, Rawlinson D, Plum F. Moderate hyperglycemia augments ischemic brain damage: a neuropathologic study in the rat. *Neurology* 1982;32:1239-46.
25 National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;333:1581-7.
26 Mohr JP, Orgogozo JM, Harrison MJG, Hennerici M, Wahlgren NG, Gelmers JH, *et al.* Meta-analysis of oral nimodipine trials in acute ischaemic stroke. *Cerebrovasc Dis* 1994;4:197-203.

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Randomised comparison between adrenaline injection alone and adrenaline injection plus heat probe treatment for actively bleeding ulcers

Sydney S C Chung, James Y W Lau, Joseph J Y Sung, Angus C W Chan, C W Lai, Enders K W Ng, Francis K L Chan, M Y Yung, Arthur K C Li

Abstract

Objective: To compare endoscopic adrenaline injection alone and adrenaline injection plus heat probe for the treatment of actively bleeding peptic ulcers.
Design: Randomised prospective study of patients admitted with actively bleeding peptic ulcers.
Setting: One university hospital.
Subjects: 276 patients with actively bleeding ulcers detected by endoscopy within 24 hours of admission: 136 patients were randomised to endoscopic adrenaline injection alone and 140 to adrenaline injection plus heat probe treatment.
Main outcome measures: Initial endoscopic haemostasis; clinical rebleeding; requirement for operation; requirement for blood transfusion; hospital stay, ulcer healing at four weeks; and mortality in hospital.
Results: Initial haemostasis was achieved in 131/134 patients (98%) who received adrenaline injection alone and 135/136 patients (99%) who received additional heat probe treatment (P = 0.33). Outcome as measured by clinical rebleeding (12 *v* 5), requirement for emergency operation (14 *v* 8), blood transfusion (2 *v* 3 units), hospital stay (4 *v* 4 days), ulcer healing at four weeks (79.1% *v* 74%), and in hospital mortality (7 *v* 8) were not significantly different in the two groups. In the subgroup of patients with spurting haemorrhage 8/27 (29.6%; 14.5% to 50.3%) patients from the adrenaline injection alone group and 2/31 (6.5%; 1.1% to 22.9%) patients from the dual treatment group required operative intervention. The relative risk of this was lower in the dual treatment group (0.17; 0.03 to 0.87). Hospital stay was significantly shorter in the dual treatment group than the adrenaline injection alone group (4 *v* 6 days, P = 0.01).
Conclusion: The addition of heat probe treatment after endoscopic adrenaline injection confers an advantage in ulcers with spurting haemorrhage.

Introduction

A decade ago surgery was the only effective method of controlling bleeding ulcers. With the advent of effective means of endoscopic haemostasis, endoscopic treatment has emerged as the first line treatment of ulcer haemorrhage. Many methods, such as laser, contact thermal probes, or injection therapy, have been proved to be clinically useful.[1-10] Which one of these methods is superior remains controversial.

Contact thermal probes use the principle of captive coagulation: the vessel wall is pressed together by the probe before the probe is activated. The vessel is sealed by a combination of pressure and heat. Heat probe treatment has been shown to improve clinical outcome in patients with actively bleeding ulcers and high risk stigmata. For optimum effect, the larger (10 French gauge, 3.2 mm) probe has to be used. A larger, less manoeuvrable therapeutic endoscope with a 3.7 mm instrument channel is therefore required. The successful application of a heat probe also demands accurate targeting and firm tamponade of the bleeding vessel. In the presence of flowing blood this is not always possible.

We have previously compared heat probe treatment with adrenaline injection in the treatment of actively bleeding ulcers.[11] The success in stopping active bleeding at the time of endoscopy was lower with the heat probe compared with adrenaline injection (83% *v* 96%). Adrenaline injection is highly effective in stopping active ulcer bleeding. In our previous studies with this technique the success rate in stopping active bleeding ranged from 93% to 100%.[7 11-13] Adrenaline, however, does not induce permanent thrombosis in blood vessels. About 13% to 20% of patients develop further bleeding, which often results in emergency surgery. We attempted to improve the results by the additional injection of a sclerosant. Neither the additional injection of 3% sodium tetradecyl sulphate nor absolute alcohol reduced the incidence of rebleeding.[12 13] The dual treatment of adrenaline injection followed by heat probe application was therefore theoretically appealing. Active bleeding is first controlled by injection so that the eroded vessel can be clearly seen, allowing accurate placement of the heat probe. Cessation of active bleeding also means that heat energy delivered by the probe is not carried away by the flowing blood.

We report the results of a randomised prospective trial that compared adrenaline injection alone with adrenaline injection followed by heat probe treatment in actively bleeding ulcers. We examined whether the dual treatment improves permanent haemostasis and would therefore reduce mortality in patients actively bleeding from peptic ulcers.

Patients and methods

The Prince of Wales Hospital in Hong Kong is a teaching hospital serving a population of about 1.2 million. Patients admitted with acute upper gastrointestinal bleeding underwent endoscopy within 24 hours of admission. Patients with fresh haematemesis and those who were haemodynamically unstable underwent endoscopy after initial resuscitation. In all patients informed consent was obtained for possible endoscopic haemostasis. Gastric lavage was used only if a good view of the bleeding point could not be obtained, in which case an overtube was passed. Blood covering

Department of Surgery, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, New Territories, Hong Kong
Sydney S C Chung, *professor*
James Y W Lau, *senior medical officer*
Angus C W Chan, *lecturer*
Enders K W Ng, *senior medical officer*
M Y Yung, *research assistant*
Arthur K C Li, *chairman and professor*

Department of Medicine, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, New Territories, Hong Kong
Joseph J Y Sung, *reader*
C W Lai, *senior medical officer*
Francis K L Chan, *senior medical officer*

Correspondence to: Dr Li.

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Table 1 Demographic data of patients with actively bleeding peptic ulcers according to treatment

Detail	Adrenaline injection alone	Adrenaline injection plus heat probe
No of patients	136	140
No of patients excluded	2	4
Mean (range) age (years)	58.8 (21-92)	58.2 (19-95)
No of men	98	89
Location of ulcer:		
Duodenum	92	84
Gastric mucosa	39	48
Stoma	3	4
Haemoglobin < 100 g/l on admission	77	77
No with shock (systolic blood pressure < 90 mm Hg)	38	29
Bleeding:		
Spurting	27	31
Oozing	107	105
No with relevant medical illnesses	62	64
No who used non-steroid anti-inflammatory drugs	37	33

the ulcer was washed away with a "Waterpik."[14] Patients with actively bleeding ulcers (spurting or oozing haemorrhage) identified at the time of endoscopy were recruited into the present study. Patients with non-bleeding visible vessels, adherent blood clots, clean based ulcers, or ulcers with contact bleeding only were excluded.

Approval was obtained from the local ethics committee before we started the trial. Patients were then randomised to receive either adrenaline injection alone or adrenaline injection followed by heat probe treatment. Randomisations took place at the time of endoscopy when actively bleeding ulcers were seen. The endoscopy nurse then opened a sealed envelope containing the treatment option, which had previously been determined by a random number list generated by a computer. Treatment was concealed from the endoscopist when the patient was admitted into the trial.

Adrenaline in 1:10 000 dilution was injected in 0.5-1 ml aliquots into and around the bleeding point until the bleeding was controlled. The group randomised to dual treatment received additional captive coagulation with an Olympus heat probe unit (Olympus Optical, Tokyo). The 10 French gauge heat probe (Olympus CD-1OZ) was used to tamponade the bleeding point firmly for three pulses of 30 J at any one site. The end point of treatment with the heat probe was defined as flattening or cavitation of the bleeding point. If a regular diagnostic endoscope was used initially, a dual channel therapeutic endoscope (2T-10 or 2T-200; Olympus, Japan) was used for the heat probe treatment usually after the initial control of bleeding by adrenaline injection.

The patients were returned to the surgical gastroenterology ward after treatment. They were managed by surgeons blind to the treatment option. Blood transfusion was given to maintain the haemoglobin concentration at around 100 g/l. All patients underwent endoscopy 24 hours later, and a further injection of adrenaline alone was given if active bleeding was again seen. Heat probes were not used at the second endoscopy because of the risk of perforation.[11] Criteria for emergency surgery were drawn up and strictly adhered to. These were arterial bleeding not controlled at the time of endoscopy; clinical rebleeding defined as fresh haematemesis or melaena associated with tachycardia (pulse rate >110 beats/min) or hypotension (systolic blood pressure $<$ 90 mm Hg); or total transfusion exceeding 8 units of blood to maintain a haemoglobin concentration of around 100 g/l. Histamine receptor antagonists, omeprazole, or triple treatment for eradication of *Helicobacter pylori* were given on discharge, and endoscopy was carried out four weeks later to assess ulcer healing. At follow up endoscopy, endoscopists were blind to the initial treatment option.

The outcome assessments (decided a priori) compared between the two treatment groups were initial endoscopic haemostasis, rebleeding, requirement for surgery, requirement for blood transfusion, length of hospital stay, and mortality in hospital.

From our previous trials, rebleeding after adrenaline injection alone varied between 15% and 20%. No such data existed for the dual treatment of adrenaline injection plus heat probe treatment. If we assumed a rate of rebleeding of 5-10%, a sample size between 176 and 438 would be required to achieve a statistical power of 80% at 5% type I error. An interim analysis at around 220 enrollments was planned, and significance was taken at 3% type I error. We used Student's t test for comparisons of continuous variables, two tailed Pearson's χ^2 test or Fisher's exact test for comparisons of categorical variables, and non-parametric Mann-Whitney U test for comparisons of requirements for blood transfusions and length of hospital stay.

