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Non-fasting serum triglyceride concentration and mortality from coronary heart disease and any cause in middle aged Norwegian women

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Abstract

***Objective*—To study the association between non-fasting serum triglyceride concentrations and mortality in women from coronary and cardiovascular disease and all causes.**

***Design*—Follow up by ambulatory teams of men and women who underwent cardiovascular screening for a mean of 14·6 years.**

***Setting*—National health screening service in Norway.**

***Subjects*—25 058 men and 24 535 women aged 35-49 years.**

***Main outcome measure*—Predictive value of non-fasting serum triglyceride concentrations.**

***Results*—At initial screening total serum cholesterol concentration, serum triglyceride concentration, blood pressure, height, and weight were measured, and self reported information about smoking habits, physical activity, and time since last meal were recorded. During subsequent follow up 108 women died from coronary heart disease, 238 from cardiovascular diseases, and 931 from all causes. In women mortality increased steadily with increasing triglyceride concentration for all three causes of death. With the proportional hazards model and adjustment for age, systolic blood pressure, total cholesterol concentration, time since last meal, and number of cigarettes a day the relative risk between triglyceride concentration $\geq 3{\cdot}5$ mmol/l and $< 1{\cdot}5$ mmol/l was 4·7 (95% confidence interval 2·5 to 8·9) for deaths from coronary heart disease, 3·0 (1·9 to 4·8) for deaths from cardiovascular disease, 2·3 (1·8 to 2·9) for total deaths in all women.**

***Conclusions*—A raised non-fasting concentration of triglycerides is an independent risk factor for mortality from coronary heart disease, cardiovascular disease, and any cause mortality among middle aged Norwegian women in contrast to what is seen in men.**

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Introduction

The role of triglycerides in the development of cardiovascular disease is as yet unestablished. Many epidemiological studies have found a relation between serum triglyceride concentration and the incidence of and mortality from coronary heart disease.[1,2] The relation is weakened and often disappears, however, when other risk factors are considered.[3] Most studies have been done in men, but among the few studies in women triglyceride concentrations has come out as an independent risk factor.[4,5] Austin reviewed the importance of raised plasma triglyceride concentrations from perspectives other than the epidemiological and concluded that it is premature to dismiss triglyceride concentration as a potentially important risk factor.[2]

In various counties in Norway the National Health Screening Service has organised large scale screening examinations for risk factors for the development of cardiovascular disease for the past 20 years. From these studies we have previously reported non-fasting triglyceride concentration to be a weak predictor of death from coronary heart disease in men; the strength of association depending heavily on whether total cholesterol concentration was accounted for.[6] The period of follow up is now sufficient (12 to 16 years) to give fairly precise estimates of the relation between triglyceride concentration and mortality from coronary disease in women.

Subjects and methods

During 1974-8 all men and women aged 35-49 years in three Norwegian countries were invited to attend a cardiovascular study. The attendance rate was high: 93% in women and 89% in men (24 535 women and 25 058 men). The previous study on men also included the Oslo study (1972-3) and the Tromsø study (1974), in which only men were studied.[6]

A detailed description of the study procedures has been given by Bjartveit *et al.*[7] All people participating answered a questionnaire at home about history of cardiovascular disease, diabetes, treatment for hypertension, symptoms of angina pectoris, physical activity during leisure, smoking habits, and stress factors in social life. In this study the healthy group consists of those who gave negative answers to questions about myocardial infarction, angina pectoris, other heart disease, atherosclerosis of legs, cerebral stroke, diabetes, treatment for hypertension, use of nitroglycerine, and symptoms suggesting angina pectoris or atherosclerosis obliterans, or both.

Height and weight were measured to the nearest centimetre and half a kilogram. After a minimum of two minutes' rest systolic and diastolic blood pressures were measured twice to the nearest 2 mm with a

sphygmomanometer. The interval between the two measurements was one minute, and the second recording was used in this study.

