PAPERS AND ORIGINALS

Ischaemic Heart Disease in Young Women*

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Summary

The mortality rate from ischaemic heart disease (I.H.D.) has increased in young women by about 50% in 12 years, and it is now possible to report the findings in 150 women who developed symptoms and signs of I.H.D. under the age of 45. Data obtained from 145 of these women form the basis of this report: 81 presented with myocardial infarction and 64 with angina. In the remaining five there was a definite nonatherosclerotic cause for the premature onset of I.H.D.

Hypercholesterolaemia, hypertension, or excessive cigarette smoking each occurred in a large minority, and more than one of these major risk factors was present in most patients. Hypercholesterolaemia was the commonest factor. In women in whom lipoprotein typing was undertaken the type II pattern was more frequent than type IV. The prevalence of hypercholesterolaemia and hypertension was the same in those with myocardial infarction and in those with angina.

Excessive cigarette smoking was more common in women with myocardial infarction than in those with angina. The latter did not differ in their cigarette smoking habits from the normal population.

A premature menopause had occurred in 20% of these women, but there was no relation between the early onset of I.H.D. with age at menarche, parity, or the incidence of abortion. Oral contraceptives did not increase the risk of myocardial infarction unless one of the major risk factors was also present.

Altogether 75% of patients with angina or myocardial infarction survived 12 years. Coexisting hypertension worsened the prognosis. The prognosis after myocardial infarction was similar in these women to that previously described for men under the age of 40.

*This paper formed the basis of the fourth Louis F. Bishop lecture delivered to the American College of Cardiology in 1973.

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Introduction

It has been recognized for many years that ischaemic heart disease (I.H.D.) is rare in women in the reproductive years and no definitive account has yet appeared of its characteristics or its prognosis in women of this age group. So far, our knowledge has been accumulated from small numbers (James *et al.*, 1955; Weinreb *et al.*, 1957; Goodale *et al.*, 1960; Shochet, 1960; Blackman and Koluglu, 1961; Doerken, 1961; Malmcrona *et al.*, 1961; Cochran and Gwinup. 1962; Mulcahy *et al.*, 1967; Bengtsson, 1973).

INCIDENCE

Assessment of the frequency of I.H.D. in women under 45 years of age has been based on mortality figures but, because of the small numbers of deaths which occur below this age, these are unreliable as minor variations in rate could distort mortality statistics considerably.

As a result of a community survey of the incidence of I.H.D. conducted in Edinburgh in 1968 it is now possible to appraise with greater accuracy the prevalence of I.H.D. in young women. This community survey (Armstrong *et al.*, 1972) determined the incidence of new myocardial infarctions, non-fatal and fatal, in a defined community of people of both sexes under the age of 70 years. It resulted from collaboration with most general practitioners in the city and a system was developed for confirming or refuting that the reported events truly were due to myocardial infarction. During the course of the year of survey 1,709 cases were recorded, 180 concerning people under the age of 45. The incidence of myocardial infarction per 1,000 women at risk aged 30-44 years was 0.19 (table I). For all acute myocadrial events,

TABLE I—*Incidence of Acute Ischaemic Events in General Population (Armstrong et al., 1972). Numbers of Subjects in each Group are given in Parentheses, and Patients presenting with Angina only are not included in these Figures*

Diagnosis	Incidence per 1,000 at Risk aged 30-44 years		Male: Female Ratio
	Men	Women	
Myocardial infarction or probable myocardial infarction	1·27 (51)	0·19 (8)	6·7:1
Prolonged ischaemic pain	0·67 (27)	0·21 (9)	3·2:1
Sudden cardiac death	0·50 (20)	0·09 (4)	5·5:1
Total	2·44 (98)	0·49 (21)	5·0:1

including prolonged ischaemic pain and sudden cardiac deaths but excluding angina, it was 0.49 per 1,000. This figure should be contrasted with that of 2.49 for men of the same age range.

The figures from the study give perspective, therefore, to the report which follows and indicate that, in spite of the numbers reported here, myocardial infarction is an uncommon disease in women under the age of 45. No figures are available concerning the prevalence or incidence of angina in such young women.

