Papers

Impact of postmenopausal hormone therapy on cardiovascular events and cancer: pooled data from clinical trials

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Abstract

Objective: To examine the incidence of cardiovascular diseases and cancer from published clinical trials that studied other outcomes of postmenopausal hormone therapy as some surveys have suggested that it may decrease the incidence of cardiovascular diseases and increase the incidence of hormone dependent cancers.

Design: Trials that compared hormone therapy with placebo, no therapy, or vitamins and minerals in comparable groups of postmenopausal women and reported cardiovascular or cancer outcomes were searched from the literature.

Subjects: 22 trials with 4124 women were identified. In each group, the numbers of women with cardiovascular and cancer events were summed and divided by the numbers of women originally allocated to the groups.

Results: Data on cardiovascular events and cancer were usually given incidentally, either as a reason for dropping out of a study or in a list of adverse effects. The calculated odds ratios for women taking hormones versus those not taking hormones was 1.39 (95% confidence interval 0.48 to 3.95) for cardiovascular events without pulmonary embolus and deep vein thrombosis and 1.64 (0.65 to 4.18) with them. It is unlikely that such results would have occurred if the true odds ratio were 0.7 or less. For cancers, the numbers of reported events were too low for a useful conclusion.

Conclusions: The results of these pooled data do not support the notion that postmenopausal hormone therapy prevents cardiovascular events.

Introduction

Surveys suggest that postmenopausal hormone therapy (hormone replacement therapy) may decrease the incidence of cardiovascular diseases but increase the incidence of hormone dependent cancers—for example, breast cancer.[1-6] These findings are of major public health importance, and trials have been mounted to verify them, specifically to exclude the possibility of selection bias.[7 8] The results of these trials will not be available for some years, however, and current prescribing and use depend on individual interpretations of inadequate evidence and marketing factors. Surveys and observations of physicians show that many believe postmenopausal hormone therapy to be beneficial,[9-12] and in some countries the treatment has become very common.[13-16] Thus, further reliable information on health outcomes would be useful until the data from prospective trials are available.

We investigated the utility of information on cardiovascular events and cancer derived from published clinical trials studying other, short term, aspects of postmenopausal hormone therapy. This study was stimulated by the findings of the PEPI trial (the postmenopausal oestrogen/progestin interventions trial) on risk factors for heart disease.[17] Its table on adverse experiences showed a higher incidence of cardiovascular and thromboembolic events among users of the hormones (2.1 events/100 women) than in the placebo group (no events). This difference is not significant but is in the opposite direction of the pooled results of epidemiological surveys.

Methods

We searched for randomised trials that compared hormone therapy with placebo, no therapy, or vitamins and minerals in comparable groups of postmenopausal women. Hormone therapy was defined as oestrogens, in any form, alone or together with progestin/progesterone. Women given other types of active substances were not included in the comparison group. Trials were searched from Medline (1989 to November 1995) and reference lists of various review articles, books, and articles found. Languages accepted were English, German, the Scandinavian languages, and Finnish.

After identifying a trial with a comparable no hormone group we checked for any information on cardiovascular events (such as cardiac arrest, cerebrovascular accident, ischaemic attack, myocardial infarction), thromboembolic events (pulmonary emboli, deep vein thrombi), superficial phlebitis or thrombophlebitis, and cancers (breast, uterine body, other including cervical cancer and unspecified). We had also planned to study other health outcomes (such as gall bladder disease, mental symptoms, migraine, uterine diseases) but the definitions turned out to be either vague or varying, and they were not included. Trials

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Table 1 Details of numbers of women in trials of postmenopausal hormone therapy

Reference	Regimens with daily doses	Women allocated	Cardiovascular disease*	Thromboembolic disease†	Superficial phlebitis and thrombophlebitis	Breast cancer	Uterine cancer (excluding cervical cancer)	Other cancer (including cervical cancer)
Speroff et al, 1996	Placebo	137	–	–	–	0	–	–
	Ethinyl oestradiol 1-10 μg	562	–	–	–	3	–	–
	Ethinyl oestradiol 1-10 μg+NETA 0.2-1 mg	566	–	–	–	3	–	–
Writing Group, 1995	Placebo	174	0	0	0	1	1	2
	CEE 0.625 mg	175	1	4	6	1	1	0
	CEE+MPA 10 mg/12 days	174	1			2	0	4
	CEE+MPA 2.5 mg	174	0			0	0	1
	CEE+ progesterone 200 mg/12 days	178	3			4	0	1
Aloia et al, 1995a,b	Placebo, calcium	~78‡	–	–	–	1	–	–
	CEE 0.625+MPA 10 mg/10 days	~39‡	–	–	–	0	–	–
Derman et al, 1995	Placebo	42	0§	–	–	–	–	–
	Oestradiol 2-1mg+NETA 1 mg/6 days	40	0	–	–	–	–	–
Tonstad et al, 1995	Placebo	32	–	–	–	–	–	–
	Oestradiol 2-1mg+NETA 1 mg/10 days	46	–	–	–	–	–	–
Wimalawansa, 1995	Calcium	14	1	–	–	–	–	1
	Transdermal oestradiol 1.5 mg+progesterone 200 mg/12 days	15	0	–	–	–	–	0
Munk-Jensen et al, 1988,1994; Obel et al, 1993	Placebo	51	–	–	–	0	0	–
	Oestradiol 2 mg+NETA 1 mg	50	–	–	–	1	0	–
	Oestradiol 2 mg/1 mg+NETA 1 mg/10 days	50	–	–	–	1	1	–
Lufkin et al, 1992	Placebo	39	–	–	–	1	–	1
	Transdermal oestradiol 0.1 mg+MPA 10 mg/10 days	36	–	–	–	1	–	0
Svendsen et al, 1992	Placebo	25	0	0	–	–	–	0
	Oestradiol 2 mg+cyproterone 1 mg	25	0	0	–	–	–	0
	Oestradiol 2 mg+levonorgestrel 75 μg	25	0	0	–	–	–	1
Gallagher et al, 1991	Placebo	19	–	–	–	1	–	–
	CEE 0.6 mg	20	–	–	–	0	–	–
	CEE 0.3 mg+MPA 10 mg	21	–	–	–	0	–	–
Genant et al, 1990¶	Placebo	40	–	–	–	1	–	–
	Oestrone sulphate 0.3, 0.625, 1.25 mg	116	–	–	–	1	–	–
Resch et al, 1990	Placebo	16	0	–	0	–	–	–
	Oestradiol 2 mg, NETA 1 mg	15	1	–	1	–	–	–
Molander et al, 1990	Placebo	19	–	0	–	–	–	–
	Oestriol 3 mg/2 mg	21	–	1	–	–	–	–
Christiansen et al, 1990	Placebo	20	1	–	–	–	–	–
	Oestradiol 2 mg+NETA 1 mg	20	1	–	–	–	–	–
Jensen et al, 1989*; Hassager et al, 1987	Placebo	39	–	–	–	–	–	–
	Oestradiol 2 mg+cyproterone 1 mg/7 days	37	–	–	–	–	–	–
	Oestradiol 2 mg+NETA 1 mg	24	–	–	–	–	–	–
Riggs et al, 1982	Placebo, calcium	54	–	–	–	–	–	–
	CEE 0.625-2.5 mg	32	–	0	–	–	0	–
	CEE 0.625-2.5 mg+fluoride	28	–	0	–	–	0	–
Christensen et al, 1982**	Placebo	24	–	–	–	–	–	0
	Oestradiol 4 mg, oestriol 2 mg+NETA 1 mg/10 days	25	–	–	–	–	–	1
	Oestradiol 2 mg, oestriol 1 mg+NETA 1 mg/10 day s	24	–	–	–	–	–	0
	Oestradiol 1 mg, oestriol 0.5 mg+NETA 1 mg/10 days	27	–	–	–	–	–	0
Christiansen et al, 1981**	Placebo (vitamin D_3)	48	–	–	–	–	–	–
	Oestradiol 4 mg, oestriol 2 mg+NETA 1 mg/6 days	23	–	–	–	–	–	1
	Oestradiol 4 mg+vitamin D_3	21	–	–	–	–	–	0
Coope, 1981	Placebo	26	0	–	–	–	–	–
	Oestrone sulphate	29	1	–	–	–	–	–
Christiansen et al, 1980**	Placebo	121	–	–	–	1	–	1
	Oestradiol 4 mg, oestriol 2 mg+NETA 1 mg/6 days	29	–	–	–	2	–	0
	Oestradiol+thiazide	27	–	–	–		–	0
Nachtigall et al, 1979	Placebo	84	3	1	17	4	1	2
	CEE 2.5 mg+MPA 10 mg/7 days	84	1	0	13	0	0	2
Lindsay et al, 1984	Placebo	30	0	–	–	–	–	1
	CEE 1.25, 0.625, 0.3, 0.15 mg	120	0	–	–	–	–	–
Aitken et al, 1973	Placebo	66	0	–	0	–	–	1
	Mestranol 40 μg	68	3	–	1	–	–	0

CEE=conjugated equine oestrogen, NETA=norethisterone acetate, MPA=medroxyprogesterone acetate, 0=data explicitly mentioned but no cases found, – = data not mentioned. The trial of Jensen et al, 1989 and the trials of Christensen et al, 1982, Christensen et al, 1981, and Christensen et al, 1980 possibly examine the same populations.
*Includes cardiac arrest, ischaemic attack, myocardial infarction, heart failure, cerebrovascular accident. †Includes pulmonary embolus, deep vein thrombosis. ‡Exact numbers of women not given. §One pre-existing thromboembolic disorder was discovered. ¶Results not specified for oestrogen group.

with three months or more of treatment (specifically saying "no adverse events" or "no drop outs due to adverse events") were included, and women from these trials contribute to the denominators. If the fate of all those who dropped out or the women lost to follow up was not clear, such a trial did not contribute to the denominator. Trials studying the acute effects of oestrogens (three months or less of treatment) and crossover trials with treatment for three months or less in the first cycle were excluded. Trials with women who had undergone oophorectomy were specified separately. With the exception of the trial by Nachtigall et al,[18] cardiovascular and cancer outcomes were reported as incidental (reasons for drop outs or adverse effects). Such data were not given in summaries but required the reading of methods and results sections. Because of the large number of published studies on postmenopausal hormone therapy, we may have missed some pertinent trials, but this selection is unlikely to depend on the differential cardiovascular and cancer events by treatment groups.