A blood sample was taken from non-fasting subjects and analysed for serum concentrations of total cholesterol and triglycerides, both components being measured non-enzymatically on a Technicon Auto-Analyzer.[7] On later comparison with enzymatic methods, the non-enzymatic methods used gave on average 10% higher triglyceride values and 8% higher cholesterol values.[6,7] Concentration of high density lipoprotein cholesterol was not determined. The participants reported the time since their last meal, coded to five alternatives, ranging from less than one hour to eight or more hours. Adjustment for time since the last meal was made by multiplying the chemically determined value by the ratio of the total mean to the mean in the time category in question.

From a previous follow up study in middle aged men[8,9] and independent of this study a risk score for myocardial infarction has been constructed. This score was calculated for each person by multiplying the relative risks attributable to the person's serum cholesterol concentration, systolic blood pressure, and number of cigarettes smoked. In addition, it was multiplied by a factor of 1 in women and 5 in men. The risk score has values between 1 and 450 in women and 5 and 2250 in men.

Causes of death were obtained from the Norwegian central bureau of statistics according to the Norwegian version of the International Classification of Diseases eighth (until 1986) and ninth revisions (1986 and after).[10,11] Mortality from coronary heart disease is coded 410, 411, 412.0-412-3, and 413 and from cardiovascular disease 390-458 (eighth revision). The corresponding codes in the ninth revision are 410-413, 414.0-414.1, 414.3, 414.9 for coronary heart disease and 390-459 for cardiovascular disease.

The number of person years was calculated from the date of examination to date of death, date of emigration, or 31 December 1990, whichever came first. Age adjustments were done by the indirect method by using the distribution of the total study population in one year age groups as an internal standard. Adjustment for several variables with Cox's proportional hazards model (biomedical data programs package 2L).[12] In these analyses triglyceride concentrations were entered partly as a dummy variable and partly as a continuous variable. As the distribution of serum triglyceride concentration is highly skewed to the right the logarithm of the concentration is used in the continuous case.

Results

Table I shows some baseline characteristics according to four categories of triglyceride concentration. There was an increasing mean level of the risk factors with increasing triglyceride concentration. The prevalence of current smokers and the prevalence of history of cardiovascular disease, diabetes, or symptoms was also higher in the groups with the higher triglyceride concentrations. The percentage of subjects reporting four or more hours since last meal was higher in the groups with the lowest concentration and almost equal in the other three categories.

During follow up (mean 14·6 years) 108 women died of coronary heart disease, 238 of cardiovascular disease, and 931 of any cause. The mortality steadily increased with increasing non-fasting triglyceride concentrations in all three groups (table II). This also applied to the group of women who did not report any history of cardiovascular disease, diabetes, or symptoms suggesting angina pectoris. Mortality from causes other than cardiovascular disease was higher among subjects with higher concentrations of triglycerides. The same analyses with triglyceride concentrations adjusted for time since last meal gave similar results.

If mortality from coronary heart disease among all women had been at the same rate as that seen in the group with triglyceride concentrations less than 1·5 mmol/l there would have been 50 deaths from coronary heart disease instead of the observed 108 deaths. Thus 54% of coronary deaths may be attributed to a triglyceride concentration of 1·5 mmol/l or greater.

Triglyceride concentrations were also related to mortality for specific or combined causes with a reasonable number of deaths. These causes included suicide (40); accidents (38); respiratory disease (30); diabetes (10); cancer of colon (36), lung (38), breast

TABLE I—*Mean values and proportions in all women, 35-49 years, who underwent cardiovascular screening*

Factor	Triglycerides (mmol/l)			
	<1·5	1·5-2·49	2·5-3·49	3·5
No at risk	13 127	8 550	2 026	832
Age (years)	42	43	43	43
Systolic blood pressure (mm Hg)	129	133	136	141
Diastolic blood pressure (mm Hg)	80	82	84	88
Total cholesterol concentration (mmol/l)	5·9	6·5	7·0	7·4
No (%) of current smokers (% yes)	4 201 (32)	3 505 (41)	932 (46)	399 (48)
Body mass index*	24	25	27	28
No (%) with ⩾4 hours since last meal	2 363 (18)	1 026 (12)	243 (12)	108 (13)
No (%) with history of cardiovascular disease, diabetes, or symptoms	1 050 (8)	941 (11)	324 (16)	175 (21)

*Weight (kg)/(height (m))·².