The mortality rate from I.H.D. seems to have increased at a greater rate in young women between 1958 and 1970 (fig. 1). Because of this increase in mortality from I.H.D.—about 50% in women aged 35-44 years—it is appropriate to present an account of the characteristics of young women who get I.H.D.

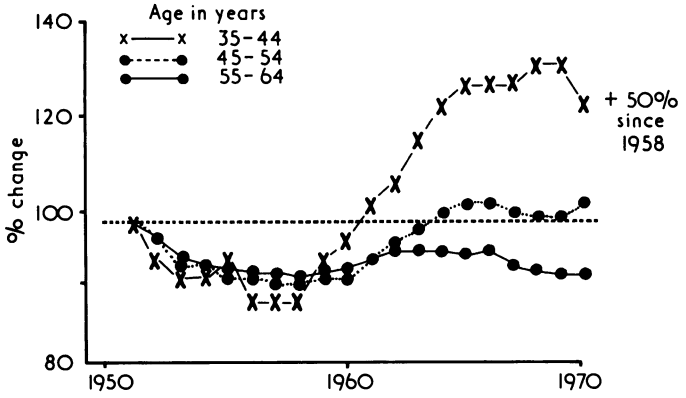


FIG. 1—Standardized mortality rates for ischaemic heart disease for women aged 35-64 years in England and Wales. Rates in 1950-2 were 8/100,000 for women aged 35-44 years, 42/100,000 for 45-54 years, and 211/100,000 for 55-64 years. Three-year moving averages were used for construction of curves. (I.C.D. 420-422 for 1950-67 and 410-414 for 1968-71.)

Subjects

Over a period of 18 years (1953-70) 192 women who developed clinical features of I.H.D. under the age of 45 years were seen by me in the department of cardiology in the Royal Infirmary of Edinburgh. There were also seven patients who presented with angina and were found to have valvular heart disease—four had clinical features of aortic stenosis and three had mitral valve disease—who were excluded from this series.

From these 192 women 150 were selected for this report on the basis of defined electrocardiographic abnormalities. The remaining 42 women had either no electrocardiographic signs to support a clinical diagnosis of I.H.D. or their features were insufficient to fulfil the defined criteria. The criteria for patients with myocardial infarction were electrocardiographic abnormalities sufficient to warrant classification as 1.1 or 1.2 using the Minnesota code (Rose and Blackburn, 1968): this means the presence of an irrefutable Q wave. Patients accepted into the study with a clinical diagnosis of angina had either to have electrocardiographic abnormalities codable as 4.1 (S-T depression $\geqslant 1$ mm) or 5.1 (T-inversion $\geqslant 5$ mm) at rest or, in the absence of one of these, an abnormal exercise tolerance test result codable as 11.1 or 12.1 (these indicate a change from no codable item at rest to S-T depression $\geqslant 1$ mm or T-inversion $\geqslant 5$ mm). The criteria of abnormality in the resting electrocardiogram was based on an orthodox 12-lead record. The post-exercise abnormalities were based during the earlier years of this study on the results of a Master 2-step test and during the years 1968-70 on bicycle ergometry with submaximal testing using W.H.O. standards (World Health Organization, 1968).

Of the 150 women 85 satisfied the criteria for myocardial infarction and 65 the criteria for angina. Five of the women (four with myocardial infarction and one with angina) were shown to have nonatherosclerotic causes for the premature development of I.H.D. These five women had a mean age of 37 years. The remaining 81 patients with myocardial infarction and 64 with angina had mean ages of 40 and 41 respectively. The study group, which was followed up from two to 20 years, comprised these 145 women with a mean age of 40 years. None of the women had had previous myocardial infarction.

The details of five women whose I.H.D. was thought not to be due to coronary atherosclerosis are shown in table II. In the four women who presented with myocardial infarction there was a definite cause other than atherosclerosis. In the fifth angina was associated with haemoglobin levels in the region of 4 g/100 ml, and with correction of the anaemia the angina disappeared and the electrocardiogram returned to normal.