We identified 22 pertinent trials (appendix). Some trials—for example, the Danish trial from 1983-5—were included in several different reports, and their results were combined. Most trials concerned a very selective group of healthy women, but some included special subgroups. Because of the varying lengths of treatment, regimens used (see table 1), and the vagueness of describing health outcomes a formal meta-analysis was not carried out. Whether the data concerned numbers of patients or numbers of events was not always clear, but whenever possible, we took the numbers of patients. The number of women originally allocated to the groups was used as the denominator.

Odds ratios (of the outcome in question with postmenopausal hormones divided by the outcome among controls) and their 95% confidence intervals were calculated by summing the events and denominators of the trials. Two different P values were calculated for cardiovascular diseases. The first one gives the probability of obtaining the calculated odds ratio when 0.7 (a hypothetical benefit concluded from previous literature) is assumed.[19] The second P value gives similar probability assuming the correct odds ratio to be 0.5.

Results

The types and dosages varied in different studies and, with the exception of the PEPI trial[17] and the trial by Speroff et al,[20] the numbers of women were small (table 1). In most reports the data on cardiovascular events and cancer were given incidentally, without description of how the event was defined, when it was detected, or how serious it was. Often all reasons for drop outs were not specified but said to be "unrelated to treatment." Sometimes the timing of the event was given, especially if the event occurred very soon after the treatment. In most studies the data on cardiovascular events and cancers were available as reasons for dropping out and thus refer to numbers of patients. In the PEPI trial adverse events were given (110 events experienced by 97 women), and it is therefore possible that some women appear more than once in table 2.

There were fewer women with cardiovascular and thromboembolic events in the groups who did not receive hormone therapy than in the groups who did (table 2). The 95% confidence interval includes 1, but, as shown by the P values, it is unlikely that such a finding would have been found if the true odds ratio was 0.7. The likelihood of finding of an odds ratio of 1.64, if the true odds ratio was 0.7, is 0.04.

Table 2 Numbers of women with events, with odds ratios and probability of finding observed odds ratio*

Event	Hormone	Control	Odds ratio (95% CI)	P_1	P_2
Cardiovascular and thromboembolic:	17	6	1.64 (0.65 to 4.18)	0.04	0.01
Cardiovascular	12	5	1.39 (0.48 to 3.95)	0.10	0.03
Thromboembolic	5	1	2.89 (0.34 to 24.78)	0.10	0.05
Phlebitis	21	17	0.71 (0.37 to 1.35)	0.48	0.14
Breast cancer	19	9	0.85 (0.38 to 1.89)	NA	NA
Uterine cancer	2	2	0.58 (0.08 to 4.10)	NA	NA
Other cancers	12	8	0.86 (0.35 to 2.12)	NA	NA

*Numbers of women in hormone and control groups trials 1818 and 1041.
P_1=probability of obtaining this odds ratio when 0.7 is true value.
P_2=probability of obtaining this odds ratio when 0.5 is true value.
NA=not applicable.

To see how sensitive the odds ratios were for inclusion of different kinds of trials we calculated odds ratios for each outcome in three other ways: excluding trials with oophorectomised women; excluding the trial by Nachtigall et al[18] (because the results of that trial differed from those of other trials notably); and also excluding the trials with less than one year of treatment. None of these calculations suggested that women receiving hormone therapy would have fewer cardiovascular events. In all analyses the difference in regard to thromboembolic events was larger than that for cardiovascular events.

Superficial thrombophlebitis was reported in only three trials. The incidence in the hormone group was higher in the PEPI trials and lower in the trial by Nachtigall et al[18]. Because reporting it as a reason for dropping out is less likely than for the more serious reasons it was not combined among the rest of thromboembolic diseases.

When we included all trials the rate of breast cancer was lower in the hormone group (table 2). Only four women with uterine cancer (two in both groups) were reported (odds ratio 0.58). The number of uterine cancers in the hormone groups, however, is probably underestimated. It was commonly reported that women were excluded because of irregular or continuous bleeding or sometimes endometrial hyperplasia was reported. But the cause of the bleeding or outcome of hyperplasia was not specified.

Discussion

The results of these pooled (mostly) randomised data do not support the notion that postmenopausal hormone therapy prevents cardiovascular events. It is unlikely that the calculated odds ratios would have been found if the true odds ratio was 0.7 or less. The numbers of women with events, however, as well as the total numbers of women were small.

There is no reason to believe that events were reported differently by group, but the absolute risk of adverse effects cannot be concluded. If the woman continued in the study an adverse effect would probably have remained unreported. Furthermore, in many trials women were lost to follow up, and even

Key messages

- The results of these pooled data do not support the notion that postmenopausal hormone therapy prevents cardiovascular events
- These results concern only short term effects of postmenopausal hormone therapy, and long term effects may be different
- There have been hundreds of trials studying the impact of hormones on various physiological phenomena, laboratory values, osteoporosis, symptoms, or various health problems but few fully report adverse effects. Small trials would be useful in studying unintended effects if they were more systematically reported

more trials gave no data on reasons or numbers of drop outs or losses to follow up. Most trials had selected only healthy women. Therefore the effects of postmenopausal therapy on sick women cannot be inferred from these results. This is especially noteworthy because currently many experts recommend hormone therapy for women either with cardiovascular diseases or those at high risk.

Our results concern short term effects of postmenopausal hormone therapy. It is quite possible that long term effects are different, both for cardiovascular diseases and for cancer. Short term effects on cardiovascular diseases are likely to occur through changes in blood viscosity, the arterial wall, and blood pressure and through cardiac arrhythmias. Long term effects—for example, because of blood lipids and various general physiological and psychological effects—may take years to have their impact. Breast cancer detected soon after a treatment—if it is related to the treatment—is likely to result from a promotion or activation of a pre-existing cancer. Carcinogenic effects or slower tumour promotion may take years or decades to show up.

The searches for this study revealed hundreds of trials studying the impact of hormones on various physiological phenomena, laboratory values, osteoporosis, symptoms, or health problems other than those of interest in this study. But usually they did not report adverse effects fully if at all. Pooled analyses, including meta-analysis, have greatly enhanced the usefulness of small trials in studying intended effects. The same could be true for adverse effects and other unintended effects, if they were always systematically reported.

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Appendix

Papers revealed by searches

A table describing the following trials is available from EH.

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A memorable patient

Early treatment of *H pylori*

Summarising yet another set of notes the other day, I came across a consultation from nearly 10 years ago that I easily recalled. At the time it had made an impact as I thought the patient most strange. Much later it had come back to me as I realised that he was right and I was wrong. I had not managed to remember who he was so could not confirm the details, until now.

The patient was a man in his middle years who had come for his tablets. He had acne rosacea and was on intermittent six week courses of oxytetracycline. He needed them only two or three times a year to keep it at bay. As I was new to the practice and he did not come in often, I remember asking him if he was otherwise fit and well. He mentioned his occasional indigestion and then said something that struck me as quite odd. My note of the consultation reads "Repeat Rx Oxytet 100. Occ. Indigestion. Says oxytet cures it!" I had underlined the latter and added the exclamation mark as I was so surprised. I remember asking him to clarify which tablets he thought helped his indigestion and having it confirmed. He had not bothered to finish the course of cimetidine given by my colleague a few months before; they had not worked. At the time I thought him very strange. Antibiotics did not cure indigestion in 1987.

A few years later, when the bug that was to be named *Helicobacter pylori* was discovered, I had cause to remember this consultation. One of the original recommendations for the treatment of *H pylori* was tetracyclines, and some regimens still suggest them. Resistance is now a problem but this patient had made an observation. If only I had realised that he was right and that I was wrong, I might have made the breakthrough. Oh well, that was obviously not to be my destiny. Had I told my colleagues of this "breakthrough" I would have been laughed at—H2 blockers were the mainstay of treatment then, not antibiotics.

This man taught me several things. The simplest consultation can stick in your mind in great detail and come back years later, when its significance is realised. The patient may seem peculiar, but he may be telling you something that is revolutionary. We ignore such things that do not fit into the standard view at our peril.

Trefor Roscoe, *general practitioner, Sheffield*

We welcome filler articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake,* or any piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk.