TABLE II—*Relation between non-fasting triglyceride concentration and mortality. All women (35-49 years) and women without cardiovascular disease, diabetes, or symptoms at baseline*

Triglyceride concentration (mmol/l)	No at risk	Person-years	Mortality from coronary heart disease			Mortality from cardiovascular disease			Mortality from causes other than cardiovascular disease			Total mortality		
			No	Rate*	Relative risk† (95% confidence interval)	No	Rate*	Relative risk† (95% confidence interval	No	Rate*	Relative risk† (95% confidence interval)	No	Rate*	Relative risk† (95% confidence interval)
All women														
<1·5	13 127	192 963	25	14	1·0	72	39	1·0	316	173	1·0	388	212	1·0
1·5-2·49	8 550	125 023	42	32	1·7 (1·0 to 2·8)	95	73	1·5 (1·1 to 2·1)	247	189	1·0 (0·9 to 1·2)	342	261	1·1 (0·9 to 1·3)
2·5-3·49	2 026	29 209	22	68	2·9 (1·6 to 5·2)	44	137	2·4 (1·6 to 3·6)	76	236	1·3 (1·0 to 1·6)	120	373	1·5 (1·2 to 1·9)
⩾3·5	832	11 725	19	145	4·7 (2·5 to 8·9)	27	206	3·0 (1·9 to 4·8)	54	408	2·1 (1·6 to 2·9)	81	614	2·3 (1·8 to 2·9)
Women without cardiovascular disease, diabetes, or symptoms														
<1·5	12 147	178 424	16	9	1·0	59	34	1·0	282	167	1·0	340	200	1·0
1·5-2·49	7 618	111 339	19	16	1·3 (0·6 to 2·5)	63	55	1·3 (0·9 to 1·8)	226	193	1·1 (0·9 to 1·3)	283	243	1·1 (1·0 to 1·3)
2·5-3·49	1 710	24 691	13	50	2·9 (1·4 to 6·4)	27	102	2·3 (1·4 to 3·7)	64	236	1·3 (1·0 to 1·7)	91	338	1·5 (1·2 to 1·9)
⩾3·5	657	9 341	9	92	4·1 (1·7 to 9·8)	13	128	2·3 (1·2 to 4·4)	36	344	1·9 (1·3 to 2·7)	49	472	2·0 (1·4 to 2·7)

*Rate per 100 000 person years adjusted for age.
†Relative risk estimated by Cox's proportional hazards regression with age, systolic blood pressure, total cholesterol concentration, number of ciagarettes a day, and time since last meal as additional covariates.

TABLE III—*Mortality (per 100 000 person years adjusted for age) by non-fasting triglyceride concentration and total cholesterol concentration. All women aged 35-49 years at baseline*

Total cholesterol (mmol/l)	Triglyceride concentration (mmol/l)	Person years	Mortality from coronary heart disease		Mortality from cardiovascular disease		Mortality from causes other than cardiovascular disease		Total	
			No	Rate	No	Rate	No	Rate	No	Rate
<6·5	<1·5	109 317	5	5	28	29	165	171	193	199
	1·5-2·49	43 213	6	15	22	54	78	192	100	246
	2·5-3·49	6 728	2	36	5	71	14	206	19	279
	≥3·5	1 590	1		1		5	307	6	373
6·5-7·99	<1·5	66 163	8	12	27	41	112	169	139	209
	1·5-2·49	55 666	17	28	42	71	110	185	152	256
	2·5-3·49	12 585	9	66	20	148	32	237	52	385
	≥3·5	4 602	6	119	10	197	20	395	30	593
≥8·0	<1·5	17 483	12	62	17	88	39	201	56	289
	1·5-2·49	26 143	19	61	31	102	59	192	90	293
	2·5-3·49	9 896	11	92	19	161	30	252	49	413
	≥3·5	5 533	12	183	16	247	29	443	45	698