TABLE II—*Diagnoses and Outcome in Five Women with Nonatherosclerotic Causes for I.H.D.*

Case No.	Age	Presentation	Diagnosis	Outcome
1	26	Myocardial infarction	Fulminating acute myocarditis	Died, necropsy confirmation
2	26	Angina	Extreme anaemia	Well 15 years later
3	34	Myocardial infarction	Accidental—intravenous adrenaline	Well 16 years later
4	38	Myocardial infarction	Systemic lupus erythematosus	Died, necropsy confirmation
5	39	Myocardial infarction	Syphilis and gross aortic incompetence	Angina, died 8 years later

Methods

All patients had a physical, electrocardiographic, and radiological examination. Blood pressure was recorded in the semi-recumbent position in the right arm and the lowest reading of three was taken over a period of 10 minutes and was the figure registered for the study. Patients under treatment for hypertension and those with diastolic blood pressure of 100 mm Hg or more when first seen or within one year of myocardial infarction were recorded as having hypertension.

Serum cholesterol was initially measured by the method of Jurand and Albert-Recht (1962), a modification of the Kendall-Abel method, and more recently by a Technicon AutoAnalyzer method. Serum triglycerides were initially measured by the glyceride-glycerol method of Carlson (1963) and more recently by a Technicon AutoAnalyzer method. Blood glucose was estimated by a glucose oxidase method. Lipoprotein phenotyping was undertaken on polyacrylamide gel (Frings *et al.*, 1971), while in some patients a scatter-light nephelometer was also used (Stone *et al.*, 1971).

Results

RISK FACTORS

Major risk factors were defined as a serum cholesterol level of 270 mg/100 ml or more, diastolic hypertension of 100 mm Hg or more, and a consumption of 20 or more cigarettes daily. Many of the 145 patients had one or more major risk factors. There was no significant difference in the incidence of these major risk factors between women who presented with myocardial infarction and those who presented with angina (table III). Hypercholesterolaemia was the most common and was present in 46% of the group. Diastolic hypertension occurred in 34%. Excessive cigarette smoking was also common but more so in those with myocardial infarction than in those with angina (table IV).

TABLE III—*Prevalence of Major Risk Factors in 81 Patients with Myocardial Infarction and in 64 with Angina*

	Myocardial Infarction Patients (%)	Angina Patients (%)	Total (%)
No major risk factors ..	21	31	26
One major risk factor ..	42	41	41
Two major risk factors ..	32	27	30
Three major risk factors ..	6	2	3

TABLE IV—*Prevalence of Each Major Risk Factor in 81 Patients with Myocardial Infarction and 64 with Angina*

	Myocardial Infarction Patients (%)	Angina Patients (%)	Total (%)
Hypercholesterolaemia (≥270 mg/100 ml)	48	44	46
Diastolic hypertension (≥100 mm Hg)	39	28	34
Cigarettes (≥20/day)	43	19	32
Total	79	69	74

TABLE V—*Prevalence of Minor Risk Factors in 81 Patients with Myocardial Infarction and 64 with Angina*

	Myocardial Infarction Patients (%)	Angina Patients (%)	Total (%)
Premature menopause	22	17	20
Oral contraceptive	14	2	8
Obesity alone (≥15% standard)	4	6	5
Diabetes mellitus	2	3	3
Abnormal oral G.T.T. result*	2	2	2
No evident predisposing factor	9	14	11

*G.T.T. (Glucose Tolerance tests) were undertaken in 94 women.

One major risk factor was present in 74% of patients (table IV) and a number of minor risk factors were also identified (table V): the commonest was a premature menopause.

Diabetes was not commonly associated with I.H.D. in these young women but because it has in the past been thought to be important (Herman and Gorlin, 1965) an oral glucose tolerance test was undertaken in 94 of the 145 women. This comprised an oral load of 75 g glucose with half hourly blood sampling. Four of the 94 women had abnormal glucose tolerance which had not previously been known and five had flat glucose tolerance curves.

Only 11% of the total group did not have some associated risk factor.

There was no statistically significant difference with regard to all predisposing factors (major and minor) between the myocardial infarction and angina groups, though cigarette smoking was more common in the group with myocardial infarction.

HYPERLIPIDAEMIA

Hypercholesterolaemia, defined as a serum cholesterol of 270 mg/100 ml or more, was the commonest of the major risk factors and was present in 46% of the total group (table VI). The most frequent associated finding was a history of I.H.D. in first degree relatives. A premature menopause and obesity were also common associations.