Randomised, double blind, multicentre comparison of hydrochlorothiazide, atenolol, nitrendipine, and enalapril in antihypertensive treatment: results of the HANE study

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Abstract

Objective: To compare the effectiveness and tolerability of hydrochlorothiazide, atenolol, nitrendipine, and enalapril in patients with mild to moderate hypertension.
Design: Randomised multicentre trial over 48 weeks with double blind comparison of treatments.
Setting: 48 centres in four countries.
Patients: 868 patients with essential hypertension (diastolic blood pressure 95-120 mm Hg)
Interventions: Initial treatment (step 1) consisted of 12.5 mg hydrochlorothiazide (n = 215), 25 mg atenolol (n = 215), 10 mg nitrendipine (n = 218), or 5 mg enalapril (n = 220) once daily. If diastolic blood pressure was not reduced to < 90 mm Hg within four weeks, doses were increased to 25 mg, 50 mg, 20 mg, 10 mg, respectively, once daily (step 2) and after two more weeks to twice daily (step 3). The eight week titration phase was followed by an additional 40 weeks for patients who had reached the target diastolic pressure.
Main outcome measure: Blood pressure by means of an automatic device with repeated measurements.
Results: After eight weeks the response rate for atenolol (63.7%) was significantly higher than for enalapril (50.0%), hydrochlorothiazide (44.7%), or nitrendipine (44.5%). After one year atenolol was still more effective (48.0%) than hydrochlorothiazide (35.4%) and nitrendipine (32.9%), but not significantly better than enalapril (42.7%). The treatment related dropout rate was higher ($P < 0.001$) in the nitrendipine group (n = 28).
Conclusions: There is no evidence of superiority for antihypertensive effectiveness or tolerability of the "new" classes of antihypertensives (calcium channel blockers and angiotensin converting enzyme inhibitors). As these drugs are now widely used as treatment of first choice, our results further emphasise the need for studies confirming that they also reduce morbidity and mortality, as has been shown for diuretics and β blockers.

Introduction

In the past three decades remarkable progress has been made in the treatment of hypertension by introduction of new well tolerated drugs. In large scale and properly controlled trials β adrenergic blockers and thiazide diuretics have been shown to reduce clinical end points related to strokes, coronary artery disease, left ventricular failure, and mortality.[1-4]

The fact that other classes of drugs exert a favourable influence on a number of important but substitute end points—such as lipid concentrations, left ventricular mass, insulin resistance, microalbuminuria—can affect the choice for an individual patient, but it does not eliminate the need for unequivocal proof that the incidence of clinical end points is in fact reduced. Several national and international committees have nevertheless recommended the use of angiotensin converting enzyme inhibitors and calcium channel blockers for initial single drug therapy as an alternative to the established treatment with β blockers and diuretics,[5-8] but only a few studies have been carried out to compare these four classes of antihypertensive drugs in long term controlled trials with sufficiently large populations.[9-11] One of the studies referred only to men[10] and another referred to hypertensive patients with a diastolic pressure < 100 mm Hg (mean 92 mm Hg).[9]

We therefore evaluated the effectiveness and the tolerability of these four important therapeutic principles in hypertensive patients in a double blind controlled study over one year. Hydrochlorothiazide, atenolol, nitrendipine, and enalapril were selected as representatives of these antihypertensive classes and are recommended for once daily application. All these drugs have been well known for many years, and all have been studied in large controlled trials.

Patients and methods

The HANE (hydrochlorothiazide, atenolol, nitrendipine, enalapril) study was designed as a double blind, randomised, multicentre trial with the primary objective of comparing the antihypertensive effectiveness and tolerability of the four drugs. Specifically, we sought to determine the ability to control blood pressure over time and the incidence of premature terminations of treatment for medical reasons. Secondary objectives were to analyse the influence of characteristics of patients that determine the effectiveness of treatment.

The study design of the HANE study was similar to that of the VERDI (verapamil diuretic) study, in which we compared verapamil and the diuretic drug hydrochlorothiazide.[12] The study comprised a single blind placebo phase lasting two weeks followed by double blind active treatment. All antihypertensive medication used before enrollment in the trial was discontinued within two weeks of the initial visit. The study population comprised male and female outpatients with an age range of 21-70 years and a resting (sitting) diastolic blood pressure of 95-120 mm Hg.

Exclusion criteria

Exclusion criteria were as follows. Firstly, contraindications with regard to the drug classes under evaluation: frank congestive heart failure; atrioventricular blocks; sick sinus syndrome; sinus bradycardia (< 50 beats/min); pregnancy; known renovascular hypertension; and known intolerance to the drugs. Secondly, patients

with unacceptable risks with regard to the wash out and placebo phase: a diastolic blood pressure <95 or >120 mm Hg at the beginning or at the end of the placebo phase; myocardial infarction within the past six months. Thirdly, possible interactions of the primary and secondary objectives of the trial: concomitant use of any other drug with antihypertensive potency (that is, for other diseases); hyperuricaemia, hyperlipidaemia or diabetes mellitus requiring treatment with drugs; the use of oral contraceptives; serum creatinine ≥ 150 µmol/l; hypokalaemia <3.6 mmol/l. Finally, we excluded any other patients who had a history of or evidence for malignancy or other serious diseases sufficient to interfere with long term adherence to trial protocol and those over 30% overweight.

Patients were included only after consent had been obtained after detailed written explanation of the nature and purpose of the investigation. The study protocol was approved by the ethics committee of the German Society of Hypertension.

Measurement of blood pressure

To ensure standardised blood pressure recordings at all participating centres the blood pressure was measured by means of an automatic instrument (Tonoprint electronic, Speidel und Keller, Jungingen, Germany) as described in the VERDI study.[12] The blood pressure and pulse rate values are printed out with the date and time of day. The Tonoprint has been tested and evaluated as described.[12] After 5 minutes of rest six recordings were taken every 2 minutes while the patient was sitting. All decisions about admission to the study and about changes in treatment were based on the average of the first five recordings. The printout dates were included in the follow up records and checked by the central office.

Patients

Between 1991 and 1993 a total of 1218 patients were screened at 48 centres (see appendix) for possible inclusion; of these, 287 patients could not be considered for randomisation because the diastolic pressure had dropped below the limit of 95 mm Hg or was over 120 mm Hg under placebo at any visit. Four centres with a total of 38 patients were excluded in an early phase of the trial because of incorrect use of the automatic blood pressure device. Twenty five patients were excluded for other reasons, including over 30% overweight ($n=14$), concomitant use of antihypertensive drugs ($n=3$), and other violations of the protocol ($n=8$). Of the remaining 868 patients, 215 were randomised to hydrochlorothiazide, 215 to atenolol, 218 to nitrendipine, and 220 to enalapril.

Study course and drug doses

Treatment was started with a dose titration phase during which the blood pressure was taken at two week intervals. The initial low dose was maintained for four weeks and was then increased stepwise if the diastolic blood pressure had not been lowered to below 90 mm Hg. Specifically, the dose of hydrochlorothiazide was increased from 12.5 mg (step 1) to 25 mg once daily (step 2) and then to 50 mg (step 3), this last dose being given as 25 mg twice daily; atenolol was increased from 25 mg to 50 mg once daily and then to 50 mg twice daily; nitrendipine from 10 mg to 20 mg once daily and then to 20 mg twice daily; and enalapril from 5 mg to 10 mg once daily and finally to 10 mg twice daily. The eight week titration phase was followed by a long term phase of an additional 40 weeks for those patients who had reached the target of diastolic pressure below 90 mm Hg. Patients who did not reach the target blood pressure at the end of the titration period were considered to be non-responders and were withdrawn. During the long term phase, blood pressure was checked after 4, 8, 16, 28, and 40 weeks.

If at one visit during the study the target blood pressure was not achieved after at least two weeks on the highest dose (step 3) the patients were withdrawn from the main trial. Other reasons for discontinuation of treatment were specified as a diastolic pressure >120 mm Hg in the course of the study, severe adverse events, non-compliance, development of a new serious disease unrelated to the test treatment, and emergence of a new exclusion criterion. Patients withdrawn because of blood pressure, adverse events, or non-compliance were counted as non-responders. Withdrawals because of one of the remaining reasons were considered non-evaluable with respect to patients' response to the respective treatment.

The drugs were specially manufactured for study purposes and tested for bioequivalence with commercially available standard formulations. As all active treatments could not be provided in the same manner, two different tablets were made up—one kind for blinding of hydrochlorothiazide and enalapril and the other for blinding of atenolol and nitrendipine.

Randomisation was performed centrally in the biometrical trial office.

At each visit blood pressure and pulse rate were measured as close as possible to 24 hours after the last medication during the placebo period and during steps 1, 2 (once daily treatment), or as close as possible to 12 hours after the last medication during step 3 (twice daily treatment).

Statistical analysis

The confirmatory part of the analysis consisted of tests for differences in the response rates (diastolic pressure <90 mm Hg) between all pairs of treatments obtained after 8, 24, and 48 weeks of single drug treatment. To ensure a multiple significance level of 5% for all comparisons referring to the same trial period, the P values obtained from the respective set of six pairwise χ^2 tests were assessed by means of HOLM's sequentially rejective multiple test procedure.[13]

With 200 patients per group the power of this multiple test to detect a difference of 0.15 between the

Table 1 Baseline data on patients treated with hydrochlorothiazide, atenolol, nitrendipine, and enalapril

Detail	Atenolol	Enalapril	Hydrochlorothiazide	Nitrendipine
No of patients	215	220	215	218
Mean age (years)	53.4	53.1	53.5	53.0
Broca index (%)	111.1	110.3	109.4	109.1
Men/women	1.1	1.3	1.1	1.2
Systolic blood pressure (mm Hg)	151.8	151.9	151.4	152.0
Diastolic blood pressure (mm Hg)	103.7	103.5	103.3	103.7
Pulse (beats/min)	76.8	77.4	77.7	78.4

Broca index=(height−100)/weight in %.