(93), cervix uteri (27), and ovary (58); and other cancers (232). Positive relations were detected but significance was reached only for diabetes and cancer of cervix uteri after we adjusted for age and cigarette smoking.

Table III shows age adjusted mortality for triglyceride concentrations and three concentrations of total cholesterol. The association between triglyceride concentration and mortality was present at the three concentrations of total cholesterol, and a raised total cholesterol concentration was related to an excess mortality at a given concentration of triglycerides.

The relation of triglyceride concentration to mortality from coronary heart disease in women was present at all body mass indices (fig 1). It is evident that the different predictive power of triglyceride concentrations in men and women can hardly be ascribed to a manifestation of general obesity.

Table IV shows the relative risks of death from coronary disease and total death associated with about 1 SD, as estimated from Cox's proportional hazards regressions. The results in the healthy group show that the relative risk for log (triglyceride concentration) is distinctly higher in women than in men when coronary death is the end point. The major risk factors of cholesterol concentration and systolic blood pressure are equally strong in men and women. Age is a stronger predictor in men whereas smoking is a somewhat stronger predictor in women. This is probably because of a different age-smoking relation in men and women. Among men there are similar proportions of current smokers in all age groups whereas in women the proportion of smokers decreases with age,[13] and some of the age gradient in women is probably attributable to this. For total death as end point there are small differences between the sexes.

To test whether the relation of triglyceride concentration to mortality from coronary heart disease was the same in all three counties two Cox's regressions were carried out; one with and one without interaction terms of triglyceride concentration and county. The log likelihoods were nearly the same.

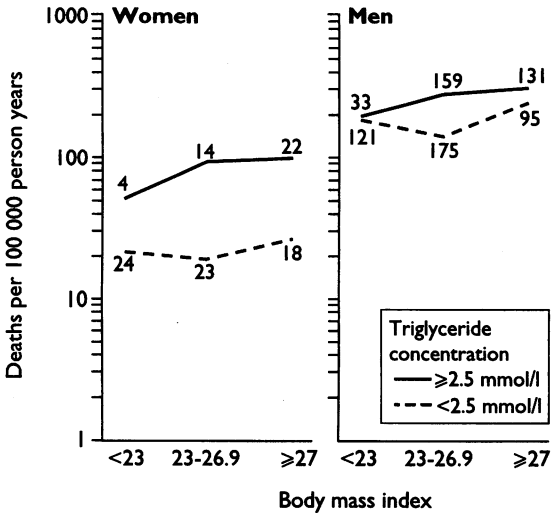

FIG 1—*Age adjusted mortality from coronary heart disease by body mass index at two serum concentrations of triglycerides in all men and women aged 35-49 years. Figures are numbers of deaths*

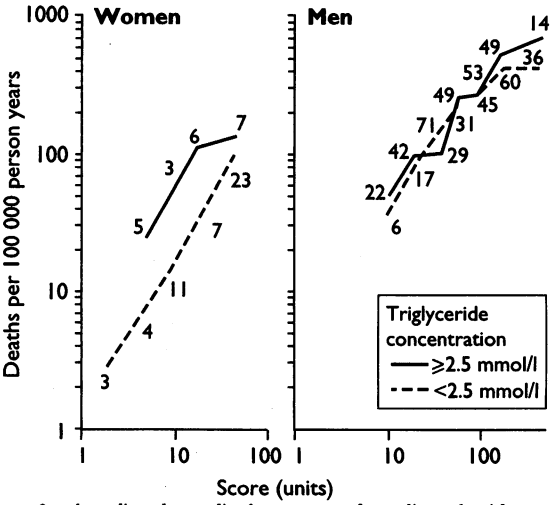

FIG 2—*Age adjusted mortality from coronary heart disease by risk score for myocardial infarction at two serum concentrations of triglycerides in men and women aged 35-49 years with no history of cardiovascular disease or diabetes or symptoms. Figures are numbers of deaths*