Results

Between 1 September 1992 and 7 June 1994 a total of 3558 patients were admitted to the Prince of Wales Hospital with upper gastrointestinal bleeding; 2170 were bleeding from peptic ulcers. Among them, 303 patients were actively bleeding at the time of endoscopy. Twenty seven patients were not randomised; in three the source of bleeding could not be identified because of torrential bleeding, and one patient was not cooperative at time of endoscopy. Heat probe treatment was not possible in 23 patients because the probe unit was out of order from 24 November 1992 to 1 January 1993. A total of 276 patients were recruited into the study. They were randomised to receive either endoscopic injection of adrenaline alone (136) or adrenaline injection plus heat probe treatment (140). Six patients were excluded after randomisation (2 v 4) as their ulcers were subsequently found to be malignant. The two groups were matched in patients' characteristics and severity of bleeding (table 1). There were no significant differences in the age and sex distribution and the proportion of duodenal, gastric, and anastomotic ulcers.

Initial success in endoscopic haemostasis was comparable in the two groups (98% v 99%; odds ratio 3.09; 95% confidence interval 0.32 to 30.12). Primary haemostasis was not possible in three patients from the adrenaline injection alone group and one patient from the dual treatment group. These four patients went directly to surgery, and one subsequently died. At the second endoscopy 13 from the adrenaline injection alone group and nine from the dual treatment group required further treatment for endoscopic rebleeding.

Two patients from the injection alone group and one patient from the dual treatment group went directly to surgery as bleeding could not be controlled endoscopically. Further treatments with adrenaline alone were successful in the remaining patients.

In the entire group 12 (9.0%; 4.2% to 13.8%) from the adrenaline injection alone group and five (3.7%; 1.4% to 8.8%) from the dual treatment group had clinical evidence of rebleeding (odds ratio 0.39; 0.13 to 1.13). The difference, however, was not significant. Emergency operations were performed in 14 patients (10.4%; 5.2% to 15.6%) in the adrenaline injection alone group and eight (5.9%; 2.8% to 11.7%) in the dual treatment group (0.54; 0.22 to 1.32). The total number of blood transfusions, length of hospital stay, ulcer healing at four weeks, and mortality in hospital were not significantly different in either group (table 2).

In patients with spurting haemorrhage (table 3) six (22.2%; 9.4% to 42.7%) assigned to adrenaline injection alone rebled clinically with circulatory instability or fresh haematemesis whereas only two (6.5%; 1.1% to 22.9%) from the dual treatment group rebled (0.02; 0.05 to 1.33). Eight patients (29.6%; 14.5% to 50.3%) from the adrenaline injection alone group underwent surgery: six for clinical rebleeding and two because they required more than 8 units of blood. In the dual treatment group two (6.5%; 1.1% to 22.9%) with clinical rebleeding needed surgery. The relative risk of the need for operation was lower in the dual treatment group (0.17; 0.03 to 0.87). Length of hospital stay in the dual treatment group was significantly shorter than that in the injection alone group (4 *v* 6 days; P = 0.01, Mann-Whitney U test). Requirement for blood transfusion in the dual treatment group was arithmetically less than that in the injection alone group, although this did not reach significance (median 4 *v* 5 units; P = 0.06, Mann-Whitney U test).

In patients with oozing haemorrhage no difference between two groups was observed in their clinical outcome (table 4). There were two perforations related to the heat probe in the dual treatment group. No complications related to treatment were seen in the adrenaline alone group.

Only 91/134 patients (67.9%) from the adrenaline injection alone group and 96/136 patients (70.6%) from the dual treatment group returned for follow up endoscopy at four week. Ulcer healing was documented in 72/91 patients (79.1%) in the adrenaline injection alone group and 71/96 patients (74%) in the dual treatment group (P = 0.41, Pearson's χ^2 test). When we had enrolled 220 patients we carried out an interim analysis while we continued to randomise eligible patients. As an entire group the difference in outcome between two treatment groups was small. In the subgroup of patients with spurting haemorrhage the observed difference between the two treatment groups in their requirement for operation was associated with a statistical power of 27%. We estimated that we would need a sample size of 180 and a further four years of recruitment to achieve a statistical power of 80% at 5% type I error. As it was unlikely that we could continue for such a period we terminated the trial with the enrollment number at 276 and conducted a final analysis.

Table 2 Assessment of outcome according to treatment. Figures are numbers (percentages) of patients unless stated otherwise

Detail	Adrenaline injection alone	Adrenaline injection plus heat probe	P value
No of patients	134	136	
Initial success	131 (97.8)	135 (99)	0.33
Clinical rebleeding	12 (9.0)	5 (3.7)	0.08
Emergency operations	14 (10.4)	8 (5.9)*	0.17
Median (range) transfusion (units)	2 (0-18)	3 (0-29)	0.93
Median (range) hospital stay (days)	4 (0-34)	4 (1-59)	0.52
Ulcer healing at four weeks	72/91 (79.1)	71/96 (74)	0.41
Mortality in hospital	7 (5.2)	8 (5.9)	0.81
Perforations	0	2 (1.5)	0.50

* Two patients were operated on for perforations related to heat probe.

Table 3 Assessment of outcome for spurting haemorrhage according to treatment. Figures are numbers (percentages) of patients unless stated otherwise

Detail	Adrenaline injection alone	Adrenaline injection plus heat probe	P value
No of patients	28	32	
No of patients excluded	1	1	
Initial success	25 (92.6%)	31 (100%)	0.27
Clinical rebleeding	6 (22.2%)	2 (6.5%)	0.10
Emergency operation	8 (29.6%)	2 (6.5%)	0.03
Median (range) transfusion (units)	5 (0-16)	4 (0-11)	0.06
Median (range) hospital stay (days)	6 (3-33)	4 (1-23)	0.01

Table 4 Assessment of outcome for oozing haemorrhage according to treatment. Figures are number (percentages) of patients unless stated otherwise

Detail	Adrenaline injection alone	Adrenaline injection plus heat probe	P value
No of patients	108	108	
No of patients excluded	1	3	
Initial success	106 (99)	104 (99)	0.42
Clinical rebleeding	6 (5.6)	3 (2.9)	0.32
Emergency operation	6 (5.6)	6 (5.7)*	1.00
Median (range) transfusion (units)	2 (0-18)	3 (0-29)	0.59
Median (range) hospital stay (days)	4 (0-34)	4 (1-59)	0.81

* Two patients were operated on for perforations related to heat probe.

Discussion

In recent years many randomised clinical trials on the endoscopic treatment of bleeding ulcers have been reported.[1-3 5-8 10] Most trials that compared endoscopic treatment against standard medical treatment reported improvement in patient outcome as measured by reduced blood transfusion, decreased requirement for surgical intervention, and reduced length of hospital stay. An impact on mortality is more difficult to show as mortality in patients with bleeding ulcers is less than 10% in most series and the number of patients in individual trials is small. Recent meta-analyses, however, showed reduction in mortality with endoscopic haemostasis.[15 16] As differences in efficacy among different endoscopic devices are likely to be small, comparative studies of different endoscopic treatments have in general failed to show any superiority of one technique over another.[11 17-19]

Inclusion of patients at high risk

In up to 80% of patients with bleeding ulcers bleeding stops spontaneously. Endoscopic treatment should be targeted to those who are at high risk of developing further bleeding. In conducting clinical trials on endoscopic ulcer haemostasis, it is important to include only

patients at high risks of recurrent haemorrhage so that significant results in high risks groups are not overshadowed by patients who are unlikely to rebleed.[20] The National Institutes of Health consensus conference recommended that only ulcers with active bleeding or visible vessels should be treated endoscopically.[21] Recent evidence indicates that patients with ulcers with an adherent clot may also constitute a high risk group.[22] The endoscopic diagnosis of stigmata of recent haemorrhage, however, depends on the observer. The agreement between observers in the interpretation of visible vessels is poor even among international experts with interests in endoscopic ulcer haemostasis.[23] For this reason, we included only patients with actively bleeding ulcers in the present study.

Attempts at improving permanent haemostasis

We have successfully used adrenaline injection for over 10 years in patients with actively bleeding peptic ulcers. Haemostasis can be achieved in most cases. Considerable rebleeding that required surgical intervention occurred in 15% of patients. From a technical stand point dual treatment with adrenaline injection followed by heat probe treatment is attractive. The spurting haemorrhage is first controlled by injection, which does not need to be accurately targeted as injection close to the bleeding point will suffice to control bleeding. As submucosally injected adrenaline does not damage tissue or have appreciable systemic effects, large volumes can be used without fear of complications.[24] Once the active bleeding is controlled the heat probe can be targeted on to the bleeding vessel to apply firm tamponade and captive coagulation. In our previous study that compared adrenaline injection with heat probe treatment the control of active haemorrhage was inferior with the heat probe principally because of problems of accurate placement of the probe in ulcers with active bleeding. Rutgeerts *et al* showed that the combined use of adrenaline injection and photocoagulation by neodymium: yttrium-aluminium-garnet laser was more effective than adrenaline injection alone in achieving permanent haemostasis.[25] A subsequent randomised trial confirmed that the additional laser treatment provided a marginal improvement in primary haemostasis.[26] Although the additional injection of a sclerosant shares the same theoretical appeal, we have been unable to show that the additional injection of either sodium tetradecyl sulphate[12] or absolute alcohol[13] confers any advantage in improving permanent haemostasis.

Combining injection and contact thermocoagulation

As in our previous studies, practically all active bleeding was controlled by adrenaline injection at the time of endoscopy.[4 7 11-13] As an entire group, although there was a trend favouring dual treatment, clinical outcomes in the two groups were not significantly different. When we analysed data for patients with arterial spurting and non-pulsatile oozing separately, however, significant differences were apparent. In patients with arterial spurting the need for emergency surgery decreased from 29.6% to 6.5% in the dual treatment group. The length of stay in hospital was also significantly reduced ($P = 0.01$). In the non-pulsatile group (table 4), however, the clinical outcomes were identical in the two treatment arms.