Table 2 Numbers of patients withdrawn during 48 (and 8) weeks of treatment

Reason	Atenolol	Enalapril	Hydrochlorothiazide	Nitrendipine	Total
Adverse effects	11 (8)	12 (10)	9 (6)	28 (23)*	60 (47)
New disease	2 (2)	1 (0)	2 (0)	0 (0)	5 (2)
New exclusion criterion	3 (0)	4 (4)	4 (3)	1 (0)	12 (7)
Compliance	13 (6)	14 (9)	9 (4)	15 (7)	51 (26)
Other reasons	1 (0)	1 (0)	4 (1)	4 (1)	10 (2)
Total	29 (16)	32 (23)	28 (14)	48 (31)	137 (84)

*P<0.001.

Table 3 Rates of response (in percentages) to various treatments for hypertension according to attainment of diastolic blood pressure <90 mm Hg. Values in parentheses are numbers of patients

Week of treatment	Atenolol (n=215)	Enalapril (n=220)	Hydrochlorothiazide (n=215)	Nitrendipine (n=218)
8	63.7 (137)	50.0 (110)	44.7 (96)	44.5 (97)
48	48.0 (103)	42.7 (94)	35.4 (76)	32.9 (72)

responder rates when one of them equals 0.50 was computed to be about 70%. (The exact numerical value of the power depended on the magnitude of the differences between all other pairs of responder rates.)

Numerous additional analyses for subpopulation comparisons were performed only in an explorative manner with respect to treatment effects. P values obtained from these additional tests are reported for descriptive information only.

Results

Characteristics of the patients

Table 1 gives the characteristics of patients on entry into the study. All four treatment groups were well balanced in terms of systolic and diastolic blood pressure, heart rate, sex, age, weight, and previous treatment.

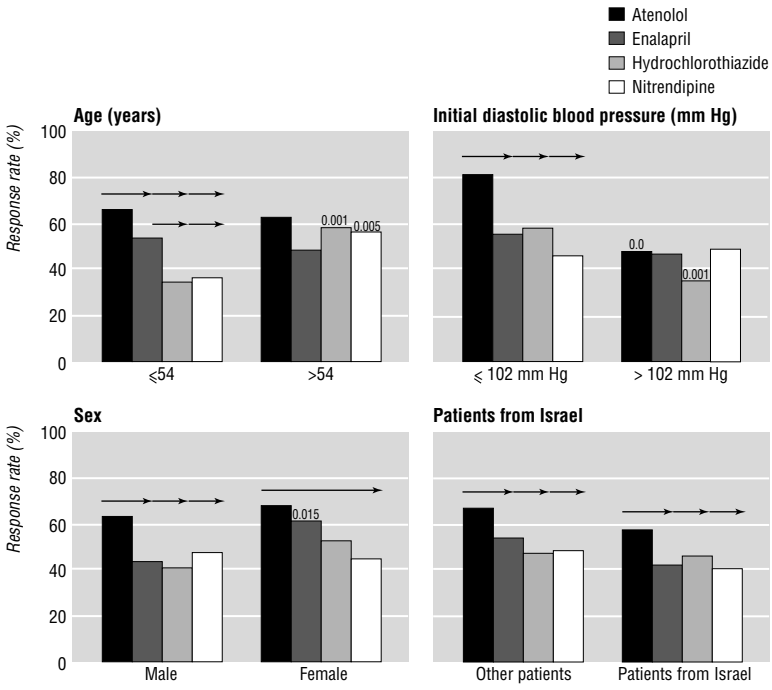

Fig 1 Rates of response to various treatments for hypertension after eight weeks of treatment in various subgroups. Arrows show significantly higher response rate at multiple 5% level. Descriptive P values within therapeutic regimens are also given

Response rate

Titration phase—Eighty four patients did not finish the titration phase because of adverse events and administrative causes (table 2). Of the 868 patients available for the titration period, 440 (50.7%) achieved the target diastolic pressure <90 mm Hg. With all regimens of steps 1 to 3, target blood pressure at the end of the titration period was more often achieved with atenolol (63.7%; 23.3% and 40.7% on step 1 and 2, respectively) than with enalapril (50.0%; 17.0% and 32.8%), hydrochlorothiazide (44.7%; 12.1% and 30.3%), or nitrendipine (44.5%; 14.1% and 28.5%). At the multiple 5% level the response rate to atenolol was significantly higher than that to the three other drugs. The differences between enalapril, hydrochlorothiazide, and nitrendipine were not significant (table 3).

Long term phase—Four hundred and forty patients were included in the long term phase and 324 patients finished the study after 48 weeks with blood pressure below the target: 96 (74 reached target blood pressure) treated with hydrochlorothiazide, 137 (98) treated with atenolol, 97 (69) with nitrendipine, and 110 (93) with enalapril. After 48 weeks of treatment the diastolic pressure was below the target in 48.0% of those initially treated with atenolol. The response rate to atenolol was no longer significantly different from that to enalapril (42.7%), but atenolol was still significantly better than hydrochlorothiazide (35.4%) and nitrendipine (32.9%) ($P<0.001$; table 3).

Sex, age, and blood pressure before treatment

Figure 1 shows the response rates for various subgroups after week 8 according age, sex, and blood pressure of the patients. Age and diastolic blood pressure were dichotomised by using the respective median values (54 years and 102 mm Hg) as the cut points.

In younger patients ($\leq$54 years) atenolol and enalapril were more effective ($P<0.001$) than hydrochlorothiazide and nitrendipine after eight weeks and after 48 weeks. Within the pairs (atenolol and enalapril versus hydrochlorothiazide and nitrendipine) there were no clear differences. In older patients (>54 years) no differences could be found within the therapeutic regimens.

Both nitrendipine (descriptive P value <0.001) and hydrochlorothiazide ($P=0.004$) were significantly more effective in older than in younger patients (fig 1). This result could not be explained by a baseline difference in blood pressure (mean diastolic pressure 103.4 mm Hg in younger and 103.7 mm Hg in older subgroup).

In men the higher effectiveness of atenolol compared with enalapril, hydrochlorothiazide, and nitrendipine was found only at week 8 ($P<0.001$), whereas at week 48 no difference could be found. In women the response rate to atenolol was higher than that to nitrendipine at week 8 ($P<0.001$) and week 48, whereas no substantial differences between the other regimens were observed.

Women responded better in general to antihypertensive treatment than men (55.0% *v* 47.7%). Among these enalapril was clearly more effective in women (59.0% *v* 42.5%; $P=0.015$) (fig 1).

As expected the response rate was significantly higher for atenolol and hydrochlorothiazide ($P<0.001$) at lower levels of pretreatment blood pressure

(≤102 mm Hg), whereas the effect of enalapril was only slightly more pronounced (P = 0.042). This, however, did not apply to nitrendipine, which turned out to be equally effective in patients with higher blood pressures. In the subgroup with higher blood pressures no drug was superior.

Overall, patients treated in Israel responded less well (44.0% *v* 52.3% for the other patients), but atenolol was again the most effective drug (fig 1).

Withdrawals and adverse events

One hundred and thirty seven patients had to be withdrawn from treatment for various reasons (table 2), 84 of them during the dose titration period. In the nitrendipine group the incidence of withdrawals because of adverse events was significantly higher (P < 0.001) than in the other groups. The main reasons for withdrawal with nitrendipine were headache, flush, or palpitations (22/28) and intolerable oedema (3). The major reasons for dropout in the hydrochlorothiazide patients were gastrointestinal complaints (4/9) and muscle cramps (2); in the atenolol group they were fatigue (6/11) and cold hands (3), and in the enalapril group they were cough (6/12) and gastrointestinal complaints (4). An age dependence of dropouts related to adverse events was observed only in patients treated with nitrendipine (23 in younger patients *v* 5 in older patients) and atenolol (3 *v* 8, respectively).

Discussion

The HANE study was designed to compare the four most commonly used classes of antihypertensive drugs in the initial treatment of mild to moderate hypertension. The individual representatives of these classes were selected on the grounds of long term experience and on their recommendation for once daily application. The comparison was undertaken because up to now there have not been any long term intervention studies providing evidence for a reduction in mortality and morbidity with the use of calcium channel blockers and angiotensin converting enzyme inhibitors. In the absence of such comparisons a minimum requirement for recommending them as antihypertensive agents of first choice should be that they are as effective and as tolerable as the established classes of diuretics and β blockers in populations of patients of sufficient size treated for a sufficiently long time.

The size of our study population, with more than 200 patients per treatment group, and the duration of the study of nearly one year ensured adequate power to detect differences between the test drugs in antihypertensive effectiveness and in tolerability.

Qualitative differences between antihypertensive drugs can be assessed principally by comparing first their antihypertensive potency (the responder rates) and then their tolerability (the incidence of adverse events and dropout rates). On this basis two compounds which do not differ in these two respects could be said to be "equivalent" antihypertensive drugs. The comparison becomes more difficult, however, if superior antihypertensive potency of one drug is associated with poorer tolerability or vice versa.