Figure 2 shows the relation between mortality from coronary heart disease and the risk score for myocardial infarction in the healthy group. At a given risk score in women there is a relative risk in order of two to three between the two ranges of triglyceride concentration in contrast to what is seen in men, in whom the triglyceride concentration give no additional risk. People with a risk score of 100 or above were recommended a follow up examination at their local heath clinic, and the levelling off of mortality in men at high risk may be the result of intervention.

TABLE IV—*Relative risks* with 95% confidence intervals from Cox's proportional hazards regression with coronary death and total deaths as end point. Men and women aged 34-49 years without history of cardiovascular disease, diabetes, or symptoms*

Risk factor (unit increase)	Relative risk (95% confidence interval) for coronary deaths		Relative risk (95% confidence interval) for total deaths	
	Men (508 deaths)	Women (56 deaths)	Men (1535 deaths)	Women (735 deaths)
Age (4 years)	1·4 (1·2 to 1·5)	1·0 (0·8 to 1·4)	1·3 (1·3 to 1·4)	1·4 (1·3 to 1·5)
Log (triglycerides) (0·2 mmol/l)	1·1 (1·0 to 1·2)	1·6 (1·2 to 2·1)	1·1 (1·0 to 1·1)	1·2 (1·1 to 1·3)
Total cholesterol concentration (1·2 mmol/l)	1·3 (1·2 to 1·4)	1·3 (1·1 to 1·6)	1·1 (1·1 to 1·2)	1·0 (1·0 to 1·1)
Systolic blood pressure (15 mm Hg)	1·4 (1·3 to 1·5)	1·4 (1·2 to 1·7)	1·2 (1·2 to 1·3)	1·1 (1·1 to 1·2)
No of cigarettes a day (5)	1·3 (1·2 to 1·3)	1·5 (1·3 to 1·8)	1·2 (1·2 to 1·3)	1·3 (1·2 to 1·4)
Body mass index (3 kg/m²)	1·0 (0·9 to 1·1)	1·1 (0·9 to 1·3)	1·0 (0·9 to 1·0)	1·0 (0·9 to 1·1)
Physical activity during leisure time (0·6 categories)†	0·9 (0·8 to 1·0)	0·9 (0·7 to 1·2)	1·0 (0·9 to 1·0)	0·9 (0·8 to 1·0)
Time since last meal (one category)‡	1·0 (0·9 to 1·1)	1·0 (0·8 to 1·4)	1·0 (1·0 to 1·1)	1·1 (1·0 to 1·2)

*Relative risks roughly standardised—that is, relative risks between two categories differing by 1 SD.
†1 = sendentary, 2 = moderate, 3 = intermediate, 4 = intensive.
‡1 = < 1 hour, 2 = 1-2, 3 = 2-4, 4 = 4-8, 5 = 8 hours or more.

Discussion

In this prospective study of nearly all women aged 35-49 in three counties in Norway with a complete follow up with respect to death we found triglyceride concentration to be an indepedent risk factor of mortality from coronary heart disease, cardiovascular disease, and all causes. Furthermore, we found a difference between men and women in that triglyceride concentrations were not an independent risk factor for mortality from coronary heart disease in men.

Some effect of high triglyceride concentration is probably mediated through a low concentration of high density lipoprotein cholesterol,[1 14] which, however, was not analysed in this study. Nevertheless, there was a distinction between the sexes as triglyceride concentration stood out as a predictor in women independent of variables adjusted for in contrast to what was seen in men (see table IV). In a second cardiovascular screening three to five years later the concentration of high density lipoprotein cholesterol was determined. A follow up study showed that the univariate relation of concentration of high density lipoprotein cholesterol to coronary death in women was much weaker than the univariate relation of triglyceride concentration to coronary death in this study.[15] There were too few deaths to allow a more detailed analysis for women in that study.