Key messages

- Endoscopic injection of adrenaline alone is effective in stopping bleeding peptic ulcers
- Further bleeding after adrenaline injection alone, however, occurs in 15-20% of patients, and the addition of heat probe thermocoagulation may improve permanent haemostasis and therefore patient outcome
- When compared with adrenaline injection alone the dual treatment significantly reduced the requirement for operative intervention and the length of hospital stay in the subgroup of patients with spurting ulcer haemorrhage
- In the endoscopic treatment of spurting ulcer haemorrhage heat probe thermocoagulation should be added after adrenaline injection

Arterial spurting at the time of endoscopy is a grave prognostic sign. In one of our previous studies seven out of 10 patients with arterial spurting required emergency surgery if no endoscopic treatment was carried out.[7] Although adrenaline injection is highly effective in controlling active bleeding even in spurting haemorrhage, it does not induce permanent vessel thrombosis. The exact mechanism of action is probably a combination of vasoconstriction, tissue tamponade, and platelet aggregation.[27-29] A thrombus then seals the vent in the eroded artery. In ulcers in which a large vessel is eroded rebleeding may occur when the thrombus dislodges. Our results indicate that captive coagulation of the bleeding vessel, even after haemostasis by adrenaline injection, reduces further bleeding and the requirement for an operation in patients presenting with arterial spurters. Compared with ulcers with arterial spurting, ulcers with non-pulsatile oozing are probably bleeding from smaller blood vessels. The chance of dislodgment of the clot and recurrent haemorrhage is therefore smaller, and the advantage of additional captive coagulation not apparent. Ulcers with oozing haemorrhage constitute a heterogenous group. Steele proposes that oozing should be further classified into oozing without a visible vessel, oozing with a visible vessel, and oozing under an adherent clot (personal communication).

We conclude that in the endoscopic treatment of ulcers with spurting haemorrhage the addition of heat probe thermocoagulation to adrenaline injection seems to reduce rebleeding and the need for subsequent emergency surgery and should be carried out even if bleeding is initially controlled by adrenaline injection.

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1 Swain CP, Kirkham JS, Salmon PR, Bown SG, Northfield TC. Controlled trial of Nd-YAG laser photocoagulation in bleeding peptic ulcers. *Lancet* 1986;i:1113-7.
2 O'Brien JD, Day SJ, Burnham WR. Controlled trial of small bipolar probe in bleeding peptic ulcers. *Lancet* 1986;i:464-7.
3 Krejs GJ, Little KH, Westergaard H, Hamilton JK, Spady DK, Polter DE. Laser photocoagulation for the treatment of acute peptic ulcer bleeding: a randomised controlled clinical trial. *N Engl J Med* 1987;316:1618-21.

4 Leung JWC, Chung SCS. Endoscopic injection of adrenaline in bleeding peptic ulcers. *Gastrointest Endosc* 1987;33:73-5.
5 Panes J. Viver J. Forne M, Garcia-Olivares E, Marco D, Garau J. Controlled trial of endoscopic sclerosis in bleeding peptic ulcers. *Lancet* 1987;ii:1292-4.
6 Laine L. Multipolar electrocoagulation in the treatment of active upper gastrointestinal tract hemorrhage: a prospective controlled trial. *N Engl J Med* 1987;316:1613-7.
7 Chung SCS, Leung JWC, Steele RJC, Crofts TJ, Li AKC. Endoscopic injection of adrenaline for actively bleeding ulcers: a randomised trial. *BMJ* 1988;296:1631-3.
8 Balanzo J, Sainz S, Such J, Espinos JC, Guarner C, Cusso Y, *et al.* Endoscopic haemostasis by local injection of adrenaline and polidocanol in bleeding ulcer: a prospective randomised trial. *Endoscopy* 1988;20:289-91.
9 Steele RJC, Park KG, Croft TJ. Adrenaline injection for endoscopic haemostasis in non-variceal upper gastrointestinal haemorrhage. *Br J Surg* 1991;78:477-9.
10 Fullarton GM, Birnie GG, Macdonald A, Murray WR. Controlled trial of heat probe treatment in bleeding peptic ulcers. *Br J Surg* 1989;76:541-4.
11 Chung SCS, Leung JWC, Sung JY, Lo KK, Li AKC. Injection or heat probe for bleeding ulcer. *Gastroenterology* 1991;100:33-7.
12 Chung SCS, Leung JWC, Leong HT, Lo KK, Li AKC. Adding a sclerosant to endoscopic adrenaline injection in actively bleeding ulcers: a randomised trial. *Gastrointest Endosc* 1993;39:611-5.
13 Chung SCS, Leong HT, Chan ACW, Lau JYW, Yung MY, Leung JWC, *et al.* Epinephrine or epinephrine plus alcohol for injection of bleeding ulcers: a prospective randomised trial. *Gastrointest Endosc* 1996;43:591-5.
14 Chung SCS, Leung JWC. Improving the view at emergency endoscopy. *Endoscopy* 1987;19:47.
15 Sacks HS, Chalmers TC, Blum AL, Berrier J. Pagano D. Endoscopic hemostasis: an effective therapy for bleeding peptic ulcers. *JAMA* 1990;264:494-9.
16 Cook DJ, Guyatt GH, Salena BJ, Laine LA. Endoscopic therapy for acute nonvariceal upper gastrointestinal hemorrhage: a meta-analysis. *Gastroenterology* 1992;102:139-48.
17 Matthewson K, Swain CP, Bland M, Kirkham JS, Bown SG, Northfield TC. Randomised comparison of Nd YAG laser, heat probe, and no endoscopic therapy for bleeding peptic ulcers. *Gastroenterology* 1990;98:1239-44.
18 Waring JP, Sanowski RA, Sawyer RL, Woods CA, Foutch PG. A randomised comparison of multipolar electrocoagulation and injection slerosis for the treatment of bleeding peptic ulcer. *Gastrointest Endosc* 1991;37:295-8.
19 Laine L. Multipolar electrocoagulation vs injection therapy in the treatment of bleeding peptic ulcers: a prospective, randomised trial. *Gastroenterology* 1990;99:1303-6.
20 Tedesco FJ. Thoughts and experiences in design and implementation of a trial of therapeutic endoscopy in upper gastrointestinal hemorrhage. *Dig Dis Sci* 1981;26:102-4.
21 NIH Consensus Conference. Therapeutic endoscopy and bleeding ulcers. *JAMA* 1989;262:1369-72.
22 Ulrich CD, Gostout CJ, Balm RK. Prognostic importance of the densely adherent clot in bleeding ulcer disease (PUD). A 4 year retrospective review of the Mayo clinic experience. *Gastrointest Endosc* 1994;40:89. (Abstract.)
23 Lau JYW, Sung JY, Lau JTF, Chan ACW, Ng EKW, Chung SCS. Stigmata of recent hemorrhage in peptic ulcer bleeding: is there interobserver agreement among international experts? *Gastrointest Endosc* 1995;41:368. (Abstract.)
24 Sung JY, Chung SCS, Low JM, Cocks R, Ip SM, Tan P, *et al.* Systemic absorption of adrenaline after endoscopic submucosal injection in patients with bleeding peptic ulcers. *Gastrointest Endosc* 1993;39:20-2.
25 Rutgeerts P, Vantrappen G, Broeckaert L, Coremans G, Janssens J, Hiele M. Comparison of endoscopic polidocanol injection and YAG laser therapy for bleeding peptic ulcers. *Lancet* 1989;i:1164-7.
26 Loizou LA, Bown SG. Endoscopic treatment for bleeding peptic ulcers: randomised comparison of adrenaline injection and adrenaline injection + Nd:YAG laser photocoagulation. *Gut* 1991;32:1100-3.
27 Chung SCS, Leung FW, Leung JWC. Is vasoconstriction the mechanism of hemostasis in bleeding ulcers with adrenaline? A study using reflectance spectrophotometry. *Gastrointest Endosc* 1988;34:174.
28 Rutgeerts P. Geboes K, Vantrappen G. Experimental studies of injection therapy for severe nonvariceal bleeding in dogs. *Gastroenterology* 1989;97:610-21.
29 Lai KH, Peng SN, Guo WS, Lee FY, Chang FY, Malik U, *et al.* Endoscopic injection for the treatment of bleeding ulcers: local tamponade or drug effect. *Endoscopy* 1994;26:338-41.

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Body weight: implications for the prevention of coronary heart disease, stroke, and diabetes mellitus in a cohort study of middle aged men

A Gerald Shaper, S Goya Wannamethee, Mary Walker

Abstract

Objective: To determine the body mass index associated with the lowest morbidity and mortality.
Design: Prospective study of a male cohort.
Setting: One general practice in each of 24 British towns.
Subjects: 7735 men aged 40-59 years at screening.
Main outcome measures: All cause death rate, heart attacks, and stroke (fatal and non-fatal) and development of diabetes, or any of these outcomes (combined end point) over an average follow up of 14.8 years.
Results: There were 1271 deaths from all causes, 974 heart attacks, 290 strokes, and 245 new cases of diabetes mellitus. All cause mortality was increased only in men with a body mass index (kg/m^2) <20 and in men with an index ≥ 30. However, risk of cardiovascular death, heart attack, and diabetes increased progressively from an index of <20 even after age, smoking, social class, alcohol consumption, and physical activity were adjusted for. For the combined end point the lowest risks were seen for an index of 20.0-23.9. In never smokers and former smokers, deaths from any cause rose progressively from an index of 20.0-21.9 and for the combined end point, from 20.0-23.9. Age adjusted levels of a wide range of cardiovascular risk factors rose or fell progressively from an index <20.
Conclusion: A healthy body mass index in these middle aged British men seems to be about 22.

Introduction

The ideal, desirable, or healthy body weight is usually defined as that associated with the lowest mortality.[1] For adults a body mass index (kg/m^2) of 20-27 is widely recommended as the standard weight range within which there is little benefit from further leanness in relation to all cause mortality.[2 3] However, criteria based on risk factors and morbidity may be more appropriate in determining healthy body weights.[4 5] Data from the British Regional Heart Study has shown the effect of smoking on the U shaped relation between body mass index and all cause mortality commonly found in epidemiological studies.[6] Among men who had never smoked the lowest mortality was observed in those with a body mass index of 20.0-21.9. Other reports from this study have been concerned with the independent relation between body mass index and

See editorial by Tunstall-Pedoe

Department of Primary Care and Population Sciences, Royal Free Hospital School of Medicine, London NW3 2PF

A Gerald Shaper, *emeritus professor of clinical epidemiology*

S Goya Wannamethee, *British Heart Foundation research fellow*

Mary Walker, *research administrator*

Correspondence to: Professor Shaper.