According to these definitions and to the primary objective of this study, atenolol was superior to the other three reference drugs after eight weeks of treatment because it showed the highest responder rate and a treatment related rate of dropout that was similar to the rates of withdrawals under the alternative drugs. On the other hand, our assessment of nitrendipine would be more negative as its clearly higher dropout rate related to treatment was not associated with higher antihypertensive effectiveness. After 48 weeks the responder rate of atenolol was no longer different from that of enalapril, but atenolol was still more effective than hydrochlorothiazide and nitrendipine (table 3).

This kind of global assessment has to be qualified to some extent, however, because certain characteristics of patients interacting with the relative effects of the study drugs necessitate a more detailed assessment. More precisely, atenolol is superior in patients with mild to moderate hypertension but not in those with more severe hypertension (diastolic blood pressure > 102 mm Hg). In this subgroup all the treatment differences seem to vanish.

Further findings

A surprising finding was the influence of sex on the responder rates of the individual agents. Enalapril in particular was obviously more effective in women than in men (responder rate 59.0% *v* 42.5%; P = 0.015), a finding that to our knowledge has not been reported previously. A tendency towards a higher responder rate in women was similarly observed for hydrochlorothiazide (fig 1). In other comparable studies sex differences were either not evaluated[9 11] or the study population comprised only male veterans.[10] The reason for the superior effectiveness of enalapril in women is unclear; differences in plasma renin activity are obviously not responsible because we did not observe any differences between men and women in the baseline plasma renin activity, as will be reported in detail elsewhere.

The question of whether the patient's age could be a determinant of the response to some antihypertensive drugs has often been discussed.[14-16] In line with the results of other studies in large patient populations[9 10] we did not observe a superior antihypertensive effectiveness of the β blocker atenolol in younger patients. Differences relevant to treatment between younger and older patients were found only with hydrochlorothiazide and nitrendipine. These two drugs seem to be more effective in elderly patients (fig 1), as has been reported by other authors.[12 16] There has been much speculation about the apparently enhanced effectiveness of diuretics and calcium channel blockers with advancing age, possibly because of differences in the activity of the sympathetic nervous system,[17] plasma renin activity,[16] sodium turnover,[17] and age related differences in pharmacokinetics. On the basis of our data (not presented here) we cannot say that differences in plasma renin activity between subgroups could be responsible for this apparent enhancement as plasma renin activities were similar in older and younger patients.

Age may also be an important determinant in the assessment of tolerability. With nitrendipine, withdrawals because of adverse events were much less common in elderly patients (5 *v* 23), whereas in the atenolol group 8 out of 11 withdrawals were in the older subgroup. Consequently, we conclude from our

data that in elderly patients nitrendipine is as effective as the three other antihypertensives, as effective as in patients with higher blood pressure, and better tolerated than it is in younger patients.

During the first eight weeks of treatment, atenolol was superior to all other drugs used in this trial, although during the long term treatment phase of the study the difference from enalapril was no longer significant (table 3). There are only a few studies in which three or more antihypertensive drugs derived from different classes have been compared during long term treatment.[9-11 18] In these studies the β blocker proved to be at least as effective as the reference drugs in lowering blood pressure in white patients, the only race we investigated. In our investigation the extent of superiority of β blocker treatment depended on the patient's age, sex, and initial blood pressure.

We are aware that our conclusions about the comparative effects of the drugs studied are influenced by the selected doses and that different results might have been obtained with different doses. On the other hand the doses chosen correspond to the recommendations of the selling companies and are in keeping with the anatomical therapeutic chemical classification index[19] of the World Health Organisation, which includes "defined daily doses" for plain substances.

Moreover, with regard to the possibility that different pharmacodynamic properties could be responsible for the outcome of this study, we decided that with the second increase in dose (step 3) every drug should be given twice daily, although all of these drugs are recommended for once daily application. It should also be considered that blood pressure and pulse rate were measured as close as possible to 24 hours after the last medication during once daily treatment and as close as possible to 12 hours during twice daily treatment.

Verifiable measurement

One important methodological objective of this study was to measure the blood pressure as objectively as possible and to perform those measurements in a way that would allow some verification even after they had been taken. For this purpose all participating centres used the same automatic instrument, which measured blood pressure in preset intervals and printed out the results with the date and the time of day (see methods).

With this method of objective and verifiable measurement we were unable to detect any relevant reduction in blood pressure during the placebo run-in phase, in full accord with the results of our previous VERDI study,[12] in which we used the same automatic blood pressure instrument. These results suggest that with this technique there is little if any placebo effect, in keeping with the experience with 24 hour ambulatory blood pressure measurements.[20]

Conclusions

Our results do not provide any evidence for a superior antihypertensive effectiveness or superior tolerability of the new classes of antihypertensive products—namely, calcium channel blockers and angiotensin converting enzyme inhibitors. As these new drugs are now widely accepted as treatments of first choice our results further emphasise the need for research to confirm that they do reduce morbidity and mortality, as has been shown for diuretics and β blockers.

Key messages

- Calcium channel blockers and angiotensin converting enzyme inhibitors as initial monotherapy in the treatment of hypertension
- Reduction in mortality has been shown only with established β blockers and diuretics
- Comparison of treatment with hydrochlorothiazide, atenolol, nitrendipine, and enalapril showed no superiority of the new drug classes
- Atenolol was the most effective drug, while nitrendipine showed the highest drop out rate
- Elderly patients respond better to hydrochlorothiazide and nitrendipine , and women better to enalapril, although in both subgroups the highest rate of response was with atenolol

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Conflict of interest: None.

Appendix

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Inpatient deaths from acute myocardial infarction, 1982-92: analysis of data in the Nottingham heart attack register

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Abstract

Objective: To assess longitudinal trends in admissions, management, and inpatient mortality from acute myocardial infarction over 10 years.
Design: Retrospective analysis based on the Nottingham heart attack register.
Setting: Two district general hospitals serving a defined urban and rural population.
Subjects: All patients admitted with a confirmed acute myocardial infarction during 1982-4 and 1989-92 (excluding 1991, when data were not collected).
Main outcome measures: Numbers of patients, background characteristics, time from onset of symptoms to admission, ward of admission, treatment, and inpatient mortality.
Results: Admissions with acute myocardial infarction increased from 719 cases in 1982 to 960 in 1992. The mean age increased from 62.1 years to 66.6 years ($P < 0.001$), the duration of stay fell from 8.7 days to 7.2 days ($P < 0.001$), and the proportion of patients aged 75 years and over admitted to a coronary care unit increased significantly from 29.1% to 61.2%. A higher proportion of patients were admitted to hospital within 6 hours of onset of their symptoms in 1989-92 than in 1982-4, but 15% were still admitted after the time window for thrombolysis. Use of β blockers increased threefold between 1982 and 1992, aspirin was used in over 70% of patients after 1989, and thrombolytic use increased 1.3-fold between 1989 and 1992. Age and sex adjusted odds ratios for inpatient mortality remained unchanged over the study period.
Conclusions: Despite an increasing uptake of the "proved" treatments, inpatient mortality from myocardial infarction did not change between 1982 and 1992.

Introduction

Coronary care units were first established in the 1960s,[1] and subsequently inpatient mortality fell from 23-40% to 16-18%.[1-3] It was generally believed that the fall was secondary to the detection and appropriate management of serious arrhythmias. More recently, large multicentre randomised trials have documented improvements in outcome after the use of aspirin,[4] β blockade,[5] and thrombolysis,[4 6 7] all of which have become standard management in myocardial infarction. In an overview of the thrombolytic trials, mortality at 35 days was 9.6% in those treated with thrombolysis compared with 11.5% in controls,[8] although the numerous exclusion criteria pertaining to trials mean that the general population of patients with infarction may not experience such an improvement. Although most deaths from myocardial infarction occur in the first two hours after the onset of symptoms and outside hospital, the above clinical trials have been concerned with hospital based treatments that are effective at improving survival.

We documented from a hospital perspective all admissions of patients with myocardial infarction in a defined community over 10 years. We determined the uptake of proved treatments and observed whether any changes in inpatient mortality might be related to the previously documented fall in overall death rates from ischaemic heart disease in Nottingham.[9]

Methods

The methods of data collection for the Nottingham heart attack register have been previously described,[10] but in brief all patients admitted to Nottingham's hospitals with symptoms suggesting acute myocardial infarction were identified prospectively, and an extensive record of management and outcome was documented.

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Table 1 Age of patients admitted with acute myocardial infarction in Nottingham, 1982-4 and 1989-92

Age (years)	1982	1983	1984	1989	1990	1992
<55	179	177	147	170	118	140
55-59	104	113	119	101	103	100
60-64	128	123	134	121	157	149
65-69	124	126	103	156	133	148
70-74	98	99	122	147	134	166
⩾75	86	107	124	233	195	257
Total	719	745	749	928	840	960

Data for 1991 were not collected (see text).

Patients were assigned to the following diagnostic categories after the hospital case records had been reviewed by the physician responsible for the register at the time: definite myocardial infarction; possible myocardial infarction; ischaemic heart disease; chest pain, unknown cause; and "other diagnosis." For this study we retrieved data for analysis for the years before (1982, 1983, and 1984) and after (1989, 1990, and 1992) the widespread introduction of aspirin, β blockers, and thrombolysis (data were not collected in 1991). We included data only on patients who had had a definite myocardial infarction—namely, a convincing history plus either changes in the electrocardiogram that were diagnostic or a rise in cardiac enzymes to more than twice the upper limit of normal, or both. Changes over time in patients with a possible infarction will be reported separately.