Within individual people the concentration of triglycerides varies much more than that of total cholesterol. This reflects both a larger within person biological variation, a coefficient of 20-25% with triglyceride concentration and 6-8% with cholesterol concentration,[16] and a less precise method for measurement. At the time this study was carried out the laboratory reported a coefficient of variation of 5% with triglyceride concentration and 3·3% with cholesterol concentration. Because of this large variation an attenuated association between triglyceride concentration and disease will be obtained. If repeated blood samples were drawn and triglyceride concentrations were measured with the more precise methods now available, triglyceride concentration would probably be an even stronger risk factor.

Several mechanisms have now been identified through which increased triglyceride concentrations could increase the risk of coronary heart disease. Triglycerides affect the haemostatic system through their positive correlation both with the coagulant activity of factor VII and with plasminogen activator inhibitor-I.[17 18] Triglycerides are also related to the presence of small, low density lipoprotein particles, now considered to be a genetically influenced risk factor for coronary heart disease.[2 19] Hypertriglyceridaemic very low density lipoprotein may affect endothelial cells and turn macrophages into foam cells.[3 20] Finally, postprandial hyperglyceridaemia with delayed clearance of chylomicron remnants may also increase atherosclerosis.[21] In this respect, establishing the triglyceride concentration in non-fasting subjects could prove to be more informative than measuring it in fasting subjects.

The diet used in Western societies favours the development of decreased glucose tolerance, increased triglyceride concentration, decreased concentration of high density lipoprotein cholesterol, hypertension, and abdominal obesity. People with such a clustering of risk factors, the insulin resistance syndrome,[22] are at an increased risk of developing coronary heart disease. Some of the increased risk seen here with increased triglyceride concentration may well have occurred through this mechanism. Admittedly, we did not find a relation between triglyceride concentration and body mass index, but this does not exclude the conclusion. In women obesity is mostly located around the hips (gynaecoid obesity) but it is the abdominal (android) obesity which is a coronary risk factor.[23] Body mass index is a measure of total obesity and in this connection it probably reflects gynaecoid more than android obesity.

About 80% of the women in this study were menstruating at screening. With an average follow up of nearly 15 years the menopause will have occurred during that time for a large proportion. A comprehensive report from the second screening (five years after the first) described which risk factors were related to the occurrence of menopause among those 40 years or older who had reported that menopause had not occurred at the first screening.[13] Triglyceride concentration came out as non-significant in a mutivariate analysis. The factors most strongly related to the occurrence of menopause were number of cigarettes smoked a day and body mass index (inversely). Thus, the effect of raised serum triglyceride concentration is hardly mediated through an influence on the occurrence of the menopause.

In summary, non-fasting serum triglyceride concentration stands out as an independent predictor of death from coronary disease in middle aged Norwegian women in contrast to what is seen in men.

Clinical implications

- The sex differences in mortality from coronary heart disease in middle aged people are still unexplained
- This study found that non-fasting triglyceride concentration was an independent predictor of mortality from coronary heart disease and all causes in women but not in men
- The predictive power of triglyceride concentration in women was present at all body mass indices
- The major risk factors of total cholesterol concentration, blood pressure, and smoking were related to mortality from coronary heart disease with equal relative strength in women and men
- The mechanisms through which triglyceride concentration acts as a risk factor in women warrant further investigation

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Cost effectiveness analysis of early zidovudine treatment of HIV infected patients

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Abstract

***Objective*—To compare cost effectiveness of early and later treeatment with zidovudine for patients infected with HIV.**

***Design*—Markov chain analysis of cost effectiveness based on results of use of health care and efficacy from a trial of zidovudine treatment.**