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the development of coronary heart disease and non-insulin dependent diabetes mellitus.[7 8] This paper aims to determine healthy body weight based on mortality, morbidity, and cardiovascular risk factors in middle aged men drawn from general practice registers in 24 British towns and followed up for some 15 years. It examines the prospective relation between initial body mass index and subsequent risk of death from all causes and the incidence of heart attack, stroke, and diabetes as well as the relations between body mass index and cardiovascular risk factors in these men.

Subjects and methods

The British Regional Heart Study is a large prospective study of cardiovascular disease comprising 7735 men aged 40-59 selected from the age-sex registers of one group general practice in each of 24 towns in England, Wales, and Scotland. The criteria for selecting the town, the general practice, and the subjects as well as the methods of data collection have been reported.[9] Men with pre-existing cardiovascular disease or taking regular medication were included in the study. Research nurses administered to each man a standard questionnaire that included questions on smoking habits, alcohol intake, physical activity, and medical history. Several physical measurements were made, and non-fasting blood samples were taken for measuring biochemical and haematological variables including serum lipids and packed cell volume.[9 10] Triglyceride and insulin measurements were available for men in 18 towns (7th-24th; n = 5675 and n = 5661 respectively). We adjusted for the marked diurnal variation in both parameters.[11] Details of blood pressure and heart rate and classification methods for smoking status, alcohol consumption, occupation (social class), physical activity, and body mass index have been reported.[12-14] Body mass index (calculated as weight/height^2) was used as an index of relative weight.

Follow up

All men were followed up for death from any cause, cardiovascular morbidity, and development of non-insulin dependent diabetes from the initial screening in January 1978 to July 1980 up to December 1993, a mean period of 14.8 years (range 13.5-16 years),[15] and follow up has been achieved for 99% of the cohort. Information on death was collected through the established "tagging" procedures provided by the NHS registers in Southport (England and Wales) and Edinburgh (Scotland). Criteria for accepting a diagnosis of non-fatal myocardial infarction and deaths from ischaemic heart disease have been reported[7] as has the method for ascertaining new cases of non-insulin dependent diabetes.[8]

Statistical methods

We used Cox's proportional hazards model to obtain the relative risks for the seven body mass index groups adjusted for age, smoking, physical activity, social class, and alcohol intake.[16] Smoking (five levels), physical activity (six levels), alcohol intake (five levels), and social class (seven levels) were fitted as categorical variables. Body mass index was fitted as six dummy variables for the seven groups. Tests for trend were carried out fitting body mass index in its original continuous form. Indirect standardisation was used to obtain age adjusted rates/1000 person years with the study population as the standard. The analysis of covariance was used to obtain age adjusted mean levels of the cardiovascular risk factors for the seven body mass index groups.

To assess the U shaped relation between body mass index and total mortality we entered body mass index both as a linear and quadratic term in its original continuous form in the model; the analysis indicates a U shaped relation if the quadratic term is significant.

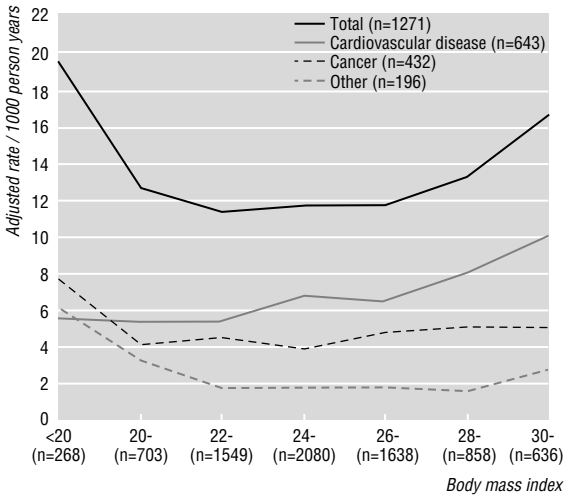

Fig 1 Age adjusted mortality/1000 person years for deaths from any cause, cardiovascular disease, cancer, and other non-cardiovascular non-cancer causes

Results

The mean (SD) body mass index was 25.48 (3.22). The men were divided into seven body mass index groups: < 20 (n = 268), 20.0-21.9 (n = 703), 22.0-23.9 (n = 1549), 24.0-25.9 (n = 2080), 26.0-27.9 (n = 1638), 28.0-29.9 (n = 858), ≥30 (n = 636). Data were not available for three men.

Mortality from any cause

During the mean follow up period of 14.8 years there were 1271 deaths from all causes. These comprised 643 deaths from cardiovascular causes and 628 from non-cardiovascular causes, of which 432 were due to cancer. Figure 1 shows the age adjusted mortality for all causes, cardiovascular disease, cancer, and other non-cardiovascular non-cancer causes. A U shaped relation was seen with all cause mortality with the lowest total mortality in the body mass index groups 22.0-27.9. Mortality was significantly increased in men with an index < 20 or ≥30. A test for the U shaped curve fitting a linear and quadratic effect of body mass index showed a significant indication of a U shaped relation (quadratic term; $P < 0.0001$). A positive association was seen between body mass index and cardiovascular mortality (test for trend, $P < 0.0001$). For cancer, mortality was significantly increased in men with a body mass index < 20 but thereafter there was no trend. For deaths from non-cardiovascular, non-cancer causes there was a significant inverse trend ($P < 0.0001$). The

excess deaths in the leaner men (<22) were largely due to respiratory causes.

Adjustment for lifestyle factors

Body mass index was strongly and inversely associated with cigarette smoking and physical activity and positively associated with social class and alcohol intake.[17] The relation between body mass index and mortality was examined with adjustment for age and then in addition for these factors (table 1). Men with a body mass index of 20.0-21.9 were used as the reference group as this group lies at the lower end of the weight range usually regarded as acceptable.[3] There was little difference in the age adjusted risk of death from all causes in men with an index of 20.0-29.9. The additional adjustment reduced the increased risk for men with an index <20, although it remained significant, and increased the risk seen in all the heavier groups. Mortality increased slightly at an index of 28 and was significantly increased at an index of >30. For cardiovascular mortality there was a progressive increase in relative risk through all groups after full adjustment (test for trend, P<0.0001). For cancer, after full adjustment mortality remained significantly increased only in men in the <20 group. For other non-cardiovascular deaths, full adjustment had little effect on the age adjusted relative risks (test for trend, P<0.001). Exclusion of deaths which occurred within the first five years of follow up did not greatly affect the patterns of risk observed.

Cardiovascular disease and diabetes

We examined the relation between body mass index and subsequent risk of fatal and non-fatal major coronary heart disease (n=974) and stroke (n=290). Table 2 shows the age adjusted rates/1000 person years for these outcomes and the relative risks adjusted for age and then in addition for alcohol intake, physical activity, smoking, and social class. No adjustment was made for blood pressure or blood lipid concentration as these are mechanisms in the pathway linking body weight and cardiovascular disease.

Coronary heart disease—Incidence increased progressively with increasing body mass index. After age and the lifestyle factors were adjusted for, the overall trend in relative risk of coronary heart disease was significant, although the risk increased significantly only at an index of 24.0 and above compared with the baseline group.

Stroke—The age adjusted risk was increased but not significantly in lightest (<20) and heaviest men (≥30). This finding was not significant (P=0.06) after adjustment for age and lifestyle factors. The lowest risks were seen in those with an index of 20.0-21.9 and risk tended to increase thereafter.

Diabetes—All men with diabetes at screening (n=121) or who were diagnosed in the same calendar year as screening (n=14) or who had blood glucose concentrations ≥11.1 mmol/l at screening (n=22) were excluded from the analysis. In the 7575 men with no evidence of diabetes at screening there were 245 cases of non-insulin dependent diabetes during follow up. Risk of diabetes increased progressively with increasing body mass index from <20 (test for trend, P<0.0001) and was significantly raised at an index of 26 and above (table 2).

Combined end point—In all, 2033 men either died or developed one of the end points (development of heart attack, stroke, or diabetes during follow up). After the full adjustment, the lowest risks were seen in men with an index of 20.0-23.9. Risk increased slightly at an index of 24 and was significantly increased at an index of 26 and beyond.

Exclusion of men with known coronary heart disease, stroke and diabetes

There were 604 men who recalled a doctor diagnosing coronary heart disease (heart attack or angina) or stroke or who had evidence of diabetes at screening (see above). Exclusion of these men made little difference to the relations between body mass index and the specific end points. For the combined end point (n=1717) the relative risks (95% confidence intervals) adjusted for age, smoking, social class, alcohol intake, and physical activity for the seven body mass index groups (lowest to highest) were 1.17 (0.88 to1.55), 1.00, 0.97 (0.79 to 1.19), 1.05 (0.86 to 1.27), 1.26 (1.04 to 1.53), 1.36 (1.10 to 1.69), and 1.99 (1.60 to 2.47).