The methods of data collection and the diagnostic criteria[10] used have remained the same since the register was established despite inevitable changes of staff over the years. Detailed comparative tests were undertaken during changeover of staff to ensure consistency of diagnosis. Patients who had a cardiac arrest outside hospital and who never recovered consciousness were not included in this analysis.

Baseline characteristics

We recorded age, sex, length of stay, "new" pathological Q wave or non-Q wave myocardial infarction, site of infarction, and electrocardiographic evidence of previous infarction. For 1989 onwards we collected information on documented history of previous myocardial infarction, previous coronary revascularisation, and Killip class (clinical estimate of infarct severity)[11] on admission. We documented time of onset of symptoms to admission to hospital for those who could recall either accurate times or a narrow time band—for example, three to four hours—and admission or transfer to a coronary care unit within 24 hours or management on a general medical ward. We noted details of inpatient treatment with antiarrhythmics, β blockers, anticoagulants (heparin, warfarin), digoxin, diuretics, angiotensin converting enzyme inhibitors, aspirin, and thrombolysis (streptokinase or alteplase) and recorded outcome in hospital .

Statistical analysis

Changes in discrete variables over time were analysed by using the χ^2 test. Linear models were fitted to determine whether trends had occurred over time for mean age and mean length of admission, the error terms for continuous variables being checked for normality first. A log transformation was performed on length of stay in hospital. All tests of significance were two tailed, with $P < 0.05$ considered to be significant.

Crude odds ratios for mortality were calculated by using 1982 as the standard year (odds ratio = 1) and then adjusted in a logistic regression model to take into account changes in age and sex across the years. The S–PLUS statistical package was used for all analyses.[12]

Results

Demographic and clinical characteristics

The total number of patients admitted with a suspected myocardial infarction rose from 2042 in 1982 to 4717 in 1992. The number with a final diagnosis of definite myocardial infarction, however, rose much less, from 719 in 1982 to 960 in 1992. The largest increase was in patients with possible infarction, previous evidence of ischaemic heart disease, or chest pain with an unknown cause.

Table 1 shows that the increase in the number of patients admitted with myocardial infarction was 70% in those aged 70 to 74 years and 200% in those aged 75 years and over.

Table 2 Characteristics of patients admitted with acute myocardial infarction in Nottingham, 1982-4 and 1989-92. Values are numbers (percentages) of patients unless stated otherwise

	1982 (n=719)	1983 (n=745)	1984 (n=749)	1989 (n=928)	1990 (n=840)	1992 (n=960)	P value
Mean (SD) age:	62.1 (10.6)	62.5 (11.3)	63.7 (11.1)	65.6 (12.0)	66.0 (10.9)	66.6 (11.7)	<0.001
Male	60.7 (10.2)	61.0 (10.8)	61.9 (10.7)	63.7 (11.6)	63.5 (10.8)	64.8 (11.4)	<0.001
Female	67.6 (10.4)	67.5 (11.2)	68.3 (10.6)	69.8 (11.8)	71.0 (9.2)	69.7 (11.5)	<0.001
Males	567 (79)	564 (76)	539 (72)	630 (68)	557 (67)	603 (63)	<0.001
Mean (SD) length of stay (days)	8.7 (7.4)	8.6 (6.5)	8.6 (7.8)	7.5 (5.8)	7.4 (4.5)	7.2 (6.5)	<0.001*
Previous myocardial infarction†	—	—	—	240 (26)	170 (20)	215 (22)	0.017
Previous Q wave infarction from electrocardiogram	60 (8)	86 (12)	74 (10)	61 (7)	61 (7)	39 (4)	<0.001
Previous coronary surgery†	—	—	—	12 (1)	4 (0.5)	13 (1)	0.136
Q wave infarction	424 (59)	411 (55)	431 (58)	473 (51)	483 (58)	688 (72)	<0.001
Anterior infarction	334 (46)	316 (42)	313 (42)	419 (45)	359 (43)	414 (43)	0.410
Killip class†:							
1	—	—	—	418 (45)	382 (45)	539 (56)	<0.001
2	—	—	—	442 (48)	370 (44)	311 (32)	<0.001
3	—	—	—	47 (5)	77 (9)	84 (9)	<0.001
4	—	—	—	20 (2)	11 (1)	20 (2)	0.347

Data for 1991 were not collected (see text).
*P values are for the log transformation on length of admission.
†Data for 1982-4 were not collected.

Table 2 shows that between 1982 and 1992 the mean age for both men and women admitted with acute myocardial infarction increased significantly, and the proportion of male patients admitted fell. The mean length of stay fell by 1.5 days; the proportion of patients with only electrocardiographic evidence of previous infarction (old Q waves) fell, as did, to a lesser degree, the proportion of those with a definite previous myocardial infarction (from medical history or electrocardiogram). There was no change in the small numbers of patients with previous coronary revascularisation. The proportion of patients with a new Q wave infarction increased significantly in 1992, but the proportion of patients with an anterior myocardial infarct did not change. Killip class was recorded only from 1989 onwards, but between 1989 and 1992 there was an increase in the proportion of patients in class 1, a small increase in class 3, a fall in class 2, and no change in class 4 (cardiogenic shock).

Admissions to coronary care

Table 3 shows the increasing numbers of patients admitted to coronary care. (Overall, about 75% of all patients with infarction admitted to hospital in Nottingham are cared for in such units.) The proportion of those aged 75 years and over who were managed in the unit rather than an ordinary medical ward doubled. However, the proportions of patients aged under 55 years and 55 to 64 years admitted to coronary care between 1982 and 1992 fell from 96.6% to 77.9% and from 94.2% to 77.0% respectively—equivalent to almost two young patients being managed on the general ward each week. Over the 10 years the proportion of women admitted to coronary care increased significantly, from 60% in 1982 to 67% in 1992 ($\chi^2 = 23.4$, df = 5, $P < 0.001$). Men were still more likely than women, however, to be admitted to the unit in 1992 ($\chi^2 = 11.28$, df = 1, $P < 0.001$).

Time from onset of symptoms to admission

A mean of 86.7% of patients over the study period were able to provide timing data, and table 4 shows the time from onset of symptoms to admission. The proportion of patients admitted within two to six hours of onset of their symptoms improved significantly between 1982-4 and 1989-92 ($P < 0.001$); the proportions of those admitted within 1 hour, 7-12 hours, and 13-24 hours, however, hardly changed. Fewer patients were admitted more than 24 hours after onset of symptoms in 1989-92.

Management in hospital

Table 5 details temporal changes in management and shows a significant fall in the use of antiarrhythmics, a threefold increase in the use of β blockers over 10 years, and a twofold increase in the use of angiotensin converting enzyme inhibitors between 1989 and 1992. There was a high uptake of aspirin use after its widespread introduction in 1988 and a 1.3-fold increase in the use of thrombolysis from 1989 to 1992. The use of diuretics and digoxin declined during the years of the study.

The proportion of patients with contraindications to β blockers (owing to existing medical conditions) varied from 3% to 10%, to aspirin from 1% to 2%, and to thrombolysis from 6% to 15%.

Table 3 Numbers (percentages) of patients admitted or transferred to a coronary care unit within 24 hours, by age, 1982-4 and 1989-92

Age (years)	1982	1983	1984	1989	1990	1992
<55	172 (96.6)	159 (90.3)	134 (91.8)	158 (92.9)	108 (92.5)	109 (77.9)
55-59	97 (94.2)	101 (90.2)	107 (90.7)	89 (88.1)	91 (89.2)	77 (77.0)
60-64	115 (89.8)	102 (82.9)	116 (87.2)	111 (91.7)	136 (86.6)	122 (81.9)
65-69	110 (80.8)	93 (73.6)	78 (76.5)	132 (84.6)	107 (80.5)	109 (73.7)
70-74	59 (60.8)	45 (45.9)	60 (49.6)	94 (64.0)	104 (77.6)	119 (71.7)
⩾75	25 (29.1)	21 (19.8)	28 (22.6)	104 (44.6)	90 (46.2)	156 (61.2)
Total	578 (80.4)	521 (70.4)	523 (70.3)	688 (75.8)	636 (75.8)	692 (72.2)

Data for 1991 were not collected (see text).