***Setting*—Seven Veterans Affairs medical centres in the United States.**

***Subjects*—338 patients with symptomatic HIV infection and a lymphocyte count of 200×10^6 to 500×10^6 CD4 cells/l.**

***Interventions*—Zidovudine 1500 mg/day started either at recruitment to the trial or when CD4 cell count fell below 200×10^6/l.**

***Main outcome measures*—Health care costs and rates of disease progression between six clinical states of HIV infection.**

***Results*—Patients given early treatment with zidovudine remained without AIDS for an extra two months at a cost of $10 750 for each extra month without AIDS (at 1991 costs). Cost effectiveness ratio was most sensitive to the cost of zidovudine and to the quality of life of patients receiving early treatment. At treatment of 500 mg/day the cost effectiveness ratio for early treatment was $5432 for each extra month without AIDS. Patients given early treatment experienced more side effects, and if their quality of life was devalued by 8% compared with patients treated later the two treatments were equivalent in terms of quality adjusted months of life without AIDS.**

***Conclusions*—Early treatment with zidovudine is expensive and is very sensitive to the cost of zidovudine and to potential reductions in quality of life of patients who experience side effects. Doctors should reconsider early treatment with zidovudine for patients who experience side effects that substantially compromise their quality of life.**

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Introduction

Treatment with zidovudine has been shown to prolong survival in patients with newly diagnosed AIDS or advanced AIDS related complex.[1] At this stage of HIV infection zidovudine is so effective that a doctor need only treat eight patients to prevent one death after six months of treatment. There is, however, much controversy over the efficacy of zidovudine when it is prescribed earlier in the course of HIV infection. Three randomised trials have documented delayed progression to AIDS for patients receiving zidovudine early compared with placebo[2,3] or with zidovudine given later but still before development of AIDS.[4] The Concorde trial, the largest and most recent, reported no delay in progression to AIDS for patients treated early in their infection.[5] None of the published controlled trials have documented additional survival benefit when zidovudine is given before diagnosis of AIDS.

In spite of this, the current recommended medical practice is to prescribe zidovudine for patients with symptomatic HIV whose lymphocyte counts are below 500×10^6 CD4 cells/l.[6] However, the cost implications of giving zidovudine early in HIV infection have not been fully explored. We examined the cost effectiveness of early treatment with zidovudine using data recorded in a Veterans Affairs cooperative study.

Methods

Data sources—The Veterans Affairs cooperative study (number 298) was a four year, multicentre, randomised, double blind trial that compared early and later treatments with zidovudine for patients with symptomatic HIV infection and lymphocyte counts of 200×10^6 to 500×10^6 CD4 cells/l.[4] Patients were randomised to receive zidovudine (1500 mg/day) either at enrolment into the study (early treatment) or when their CD4 cell count fell below 200×10^6/l (later treatment). Patients were enrolled from January 1987 to January 1990 and were followed up until January 1991. The trial showed that patients given zidovudine early in their infection experienced a delay in the development of AIDS but no improvement in overall survival. This trial was the only one of its kind to keep detailed records of the use of health care by all patients.

Markov decision model—In order to accurately model risk of progression of HIV infection and associated health care costs over an extended period and to perform sensitivity analyses for important cost variables we employed a Markov chain analysis.[7] We defined six clinically relevant and mutually exclusive states of HIV infection; mildly symptomatic with a CD4 cell count of 200×10^6 to 500×10^6/l (state 1); mildly symptomatic with a CD4 count under 200×10^6/l (state 2); *Pneumocystis carinii* pneumonia being the first AIDS defining diagnosis (state 3); a different first AIDS defining diagnosis (state 4); two or more AIDS defining diagnoses (state 5); and death (state 6). The patients' progression through the clinical states was divided into cycles of 60 days. All the patients began in state 1, and during each subsequent cycle they could either remain in their current state or progress to another state. Patients changed from their current state to any state of greater severity except that