Smoking

Smoking is an important confounder in the relation between body mass index and mortality.[6] We therefore examined the relation between body mass index and mortality from any cause, coronary heart disease,

Table 1 Body mass index and adjusted relative risk (95% confidence interval) of death from any cause, cardiovascular disease, cancer, and other non-cardiovascular causes

Body mass index	No of deaths	Age adjusted rate/1000 person years	Age adjusted relative risk (95% CI)	Fully adjusted relative risk (95% CI)*
All causes (n=1271, 12/1000 person years)				
<20	70	19.2	1.52 (1.12 to 2.04)	1.35 (1.00 to 1.83)
20–	114	12.4	1.00	1.00
22–	224	11.0	0.87 (0.70 to 1.09)	0.99 (0.78 to 1.24)
24–	314	11.2	0.89 (0.72 to 1.10)	1.04 (0.84 to 1.30)
26–	267	11.1	0.89 (0.72 to 1.11)	1.04 (0.83 to 1.30)
28–	150	12.3	0.98 (0.77 to 1.25)	1.11 (0.87 to 1.43)
30–	132	15.3	1.24 (0.97 to 1.60)	1.44 (1.12 to 1.87)
Cardiovascular disease (n=643, 6.1/1000 person years)				
<20	20	5.5	1.05 (0.62 to 1.76)	0.86 (0.51 to 1.48)
20–	47	5.1	1.00	1.00
22–	104	5.1	0.98 (0.70 to 1.39)	1.12 (0.79 to 1.59)
24–	172	6.1	1.18 (0.86 to 1.63)	1.42 (1.03 to 1.98)
26–	136	5.7	1.07 (0.77 to 1.49)	1.30 (0.93 to 1.82)
28–	86	7.1	1.35 (0.95 to 1.93)	1.57 (1.09 to 2.25)
30–	78	9.0	1.78 (1.24 to 2.56)	2.09 (1.45 to 3.03)
Cancer (n=432, 4.1/1000 person years)				
<20	28	7.7	1.90 (1.16 to 3.10)	1.88 (1.13 to 3.09)
20–	37	4.0	1.00	1.00
22–	85	4.2	1.02 (0.69 to 1.50)	1.16 (0.78 to 1.72)
24–	98	3.5	0.86 (0.59 to 1.25)	0.99 (0.67 to 1.46)
26–	97	4.1	1.00 (0.69 to 1.47)	1.21 (0.82 to 1.79)
28–	51	4.2	1.03 (0.67 to 1.57)	1.19 (0.77 to 1.85)
30–	36	4.2	1.05 (0.66 to 1.66)	1.25 (0.78 to 2.01)
Other (n=196, 1.8/1000 person years)				
<20	22	6.0	1.79 (1.03 to 3.10)	1.54 (0.88 to 2.70)
20–	30	3.2	1.00	1.00
22–	35	1.7	0.52 (0.32 to 0.85)	0.57 (0.35 to 0.94)
24–	44	1.6	0.47 (0.32 to 0.75)	0.53 (0.33 to 0.86)
26–	34	1.4	0.43 (0.26 to 0.70)	0.44 (0.26 to 0.73)
28–	13	1.1	0.32 (0.17 to 0.61)	0.34 (0.17 to 0.65)
30–	18	2.1	0.64 (0.36 to 1.15)	0.68 (0.37 to 1.23)

*Adjusted for age, smoking, social class, alcohol intake, and physical activity.

Table 2 Body mass index and age adjusted rate/1000 person years and adjusted relative risk (95% confidence interval) of major coronary heart disease, stroke, diabetes, and the combined end point (death or developing major coronary heart disease, stroke, and diabetes during follow up)

Body mass index	No of cases	Age adjusted rate/1000 person years	Age adjusted relative risk	Fully adjusted relative risk*
Major coronary events (n=974,9.5/1000 person years)				
<20	24	6.9	0.91 (0.57 to 1.46)	0.79 (0.49 to 1.27)
20–	67	7.5	1.00	1.00
22–	156	7.7	1.03 (0.77 to 1.37)	1.12 (0.84 to 1.50)
24–	252	9.1	1.23 (0.94 to 1.60)	1.38 (1.05 to 1.82)
26–	223	9.9	1.33 (1.01 to 1.75)	1.49 (1.13 to 1.96)
28–	139	12.2	1.63 (1.22 to 2.18)	1.81 (1.34 to 2.43)
30–	113	13.7	1.88 (1.39 to 2.54)	2.13 (1.57 to 2.91)
Test for trend			P<0.0001	P<0.0001
Major stroke events (n=290, 2.8/1000 person years)				
<20	13	3.6	1.42 (0.72 to 2.80)	1.23 (0.62 to 2.44)
20–	23	2.5	1.00	1.00
22–	49	2.4	0.95 (0.58 to 1.55)	1.09 (0.66 to 1.81)
24–	73	2.6	1.03 (0.64 to 1.64)	1.20 (0.74 to 1.94)
26–	70	3.0	1.18 (0.74 to 1.89)	1.39 (0.86 to 2.25)
28–	32	2.7	1.04 (0.61 to 1.78)	1.21 (0.70 to 2.08)
30–	30	3.5	1.41 (0.82 to 2.44)	1.70 (0.98 to 2.97)
Test for trend			P=0.2	P=0.05
Diabetes (n=245, 2.4/1000 person years)†				
<20	2	0.6	0.71 (0.15 to 3.33)	0.66 (0.14 to 3.11)
20–	8	0.9	1.00	1.00
22–	19	0.9	1.06 (0.46 to 2.42)	1.12 (0.49 to 2.55)
24–	44	1.6	1.83 (0.85 to 3.89)	1.83 (0.86 to 3.91)
26–	64	2.9	3.41 (1.63 to 7.11)	3.58 (1.71 to 7.49)
28–	47	4.2	4.95 (2.34 to 10.47)	5.20 (2.44 to 11.04)
30–	61	7.7	9.31 (4.45 to 19.45)	9.68 (4.60 to 20.39)
Test for trend			P<0.0001	P<0.0001
Combined end point (n=2033, 20.3/1000 person years)				
<20	88	25.5	1.34 (1.04 to 1.74)	1.21 (0.93 to 1.57)
20–	167	18.8	1.00	1.00
22–	336	17.0	0.89 (0.74 to 1.08)	0.99 (0.82 to 1.20)
24–	481	17.8	0.94 (0.79 to 1.12)	1.07 (0.89 to 1.27)
26–	455	20.7	1.10 (0.92 to 1.32)	1.26 (1.05 to 1.50)
28–	260	23.3	1.24 (1.02 to 1.50)	1.39 (1.14 to 1.69)
30–	246	31.6	1.73 (1.42 to 2.10)	1.97 (1.61 to 2.41)
Test for trend			P<0.0001	P<0.0001

*Adjusted for age, smoking, social class, alcohol intake, and physical activity.†Excludes 158 men with diabetes or blood glucose levels ≥11.1 mmol/l at screening.

and the combined end point (death, coronary heart disease, stroke, or diabetes) separately by smoking status at screening (never smoked, former smokers, and current smokers) adjusting for age (fig 2). Current smokers showed higher mortality than former and never smokers at all body mass indices, and mortality from any cause was increased in those with an index <20 in all smoking groups. In never and former smokers, mortality increased thereafter (test for trend, $P<0.008$ and $P=0.01$ respectively). A shallow U shaped relation was seen in current smokers.

For coronary heart disease events a linear positive association was seen in never smokers and current smokers. In former smokers the lowest rates were seen in the 22.0-23.9 groups. For the combined end point, rates were lowest in the 20.0-23.9 groups in both never and former smokers and increased progressively thereafter (test for trend, $P<0.0001$). Among smokers the lowest rates were in the 20.0-25.9 groups and increased thereafter. Further adjustment for lifestyle factors made minor differences to the relations within these smoking categories.

Cardiovascular risk factors

We examined the relations between body mass index and cardiovascular risk factors after age was adjusted for (table 3). For most of these factors the levels increased (in the case of high density lipoprotein cholesterol decreased) progressively with increasing body mass index. Mean heart rate was slightly raised in those with a body mass index <20 but lower again in the 20-21.9 group and increased progressively thereafter.

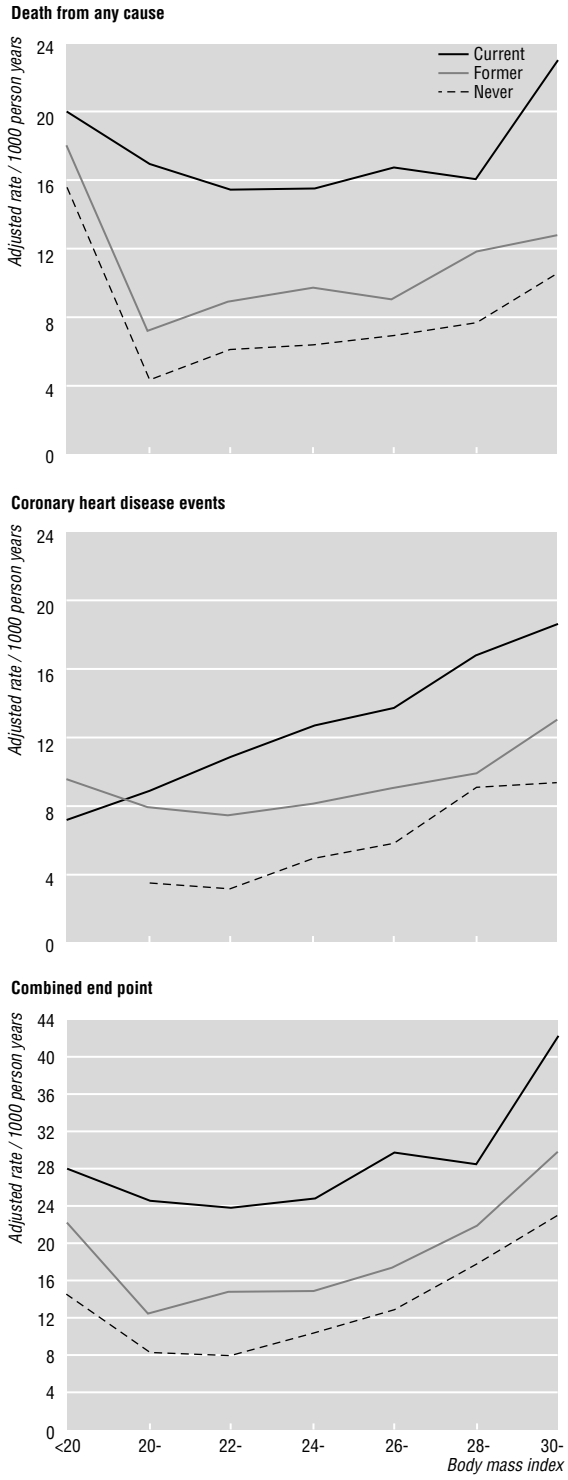

Fig 2 Mortality from any cause, coronary heart disease events (fatal and non-fatal) and a combined end point (all age adjusted rates/1000 person years) according to smoking status

Adjustment for biological factors

The positive relation between body mass index and cardiovascular mortality (table 1) and between body mass index and coronary events (table 2) was attenuated after further adjustment for systolic blood pressure and blood cholesterol concentration, although it remained significant ($P = 0.03$ and $P = 0.002$ respectively). Additional adjustment for high density lipoprotein cholesterol abolished the positive trend for both cardiovascular mortality and coronary events (data not shown).