Table 4 Time from onset of symptoms to admission for patients able to recall accurate times or narrow time band. Values are numbers (percentages) of patients

Time (hours)	1982 (n=658)	1983 (n=722)	1984 (n=732)	1989 (n=806)	1990 (n=723)	1992 (n=650)
>24	107 (16.3)	165 (22.9)	141 (19.3)	55 (6.8)	50 (6.9)	47 (7.2)
13-24	61 (9.3)	68 (9.4)	54 (7.4)	66 (8.2)	54 (7.5)	51 (7.8)
7-12	86 (13.1)	94 (13.0)	91 (12.4)	97 (12.0)	72 (10.0)	105 (16.2)
2-6	340 (51.7)	349 (48.3)	354 (48.4)	494 (61.3)	461 (63.8)	381 (58.6)
⩽1	64 (9.7)	46 (6.4)	92 (12.6)	94 (11.7)	86 (11.9)	66 (10.2)

Table 5 Number (percentage) of patients with acute myocardial infarction receiving inpatient treatment in Nottingham, 1982-4 and 1989-92

Treatment	1982 (n=719)	1983 (n=745)	1984 (n=749)	1989 (n=928)	1990 (n=840)	1992 (n=960)	P value
Antiarrhythmics	160 (22)	161 (22)	148 (20)	169 (18)	137 (16)	129 (13)	<0.001
β Blockers	97 (13)	72 (10)	84 (11)	320 (34)	320 (38)	354 (37)	<0.001
Anticoagulants	145 (20)	156 (21)	165 (22)	361 (39)	302 (36)	551 (57)	<0.001
Digoxin	120 (17)	113 (15)	76 (10)	120 (13)	96 (11)	135 (14)	0.002
Diuretics	401 (56)	377 (51)	364 (49)	468 (50)	425 (51)	445 (46)	0.008
Angiotensin converting enzyme inhibitors*	—	—	—	45 (5)	49 (6)	111 (12)	<0.001
Aspirin*	—	—	—	701 (76)	666 (79)	812 (85)	<0.001
Thrombolytics*	—	—	—	336 (36)	392 (47)	463 (48)	<0.001

Data for 1991 were not collected (see text).
*Not used in 1982-4.

Inpatient mortality

Overall inpatient mortality from myocardial infarction rose from 16.1% to 21.7% between 1982 and 1992 (table 6). However, age and sex specific inpatient mortality did not significantly change in any age or sex group over the 10 years.

The adjusted odds ratios for death from myocardial infarction, with allowance for the effects of age and sex, showed no significant change in mortality over 10 years (table 6).

Discussion

Our data clearly show an increase in admissions with acute myocardial infarction over the 10 years, although this increase is mainly confined to patients aged 75 years and over, and to a lesser extent to those aged 70 and over. We believe that the increase is partly a reflection of the increasingly elderly population[13]; partly a greater awareness by patients of the significance of symptoms of chest pain; and partly a lower threshold for admission in accident and emergency departments and greater surveillance by medical staff. Although we have previously shown that the treatment of patients with myocardial infarction at home was relatively uncommon in the early 1980s,[14] we believe that this is even more unusual now with the known benefits of

Table 6 Age and sex specific inpatient mortality (numbers of patients (percentages who died in each group)) with crude and age and sex adjusted odds ratios (95% confidence interval) for death from myocardial infarction in Nottingham, 1982-4 and 1989-92

Age group (years)	1982	1983	1984	1989	1990	1992	P value
<55:							
Men	10 (6.3)	8 (5.1)	5 (4.1)	8 (5.8)	4 (3.7)	7 (6.5)	0.907
Women	0	3 (15.8)	2 (5.9)	1 (3.2)	2 (18.9)	3 (9.1)	NA
55-59:							
Men	7 (8.1)	5 (5.6)	10 (10.6)	7 (9.1)	10 (11.6)	8 (11.6)	0.737
Women	2 (13.3)	3 (13.6)	2 (8.3)	6 (25.0)	3 (18.8)	5 (16.1)	NA
60-64:							
Men	14 (13.1)	17 (17.0)	10 (9.4)	15 (17.4)	11 (10.2)	12 (11.4)	0.392
Women	3 (15.0)	2 (9.5)	3 (12.0)	8 (22.9)	8 (16.3)	7 (15.9)	NA
65-69:							
Men	16 (16.2)	14 (14.7)	14 (18.9)	23 (20.2)	17 (17.9)	14 (15.2)	0.898
Women	3 (12.0)	10 (33.3)	8 (28.6)	10 (23.8)	9 (23.7)	10 (17.9)	0.429
70-74:							
Men	19 (29.2)	16 (23.5)	24 (31.2)	17 (16.8)	15 (19.5)	22 (20.8)	0.196
Women	7 (21.9)	9 (30.0)	11 (25.0)	16 (34.8)	9 (15.8)	22 (36.7)	0.135
⩾75:							
Men	22 (46.8)	14 (25.5)	23 (37.1)	32 (28.3)	31 (36.9)	44 (35.8)	0.183
Women	13 (33.3)	20 (39.2)	23 (59.0)	43 (35.8)	41 (36.9)	54 (40.9)	0.162
Total	116 (16.1)	121 (16.2)	135 (18.0)	186 (20.2)	160 (19.1)	208 (21.7)	0.023
Crude odds ratio	1.00	1.01 (0.78,1.31)	1.15 (0.90,1.48)	1.26 (1.00,1.59)	1.19 (0.94,1.51)	1.38 (1.10,1.73)	
Adjusted odds ratio	1.00	0.96 (0.75,1.25)	1.10 (0.86,1.42)	0.97 (0.77,1.23)	0.92 (0.72,1.17)	1.02 (0.81,1.29)	

Data for 1991 were not collected (see text). NA=not applicable (numbers too small for χ^2 test to be valid).

thrombolysis for patients of all ages. Rather than the incidence of myocardial infarction increasing, it seems that more people are now admitted with suspected infarction so that detection rates of definite myocardial infarction are greater. A similar increase in total admissions with myocardial infarction, predominantly elderly people, has been documented elsewhere.[15]

Women and older patients, despite a worse prognosis, have historically been less likely to be admitted to a coronary care unit.[16 17] There has been an encouraging increase in admissions of these groups, in particular elderly people, to the Nottingham units such that over 60% of the patients aged over 75 were admitted to coronary care in 1992.

Mortality in patients with recurrent myocardial infarction is twice that of counterparts with a first event[18 19]. Analysis of background characteristics showed a fall in the proportion of patients with only electrocardiographic evidence of previous infarction and, to a lesser extent, in those with a documented history of myocardial infarction, which might be expected to improve inpatient outcome. A reduction in duration of hospital stay over the 10 years might additionally be expected to lower mortality artefactually, but the effects of this are probably minimal as most deaths occur within the first two days of admission.[4] More patients in 1992 had evidence of a Q wave infarction, but opinions conflict about the relevance of this to outcome,[20-24] with little sensitivity or specificity of Q waves with respect to true transmural infarction.[25 26]

Despite some improvement, considerable delays still occur between the onset of symptoms and admission, and in 1992 three in 20 patients were admitted after the 12 hour time window for thrombolysis irrespective of any delays in hospital. For a "typical" year in Nottingham this equates to over 100 patients. The relation between the delay in admission and the outcome is not a simple one. We have reported that confounding by the lack of data on times of onset of symptoms in those who die soon after admission makes it difficult to assess the relation of delays to mortality.[14] Although earlier admission could lead to a paradoxical increase in mortality (as a result of admission of patients who might have died in the community), our baseline data do not suggest that we are dealing with more severe infarctions in the later years of the study. The proportion of patients with previous Q wave infarction fell; the proportion with anterior infarction remained the same; the proportion given diuretics (a marker of those with clinical cardiac failure) fell slightly; and, although data on Killip class are available only for the later years, the proportion of patients with cardiogenic shock has not changed. Other research has similarly not shown significant changes in severity of infarction over time.[27 28] Other factors, however, such as comorbidity, for which we cannot control might have masked an improvement in survival.

Inpatient treatment

The use of prophylactic antiarrhythmics fell after lack of evidence of benefit in treating warning arrhythmias and the results of the cardiac arrhythmia suppression trial.[29] The use of β blockers increased, although, even after allowance for those with contraindications, 40% of patients in 1992 might still have benefited from this treatment but did not receive it. Although some patients may start receiving the drug in outpatient departments, the poor uptake of β blockers is not unique to Nottingham.[30 31] The use of diuretics and digoxin fell slightly over the 10 years, and, although the proportion of patients receiving these drugs in 1992 seems high, our findings are similar to another recent report in unselected patients with myocardial infarction.[32] The increasing use of anticoagulants is the result of the use of intravenous and subcutaneous heparin as concomitant treatment in several thrombolytic trials during the years 1989 to 1992. Only 6.4% of patients were taking oral anticoagulants at discharge in the years 1989 to 1992.

Thrombolytic treatment was not used in 1982-4, but by 1992, 48% of patients received this treatment. Estimates of the proportion of all patients with myocardial infarction likely to be suitable for treatment vary from 25% to 33% in the United States[31] to between 70% and 80% in Britain,[33] although we believe the figure for Britain to be optimistic. Our figures suggest that 15% of patients may be admitted outside the time window of 12 hours, 15% may have a contraindication, and not all will have or develop electrocardiographic criteria for thrombolysis. Of our cohort of patients in 1992 who did not receive thrombolysis, had no contraindication, and were admitted in under six hours (the general policy which preceded publication of the late assessment of thrombolytic efficacy study[34]), 73 (5%) subsequently developed electrocardiographic criteria for lytic treatment[8] but for unknown reasons did not receive it.

Key messages

- During 1982-92 major changes in management of myocardial infarction in an unselected population have been guided by the results of randomised trials
- Adjusted odds ratios for deaths in hospital from acute myocardial infarction did not change over this period despite an overall fall in recorded deaths from ischaemic heart disease in Nottingham
- The use of existing treatments needs to be optimised and new management strategies need to be introduced if inpatient mortality from myocardial infarction is to be reduced

Inpatient mortality

Disappointingly we have seen little change in inpatient mortality over the 10 years of our study. Our findings highlight the differences between the selected patients of clinical trials and the general population of patients, who have an overall mortality of 20%, at least twice that of most patients in trials. Purchasers and those involved in clinical audit need to be aware that the proportional reductions in mortality seen in clinical trials do not necessarily translate into benefits in a general population.