Discussion

Concepts of desirable or healthy weight have depended heavily on the relation between body mass index and mortality,[1 2] although more recently the associations between body weight and cardiovascular risk profile, morbidity, and diabetes mellitus have been emphasised in considering optimal weight.[4 5 18] In this study the well established U shaped relation between mortality and body weight was confirmed, with excess deaths in very lean men largely due to cancer and other non-cardiovascular causes and the excess deaths in the heaviest men predominantly due to cardiovascular disease. The relative risk of both heart attack and of diabetes increased progressively from an index < 20 and the lowest risk of stroke was seen in those with an index of 20.0-23.9.

With a combined end point (heart attack, stroke, diabetes, or death) the lowest relative risk was in the 20.0-23.9 groups. All the major risk factors for cardiovascular disease rose progressively from an index < 20. These findings strongly suggest that the healthy, biologically normal, or optimum body weight in these middle aged men is towards the lower end of the range which is currently regarded as acceptable.

Issues of adjustment

In most studies examining the relation between body weight and outcome in terms of morbidity or mortality, adjustments have been made in multiple regression models for blood pressure and total cholesterol concentration, and occasionally for other biological factors related to body weight and risk of cardiovascular disease. Any relations observed between body weight and the end points have been considerably attenuated after adjustment, often becoming non-significant. This has then been interpreted as meaning that "body weight does not matter" as these other variables have accounted for the relations observed. Our results were also attenuated after we adjusted for blood pressure, cholesterol, and high density lipoprotein cholesterol. In trying to assess the effects of body weight it seems illogical to adjust for those factors which are almost certainly the mechanisms by which increasing body weight brings about vascular damage.

Other studies

Previous prospective studies have generally focused on the U shaped relation between body mass index and all cause mortality or on the relation between body mass index and specific end points—for example, coronary heart disease. Few studies have focused on assessing healthy weight based on risk factors or morbidity, or both. In a cross sectional study of 3582 Japanese men (mean body mass index 23.3) and 983 women (mean 21.8) aged 30-59 years, 10 medical problems (hypertension, hyperlipidaemia, hyperuricaemia, ischaemic heart disease, lung disease, anaemia, upper gastrointestinal disease, liver, and renal disease) were selected to determine morbidity.[4] The relation between body mass index and a composite morbidity index formed a J shaped curve with the lowest point at an index of 22.2 in men and 21.8 in women. The authors conclude that an index of about 22 seems to be the ideal. In the Framingham offspring study a similar conclusion was drawn after assessing the relation between the scapular skinfold (as a direct measure of adiposity) and several cardiovascular risk factors in 2447 non-smoking men and women aged 20-59 years. Healthy adiposity corresponded to a mean body mass index of 22.6 for men and 21.2 for women.[5] Although not specifically aimed at assessing ideal body weight, a Finnish study of about 16 000 men and women aged 30-59 years showed clearly that the main risk factors increased progressively from an index of 20 upwards and that from a level of 22 an increase in body weight equivalent to 1 body mass index unit was related to a 4-5% increase in coronary heart disease mortality.[19] In our study an increase in 1 body mass index unit from 20.0-21.9 onwards was associated with an approximately 10% increase in the rate of coronary events and a 10% increase in the combined end point. In the Nurses health study, in women who had never smoked and who recently had stable weight, the lowest mortality was among the leanest women (body mass index < 19.0).[20] These women were at least 15% below the United States average weight for middle aged women. All cause mortality did not increase substantially until a body mass index of 27, although trends were apparent for coronary heart disease and cancer among women at average weights and among those who were mildly overweight.

Table 3 Body mass index and age adjusted mean levels of cardiovascular risk factors

Risk factors	<20	20–	22–	24–	26–	28–	30–
Systolic blood pressure (mm Hg)	134.5	137.6	140.9	144.9	147.2	150.5	156.8
Diastolic blood pressure (mm Hg)	72.7	75.6	78.6	81.5	84.7	87.2	92.0
Cholesterol (mmol/l)	5.68	5.94	6.20	6.32	6.47	6.43	6.53
High density lipoprotein cholesterol (mmol/l)	1.33	1.26	1.18	1.15	1.10	1.07	1.04
Triglycerides (mmol/l)*	1.08	1.30	1.58	1.71	1.95	2.08	2.32
Packed cell volume	0.435	0.440	0.442	0.444	0.446	0.449	0.453
Urate (μmol/l)	314.7	326.0	343.5	357.2	368.8	383.5	396.5
Heart rate (beats/min)	71.2	69.9	70.0	70.7	70.9	70.9	73.0
Glucose (mmol/l)*	5.37	5.38	5.40	5.47	5.52	5.59	5.75
Insulin (mU/l)*	7.8	8.5	10.4	12.1	14.0	16.1	20.5

*Geometric mean.Test for trend: all P<0.0001.

Public health aspects

The British government's Health of the Nation strategy set targets for the reduction in the prevalence of obesity (body mass index ≥ 30) in men and women aged 16-64 years but made no recommendations regarding the distribution of weight in the population and set no standards for healthy body mass indices in the population.[21] The recent task forces report suggests targeting adults with a body mass index of 25-30 and expresses "a concern to develop a strategy to prevent

the population in general becoming fatter."[22] In 1993, the proportion of men and women in England who were obese was 13% and 16% respectively with a mean body mass index of 25.9 for men and 25.7 for women. As an index of 25-30 is generally regarded as overweight,[23] half of the adult population of England is overweight or obese.[24]

By contrast, in the United States, which has a similar epidemic of obesity, the focus of two recent reports has been on healthy weight rather than on obesity itself.[18 25] Both reports recommend maintaining a lean body weight throughout adult life and weight reduction in those who are overweight with or without obesity related disorders. The American Institute of Nutrition recommends a single body mass index criterion of 18-25 for both sexes and suggests that "most people will be healthier towards the lower end of the range." They proposed a format indicating gradations of risk—for example, body mass index 18-23 = lowest risk, 24-25 = mild risk, 26-29 = medium risk, and ≥30 = high risk.[25]

The American Health Foundation Expert Panel proposes a healthy weight target of a body mass index <25 for adults, representing the upper limit beyond which weight related disease risk becomes a concern and morbidity associated with obesity becomes manifest. In those exceeding the healthy weight target and without a diagnosis of a weight related disease, they propose a healthier weight goal. This represents the amount of weight loss that will reduce disease risk and is roughly two body mass index units (about 6 kg or 1 stone). This modest weight loss is regarded as achievable and maintainable and is more likely to be reached than the healthy weight target.[18]

Our findings broadly agree with the United States reports, and it is clear that the emphasis must be on maintaining healthy body weight in early adulthood and the prevention of obesity. The British focus on obesity seems to avoid the issue of a healthy weight and to direct attention to the clinical management of obesity.

Clinical aspects

It is well established that at all body mass indices individuals with visceral obesity (excess deep abdominal fat as indicated by waist-hip ratio or waist circumference) are at highest risk of cardiovascular disease.[26] Thus estimates of risk based on body mass index or other crude measures alone may not be sufficient for assessment. Clinical decisions on the importance of body mass index in individuals will depend on the distribution of fat and muscular development as well as on the overall profile of risk.

Conclusions

In industrialised societies increasing body weight is closely related to an increasing incidence of non-insulin dependent diabetes and coronary heart disease and to increasing blood pressure, blood lipid, glucose, and insulin concentrations, urate concentration, and packed cell volume—factors all involved intimately in the development of coronary heart disease. There is also considerable evidence of the benefits of weight reduction on risk factors for cardiovascular disease and diabetes.[18] Although the benefits of weight reduction in overweight people for coronary heart disease are still controversial,[27-29] the importance of maintaining a healthy weight throughout life as a major primary preventive measure against cardiovascular disease and diabetes seems incontrovertible. Within the "normal" range of body mass index (20-27) it is better to be leaner, and the optimal healthy body mass index for adults is about 22. The implications of this conclusion for public health are considerable, and with the rising tide of obesity in the industrialised world deserve to be treated with some urgency.