We have previously shown that overall mortality from ischaemic heart disease is falling in Nottingham,[9] which may be due to changes in the natural course of the disease, a reduction in community cardiac risk factors, and improved treatment of chronic ischaemic heart disease, as suggested elsewhere.[35-37] This experience is not unique to Nottingham. Goldman and colleagues in the United States in the 1970s similarly found that, although overall mortality from ischaemic heart disease had fallen, inpatient mortality from myocardial infarction was static[38]; however, this was in the years before thrombolysis and treatment with antiplatelets and β blockers. A report from the United States showed that overall inpatient mortality from myocardial infarction rose from 13.1% in 1984 to 16.8% in 1988, with no clear trends in age and multivariate adjusted mortality.[39]

Dellborg and colleagues from Sweden, however, showed a reduction in inpatient mortality between 1979 and 1990, even in an elderly population, on the basis of data from a register for a coronary care unit.[40] Further studies in Ontario[15] and the United Kingdom[41] have shown reductions in overall mortality over similar time periods of 21.0% to 17.1% and 25.4% to 20.2% respectively, but both these studies were based on hospital discharge codes and susceptible to the errors associated with these.

Conclusion

Major management changes have occurred over the period of our study as the lessons of controlled randomised clinical trials have been applied. We have shown that, despite some improvement, patients still delay seeking help for a considerable time. Undoubtedly current treatment in management of myocardial infarction, particularly thrombolysis and β blockade, needs to be optimised, and new strategies need to be introduced. A reduction in our inpatient mortality from acute myocardial infarction remains elusive.

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Increased brain serotonin function in men with chronic fatigue syndrome

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Recent neuroendocrine studies suggest that patients with chronic fatigue syndrome may have increased brain serotonin activity.[1 2] This could be relevant to the pathophysiology of chronic fatigue syndrome because serotonin pathways have a role in mediating central fatigue.[3] Currently, however, the existence of abnormal serotonin neuroendocrine function in patients with chronic fatigue syndrome is controversial because of contradictory findings from samples of heterogeneous patients[4 5] and the use of serotonin probes such as buspirone, which are of doubtful pharmacological specificity.[1] We aimed to measure the increase in plasma prolactin after administration of the selective serotonin releasing agent D-fenfluramine in men rigorously diagnosed as having the chronic fatigue syndrome and carefully matched healthy controls.

Subjects, methods, and results

Ten men (mean age 39.0 (SD 9.9) years; mean weight 84.9 (12.6) kg) were recruited from general practitioners' consecutive referrals to a hospital infectious diseases clinic. All met criteria for the chronic fatigue syndrome and the more restrictive ICD-10 (international classification of diseases, 10th revision) diagnosis of neurasthenia (which excludes patients with depressive and anxiety disorders).[3] None had taken psychotropic medication for at least four weeks. Male controls, volunteers without psychiatric disorder, were matched with patients for age (39.9 (7.6) years) and weight (83.0 (13.0) kg). Subjects gave informed consent to the study, which was approved by the local ethics committee.

Subjects came to the laboratory fasted at 9 am, when we inserted an indwelling venous cannula. After two baseline samples had been removed over 30 minutes, subjects received D-fenfluramine (30 mg orally). Further blood samples were taken over the next four hours for estimation of plasma prolactin, D-fenfluramine, and D-norfenfluramine. Prolactin was measured by a standard immunoradiometric assay, and drug concentrations were assayed by gas-liquid chromatography. Changes in plasma prolactin were analysed by a two way repeated measures analysis of covariance with diagnosis and time as the main factors. Plasma concentrations of D-fenfluramine and D-norfenfluramine were entered as time dependent covariates.

The analysis of covariance showed a significant main effect of time ($F=8.86$; $P<0.001$) and a significant interaction between diagnosis and time ($F=3.24$; $P=0.01$). Post hoc testing with Fisher's test of least significant difference showed that plasma prolactin concentrations in patients with chronic fatigue syndrome were significantly higher than in controls three and four hours after D-fenfluramine was given (fig 1). The mean area under the curve of prolactin secretion after D-fenfluramine (with subtraction of baseline secretion) was 51.7 mIU × ml/h in chronic fatigue syndrome patients and −64.2 miU × ml/h in controls (95% confidence interval of mean difference, 5.0 to 227, $t=2.20$, df = 18, $P=0.041$). Mean area under the

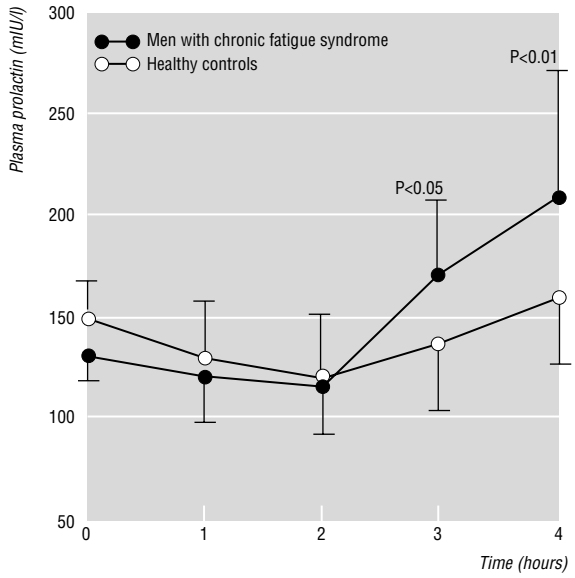

Fig 1 Mean plasma prolactin concentration (with 95% confidence intervals) in 10 male patients with chronic fatigue syndrome and 10 healthy controls

curve did not differ in patients and controls for plasma D-fenfluramine (39.9 *v* 49.4 ng×ml/h; −31 to 12, $t=0.93$, df=18, P=0.37) or D-norfenfluramine (10.4 *v* 16.8 ng×ml/h; −14 to 3, $t=1.44$, df=18, P=0.17). D-Fenfluramine and D-norfenfluramine concentrations were not significantly correlated with prolactin secretion in either patients or controls or in both groups combined (P>0.25 for all areas under the curve, Pearson's product moment coefficient).

Comment

Our data show a significant rise in prolactin responses to D-fenfluramine in men with narrowly defined chronic fatigue syndrome in comparison to healthy controls. This finding supports some,[1 2] but not all, previous neuroendocrine studies,[4 5] and suggests that the chronic fatigue syndrome is associated with increased brain serotonin function. Though depressive symptoms are common in chronic fatigue syndrome, patients with major depression have unchanged or lowered prolactin responses to D-fenfluramine,[2] making it unlikely that chronic fatigue syndrome and depression share a common pathophysiology.

We measured prolactin concentrations for only four hours after giving D-fenfluramine, whereas a five hour sampling period is customary. Another study that found increased prolactin responses to D-fenfluramine in chronic fatigue syndrome measured prolactin concentrations for five hours.[2] Though we cannot exclude the possibility that patients with the chronic fatigue syndrome have greater prolactin responses to diverse pharmacological stimuli, not specifically those mediated by serotonin, the prolactin response to insulin hypoglycaemia is blunted in patients with chronic fatigue syndrome.[4]

Raised brain serotonin activity might explain the excessive fatigue experienced by patients with the chronic fatigue syndrome.[3] Increased prolactin release mediated by serotonin in the chronic fatigue syndrome might, however, be a secondary consequence of behavioural changes such as prolonged inactivity or disturbance of the sleep-wake cycle.

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When I use a word...

Quacks

There are several pejorative names for doctors or peddlers of supposedly ineffective medicines, and most of them relate to advertising. Quacks were originally called quacksalvers, supposedly because they "quacked" or boasted about their salves; a mountebank was a man who climbed on to a soapbox (Italian: monte banco) to shout his wares at a fair; and a charlatan was wont to prattle (Italian: ciarlare) about his medicines. On the other hand, an empiric was someone whose knowledge was derived from experience only—that is, not from a sound understanding of the underlying theory—from the Greek word πείρα (peira), a trial.

I recently learnt from Glenn Mitchell's excellent *Marx Brothers Encyclopedia* (Batsford, 1997) that when the scriptwriters of *A Day at the Races* were trying out names for the doctor (actually a vet) that Groucho was to play, they settled on Hugo Z Quackenbush, a good lampoon you would think, only to find that there were over 30 doctors of that name in the United States and that they might be risking litigation if they used it; they changed it to Hackenbush. And a Dr Quackenbush is also mentioned in *Becky Sharp*, the first three colour Technicolor feature film, Rouben Mamoulian's 1937 version of *Vanity Fair*.

I have also been belatedly catching up with Roy Porter's history of quackery, *Health for Sale* (Manchester UP, 1989), in which he suggests that there were more similarities than differences between quacks and regular practitioners. The period his book covers is 1600 to 1850, but his remarks might well be applied to today. For example, in the nineteenth century digitalis was used to treat fever because, so it was argued, fever quickened the pulse and digitalis slowed it. A quackish sort of argument, you might say. But until recently we have argued that histamine receptor antagonists are effective in treating peptic ulcer because they reduce gastric acid secretion and because ulcers are caused by gastric acid. Another quackish argument? We now think that *Helicobacter pylori*, an organism that likes an acid environment, is the cause. And who knows what modern views will be looked on as quackish in 50 years time, or even next year?

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