Key messages

- The body mass index associated with the lowest mortality and the lowest incidence of coronary heart disease, stroke, and diabetes mellitus is not known
- In this study of middle aged men the risk of cardiovascular mortality, heart attack, and diabetes increased progressively from a body mass index <20
- For a combined end point (heart attack, stroke, diabetes, or death from any cause) the lowest risk was in the range 20-24
- Levels of a wide range of cardiovascular risk factors increased progressively from an index of <20
- A healthy body mass index in middle aged men seems to be around 22

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1 Metropolitan Life Insurance Company. New weight standards for men and women. *Statistical Bulletin* 1959;40:1-4.
2 Kushner RF. Body weight and mortality. *Nutrition Reviews* 1993;51: 127-36.
3 Byers T. Body weight and mortality (Editorial). *N Engl J Med* 1995;333:723-4.
4 Tokunaga K, Matsuzawa Y, Kotani K, Keno Y, Takashi K, Fujioka S, *et al*. Ideal body weight estimated from the body mass index with the lowest morbidity. *Int J Obesity* 1991;15:1-5.
5 Garrison RJ, Kannel WB. A new approach for estimating healthy body weights. *Int J Obes* 1993;17:417-23.
6 Wannamethee G, Shaper AG. Body weight and mortality in middle-aged British men: impact of smoking. *BMJ* 1989;299:1497-502.
7 Shaper AG, Pocock SJ, Walker M, Phillips AN, Whitehead TP, Mcfarlane PW. Risk factors for ischaemic heart disease: the prospective phase of the British Regional Heart Study. *J Epidemiol Comm Health* 1985;39:197-209.
8 Perry IJ, Wannamethee SG, Walker MK, Thomson AG, Whincup PH, Shaper AG. A prospective study of risk factors for non-insulin-dependent diabetes in middle-aged British men. *BMJ* 1995;310:560-4.
9 Thelle DS, Shaper AG, Whitehead TP, Bullock DG, Ashby D, Patel I. Blood lipids in middle-aged British men. *Br Heart J* 1983;49:205-13.
10 Wannamethee G, Shaper AG, Whincup PH. Ischaemic heart disease:association with haematocrit in the British Regional Heart Study. *J Epidemiol Comm Health* 1994;48:112-8.
11 Perry IJ, Wannamethee SG, Whincup PH, Shaper AG, Walker M, Alberti KGMM. Serum insulin and incident coronary heart disease in middle-aged British men. *Am J Epidemiol* (in press).
12 Shaper AG, Pocock SJ, Walker M, Cohen NM, Wale CJ, Thomson AG. British Regional Heart Study:cardiovascular risk factors in middle-aged men in 24 towns. *BMJ* 1981;283:179-86.
13 Shaper AG, Wannamethee G, MacFarlane PW, Walker M. Heart rate, ischaemic heart disease and sudden cardiac death in middle-aged British men. *Br Heart J* 1993;70:49-55.
14 Shaper AG, Wannamethee G. Physical activity and ischaemic heart disease in middle-aged British men. *Br Heart J* 1991;66:384-94.
15 Walker M, Shaper AG. Follow-up of subjects in prospective studies based in general practices. *J R. Coll Gen Pract* 1984;34:365-70.
16 Cox DR. Regression models and life tables (with discussion). *Journal of the Royal Statistical Society* 1972;34[B]:187-220.
17 Wannamethee G, Shaper AG. Blood lipids: the relationship with alcohol intake, smoking and body weight. *J Epidemiol Comm Health* 1992;46: 197-202.
18 American Health Foundation. Roundtable on healthy weight. *Am J Clin Nutr* 1996;63 (suppl):409-77.

19 Jousilhti P, Tuomilehto J, Vartiainen E, Pekkanen J, Puska P. Body weight, cardiovascular risk factors, and coronary mortality. 15-year follow-up of middle-aged men and women in Eastern Finland. *Circulation* 1996;93:1372-9.
20 Manson JE, Willett WC, Stampfer MJ, Colditz GA, Hunter DJ, Hankinson SE. Body weight and mortality among women. *N Engl J Med* 1995;333:677-85.
21 Department of Health. *The health of the nation: a strategy for health in England*. London: HMSO, 1992.
22 Department of Health. *Obesity: Reversing the increasing problem of obesity in England. A report from the Nutrition and Physical Activity Task Forces*. London: HMSO, 1995.
23 Garrow J. *Obesity and related disease*. London: Churchill Livingstone, 1988.
24 Bennett N, Dodd T, Flatley J, Freeths S, Bolling K. *Health survey of England 1993*. London: HMSO, 1993.
25 American Institute of Nutrition. Report of the AIN steering committee on healthy weight. *J Nutr* 1994;124:2240-3.
26 Larsson B, Bengtsson C, Bjorntorp P, Lapidus L, Sjostrom L, Svardsudd K. Is abdominal fat distribution a major explanation for the sex difference in the incidence of myocardial infarction. *Am J Epidemiol* 1992;135:266-73.
27 Pamuk ER, Williamson DF, Serdula MK, Madans J, Byers TE. Weight loss and subsequent death in a cohort of US adults. *Ann Intern Med* 1993;119:744-8.
28 Walker M, Wannamethee G, Whincup PH, Shaper AG. Weight change and risk of heart attack in middle-aged British men. *Int J Epidemiol* 1995;24:694-703.
29 Williamson DF, Pamuk E, Thun M, Flanders D, Byers T, Heath C. Prospective study of intentional weight loss and mortality in never-smoking overweight US white women aged 40-64 years. *Am J Epidemiol* 1995;141:1128-41.

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Prospective study of *Helicobacter pylori* seropositivity and cardiovascular diseases in a general elderly population

Timo E Strandberg, Reijo S Tilvis, Matti Vuoristo, Magnus Lindroos, Timo U Kosunen

Case-control and cross sectional studies have suggested that chronic infection with *Helicobacter pylori* is a risk factor for cardiovascular disease.[1 2] No prospective studies have examined this association in elderly people—those usually with the highest prevalence of *H pylori* infection.[3]

Subjects, methods, and results

We performed a prospective study on people from the Helsinki aging study. From the Helsinki census register random cohorts of people alive in July 1988 and born in 1904, 1909, and 1914 (300 in each group, 11.2% of the total population of 8035) were invited to participate; 795 people were alive and still living in the city of Helsinki. Altogether 144 refused to participate, leaving 651 (81.9%) people to be examined clinically up to April 1990. *H pylori* IgG, IgA, and IgM antibodies were tested by enzyme immunoassays[3] in 624 subjects (repeatibility of the test expressed as intraclass correlation coefficient $\kappa = 0.95$).

Baseline evaluation included a postal questionnaire, a structured interview conducted by public health nurses, a review of all available patient records, a clinical examination carried out by general practitioners, and laboratory investigations after an overnight fast.

Standard 12 lead resting electrocardiographic data were classified according to the Minnesota code criteria in duplicate. The results of echocardiography have been published elsewhere.[4]

The presence of disease was based either on data from hospital records or on clinical examination, with special emphasis placed on the diagnostic accuracy for cardiac disease. Subjects were assigned to a group of "healthy elderly" (n = 122) if their subjective and objective (according to the examining physicians) health was good or moderate; they did not have hypertension, diabetes, dementia, or symptoms of cardiovascular, cerebrovascular, or pulmonary diseases, cancer, or other disabling diseases; and their history showed normal exercise tolerance.

During the five year follow up 250 subjects died. The principal cause of death was determined from the death certificates by trained nosologists at the Central Statistical Office of Finland.

Data were analysed with BMDP software. The differences in laboratory variables were tested with an analysis of variance in which age and sex were included as covariates. The Cox proportional hazards model served to test the influence of *H pylori* seropositivity on survival, with age and sex used as covariates.

Among the healthy elderly, 68% were seropositive for *H pylori*. Seropositivity did not differ significantly in subjects with and without manifest vascular diseases (67% *v* 71%; difference −4.3%, 95% confidence interval −11.8% to 3.3%).

The prevalence of major electrocardiographic or echocardiographic abnormality in subjects seropositive and seronegative for *H pylori* was similar. Of the laboratory variables, only the serum concentration of high density lipoprotein cholesterol differed between the 419 seropositive subjects and the 190 seronegative subjects (1.46 mmol/l *v* 1.55 mmol/l; difference −0.09mmol/l, −0.17 to −0.01; P = 0.04).

During the five year follow up, crude mortality was 40% and cardiovascular mortality 20% in the whole series. After age and sex were controlled for, *H pylori* seropositivity was not related either to all cause or cardiovascular mortality (table 1). As expected, several baseline cardiovascular variables (clinical symptoms and signs, electrocardiographic and echocardiographic abnormalities) significantly predicted mortality—for example, total mortality among subjects with and

See p 1318

Division of Geriatrics, Department of Medicine, University of Helsinki, Haartmaninkatu 4, FIN-00290 Helsinki, Finland
Timo E Strandberg, *senior lecturer*
Reijo S Tilvis, *professor of geriatrics*
Matti Vuoristo, *physician in chief*
Department of Bacteriology and Immunology, University of Helsinki,
Timo U Kosunen, *associate professor*
Department of Cardiology, Vaasa Central Hospital, Vaasa, Finland
Magnus Lindroos, *consultant in cardiology*
Correspondence to: Professor Tilvis.

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Table 1 Relative risk (95% confidence interval) of death within five years from cardiovascular causes and all causes in people aged 75-85

Group	Cardiovascular mortality (n=127)	Total mortality (n=250)
Age (5 year groupings)	1.77 (1.41 to 2.22)	1.61 (1.38 to 1.88)
Male sex	1.16 (0.77 to 1.75)	1.59 (1.20 to 2.08)
H pylori seropositivity*	1.07 (0.73 to 1.55)	1.08 (0.83 to 1.42)

* Relative risk tested with the Cox regression analysis, controlled for age and sex.

without major electrocardiographic abnormalities at baseline (47% *v* 35%; difference 12.7%, 5.1% to 20.7%).

Comment

On cross sectional analysis we found no association between *H pylori* seropositivity and cardiovascular diseases (assessed in several ways) in our 624 elderly subjects. Because *H pylori* seropositivity did not predict total or cardiovascular mortality during a five year follow up, our results offer no evidence for an association between *H pylori* infection and coronary heart disease, and they differ from those reported recently in younger subjects.[1 2] Our results do not exclude the possibility that chronic *H pylori* infection acquired early in life may increase the lifelong risk of coronary heart disease. By analogy with serum cholesterol concentration in elderly subjects, controlled intervention studies may be needed to ascertain whether eradicating *H pylori* infection in certain subgroups is worthwhile.

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1 Patel P, Mendall MA, Carrington D, Strachan D, Leatham E, Molineaux N, *et al.* Association of Helicobacter pylori and Chlamydia pneumoniae infections with coronary heart disease and cardiovascular risk factors. *BMJ* 1995;311:711-4.

2 Murray LJ, Bamford KB, O'Reilly DPJ, McCrum EE, Evans AE. Helicobacter pylori infection: relation with cardiovascular risk factors, ischaemic heart disease, and social class. *Br Heart J* 1995;74:497-501.

3 Kosunen TU, Höök J, Rautelin HI, Myllylä G. Age-dependent increase of Campylobacter pylori antibodies in blood donors. *Scand J Gastroenterol* 1989;24:110-4.

4 Lindroos M, Kupari M, Heikkilä J, Tilvis RS. Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. *J Am Coll Cardiol* 1993;21:1220-5.]

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Helicobacter pylori infection and coagulation in healthy people

Fabrizio Parente, Giovanni Maconi, Venerina Imbesi, Ornella Sangaletti, Marina Poggio, Edoardo Rossi, Piergiorgio Duca, Gabriele Bianchi Porro

See p 1317

Department of Gastroenterology, L Sacco University Hospital, Via G B Grassi 74, 20157 Milan, Italy

Fabrizio Parente, *senior registrar*

Giovanni Maconi, *registrar*

Venerina Imbesi, *postgraduate trainee*

Ornella Sangaletti, *biologist*

Gabriele Bianchi Porro, *professor*

Department of Haematology, L Sacco University Hospital, Milan

Marina Poggio, *registrar*

Edoardo Rossi, *consultant physician*

Department of Medical Statistics and Biometry, University of Milan

Piergiorgio Duca, *associate professor*

Correspondence to: Professor Bianchi Porro.

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Helicobacter pylori infection has recently been associated with an increased risk of developing ischaemic heart disease.[1 2] It has been suggested that chronic gastritis related to *H pylori* infection may increase, through inflammatory mediators, the concentration of certain coagulation factors such as fibrinogen,[3] which are predictors of ischaemic heart disease.[4] We investigated the potential association between *H pylori* infection and abnormalities of plasma coagulation in healthy people, with particular emphasis on the possibility of *H pylori* inducing a tendency towards coagulation, thereby influencing the risk of ischaemic heart disease.

Subjects, methods, and results

Initially, 368 consecutive asymptomatic blood donors (unpaid volunteers) were recruited for this study. Exclusion criteria were age >51 years, any chronic drug treatment, recent intake of drugs interfering with blood coagulation, use of oral contraceptives, previous treatment for *H pylori* infection, pregnancy or breast feeding, and previous diagnosis of ischaemic heart disease, peptic ulcer, or any systemic chronic illness. Dietary habits, alcohol and cigarette consumption, and socioeconomic status were determined. A total of 300 subjects (229 men) aged 20-51 (mean 34.7) years fulfilled the inclusion criteria and were enrolled into the study. A resting venous blood sample was taken in all subjects and was analysed for concentrations of total cholesterol, C reactive protein, plasma fibrinogen, factor VII C, and haemoglobin; erythrocyte sedimentation rate; prothrombin time; partial thromboplastin time; and platelet and leucocyte count. Prothrombin cleavage fragment (factors I and II), an index of prothrombin activation,[5] was also assayed. IgG antibodies specific to *H pylori* were determined by using a commercial ELISA kit (Helori test, Eurospital, Trieste, Italy); a cut off value of 19% was used, based on previous analysis of 200 patients (sensitivity compared with histology, 92%; specificity, 94%). Student's *t* test and the χ^2 test were used to compare characteristics of subjects and values of haemostatic factors in subjects with and without *H pylori* infection; multiple regression was used to assess the effects of covariates.

The overall prevalence of *H pylori* infection was 53% (158/300). Table 1 shows that subjects positive for *H pylori* were significantly older than those negative for *H pylori*. The groups did not differ significantly in other characteristics or in values for plasma fibrinogen, cholesterol, leucocyte and platelet count, erythrocyte sedimentation rate, prothrombin time, partial thromboplastin time, and C reactive protein. However, concentrations of factor VII C and prothrombin cleavage fragment were significantly higher in positive than in negative subjects, though the association disappeared after adjustment by multiple logistic regression for age, sex, and social class.

Comment

As plasma fibrinogen and total leucocyte count, which are well known risk factors for ischaemic heart disease,[4] are increased in patients infected with *H pylori*,[3] the increased risk of ischaemic heart disease in people positive for *H pylori* may be mediated through raised plasma fibrinogen concentrations. However, a large cross sectional population survey failed to find a significant association between *H pylori* and fibrinogen.[2] These studies may be biased because they included patients with ischaemic heart disease, a condition which could be associated with increased concentrations of coagulation factors irrespective of patients' *H pylori* status. Comparing the concentrations of circulating coagulation factors in healthy people

Table 1 Mean (SD) age and circulating coagulation factors in healthy people with and without *Helicobacter pylori* infection, and multiple regression analysis using concentrations of factor VII C and prothrombin cleavage fragment (factors I and II) as dependent variables and *H pylori* status, smoking habits (0=no; 1=yes), sex (0=female; 1=male), and age (in years) as independent variables

	***H pylori* status**		
	Negative (n=142)	**Positive (n=158)**	**Difference *or* correlation coefficient (95% CI)**
Variable			
Age (years)	32.2 (7.4)	37.0 (7.9)	–4.8 (–6.54 to –3.06)
Platelet count ($\times 10^9$/l)	216.7 (42.9)	210.2 (50.9)	6.5 (–4.26 to 17.26)
Leucocyte count ($\times 10^6$/l)	6.41 (1.6)	6.41 (1.8)	0 (–0.39 to 0.39)
Erythrocyte sedimentation rate	5.81 (4.2)	5.57 (5.2)	0.24 (–0.84 to 1.32}
C reactive protein (mg/l)	8.0 (6.0)	9.1 (7.0)	–1.1 (–2.5 to 0.5)
Prothrombin time (ratio)	0.93 (0.1)	0.93 (0.2)	0 (–0.04 to 0.04)
Partial thromboplastin time (ratio)	1.03 (0.2)	1.00 (0.2)	0.03 (–0.02 to 0.08)
Factor VII:C (%)	84.6 (18.4)	89.3 (17.7)	–4.7 (–8.80 to –0.60)
Fibrinogen (g/l)	3.36 (8.5)	3.42 (8.7)	–0.06 (–2.20 to 1.90)
Factors 1 + 2 (nmol/l)	0.89 (0.3)	1.00 (0.4)	–0.11 (–0.19 to –0.03)
Multiple regression			
Prothrombin cleavage fragment (*R*=0.54):			
H pylori status			0.002 (–0.05 to 0.59)
Smoking			0.075 (0.020 to 0.130)
Sex			0.080 (–0.145 to –0.015)
Age			0.018 (0.014 to 0.022)
(Constant)			0.318 (0.196 to 0.440)
Factor VII C (*R*=0.40):			
H pylori status			1.209 (–2.768 to 5.186)
Smoking			8.017 (4.138 to 11.896)
Sex			–4.748 (–9.332 to –0.164)
Age			0.710 (0.458 to 0.961)
(Constant)			61.955 (53.390 to 70.520)

with and without *H pylori* infection, we found that *H pylori* infection is not associated with increased circulating concentrations of fibrinogen, factor VII:C, or prothrombin cleavage fragment, or with other haemostatic factors, which does not support the possibility of this infection inducing a tendency towards a procoagulant state. Thus it seems unlikely that *H pylori* infection predisposes the development of ischaemic heart disease through effects on the coagulation system.

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1 Mendall MA, Goggin PM, Molineaux N, Levy J, Toosy T, Strachan D, *et al.* Relation of Helicobacter pylori infection and coronary heart disease. *Br Heart J* 1994;71:437-9.
2 Murray LJ, Bamford KB, O'Reilly DP, McCrum EE, Evans AE. Helicobacter pylori infection: relation with cardiovascular risk factors, ischaemic heart disease, and social class. *Br Heart J* 1995;74:497-501.
3 Patel P, Mendall MA, Carrington D, Strachan DP, Leatham E, Molineaux N, *et al.* Association of Helicobacter pylori and Chlamydia pneumoniae infections with coronary heart disease and cardiovascular risk factors. *BMJ* 1995;311:711-4.
4 Yarnell JW, Baker IA, Sweetnam PM, Bainton D, O'Brien JR, Whitehead PJ, *et al.* Fibrinogen, viscosity, and white blood cell count are major risk factors for ischaemic heart disease. *Circulation* 1991;83:836-44.
5 Mannucci PM, Tripodi A, Bottasso B, Baudo F,Finazzi G, De Stefano V, *et al.* Markers of procoagulant imbalance in patients with inherited thrombotic syndromes. *Thrombosis and Haemostasis* 1992;67:200-2.

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A memorable book

From magic to science

I graduated in Prague, Czechoslovakia, in 1939 one month before the Czech capital was occupied by the Nazis. I was lucky to escape to Palestine, where I joined the Czechoslovak Army, later to be transferred to the Royal Army Medical Corps. In order to acquaint myself with the British pharmacopoeia—somewhat different from the central European one—I looked up in the hospital's small library a textbook of clinical pharmacology. It was in fact American—by Harry Beckmann.

Here I must point out that not only pharmacology but the whole concept of medicine at that time was different on the continent than in the Anglo-Saxon world. During our studies we were inculcated with the deepest admiration for our elders, whose views were not to be disputed. Traditions were sacred; the doctor's social status was maintained by a pompous gravitas. Sceptical questioning was frowned on, and even a trace of humour was sacrilege.

Now I opened a book written in a highly readable, entertaining style often spiced with humour. Drugs were evaluated with caution. I still remember the following story. For many years acute cholecystitis used to be treated by a drug, I forget its name as it has been long forgotten by all. A few researchers in the United States examined the bile from postoperative biliary fistulas after having administered the drug. Not a trace of it or its metabolites was found on analysis. A tenet of decades was destroyed in a matter of weeks.

The iconoclastic questioning, the constant search for proof of every hypothesis, has been the hallmark of medicine in the Anglo-Saxon world. That is what I discovered in the book. Even after 50 years living in England I am still filled with gratitude and joy at having found out what turned medicine from magic to science. Of course there are still small pockets of the old "sacred cow" attitude here as much as elsewhere, but in general the critical spirit of evidence guided medicine has taken firm root on the continent. It is up to politicians and economists to deliberate whether Britain needs Europe. In medicine, however, Europe certainly needs Britain.

Jan Pollert *is a retired chest physician in London*