In 56 of these women serum triglycerides were measured and in table VII the results of serum cholesterol and triglyceride analyses are presented. The level above which serum triglycerides were considered to be raised was 200 mg/100 ml. Abnormal plasma lipid concentrations were present in 78% of the 56 women and the most common single abnormality was raised serum cholesterol (table VII).

TABLE VII—*Frequency of Serum Lipid Abnormalities in 32 Myocardial Infarction Patients and 24 Angina Patients in whom Serum Triglycerides were measured. (High cholesterol ≥270mg/100ml: high triglycerides ≥200mg/100ml)*

	Myocardial Infarction Patients (%)	Angina Patients (%)	Total (%)
Normal cholesterol and normal triglycerides	20	26	22
High cholesterol and normal triglycerides	41	42	41
Normal cholesterol and high triglycerides	6	0	4
High cholesterol and high triglycerides	33	32	33

Of the 145 women in the series, 42 had at some time either a serum cholesterol of 350 mg/100 ml or more or a serum triglyceride concentration of 200 mg/100 ml or more. Phenotyping of the lipoprotein classes was undertaken in 34 of these 42 women (table VIII). This survey was conducted from 1953-70 when phenotyping of lipoproteins was mostly not available. Many patients were receiving treatment and so assessment of the prevalence of lipoprotein abnormalities in young women with I.H.D. was not possible though the commonest phenotype was type IIa.

TABLE VIII—*Prevalence of Gross Hyperlipidaemia*

	Myocardial Infarction Patients	Angina Patients	Total
No. with cholesterol ≥350 mg/100 ml	15/81	6/64	21/145
No. with triglycerides ≥200 mg/100 ml	3/32	2/24	5/56
No with cholesterol ≥350 mg/100 ml and triglycerides ≥200 mg/100 ml	10	6	16
No. with lipoprotein type:			
IIa	14	7	21
IIb	2	0	2
III	0	1	1
IV	7	3	10
Not known	5	3	8
No. with Xanthomata	14	7	21

DIASTOLIC HYPERTENSION

Most women classified as having diastolic hypertension also had left ventricular hypertrophy (table IX). The most common

TABLE VI—*Characteristics of Patients with Hypercholesterolaemia (≥270mg/100ml)*

	No. (%) with Hypercholesterolaemia	% with Family History of I.H.D.	% with Premature Menopause	% Obese	% on Oral Contraceptives	% with Diabetes Mellitus	% with Xanthomata
Myocardial infarction patients	39 (48)	51	26	18	13	3	18
Angina patients	28 (44)	39	36	32	0	7	11
Total	67 (46)	49	30	24	7	4	15

TABLE IX—*Characteristics of Patients with Diastolic Hypertension (≥100mm Hg)*

	No. % with Diastolic Blood Pressure ≥100 mm Hg	% with Left Ventricular Hypertrophy	% with Pregnancy Hypertension or Toxaemia	% with Family History of I.H.D.	% Obese	% with Premature Menopause
Myocardial infarction patients	32 (40)	25	37	28	19	16
Angina patients	18 (28)	20	50	55	39	17
Total	50 (34)	23	42	38	29	16

associated finding was a history of hypertension during a previous pregnancy and not infrequently that of toxaemia of pregnancy. A history of I.H.D. in first degree relatives and the presence of significant obesity were also common in these women.

EXCESSIVE CIGARETTE SMOKING

There were significantly fewer non-smokers and significantly more of those who smoked 15 cigarettes or more among patients with myocardial infarction than among those with angina pectoris (table X). There was no significant difference in the cigarette smoking habits of women with angina pectoris and normal women of comparable age in the U.K. population (Todd, 1972).

Reliance had to be placed on the cigarette smoking habits of women before they presented with I.H.D. since most, particularly those who had myocardial infarction, reduced their smoking or discontinued it completely. Thus, it was impossible to relate prognosis to cigarette smoking.

TABLE X—*Cigarette Smoking in 81 Patients with Myocardial Infarction and 64 with Angina and in Women in Normal U.K. Population*

No. of Cigarettes Smoked	Myocardial Infarction Patients (%)	Angina Patients (%)	U.K. Population Women (30-45 yrs) (%)
None	12	39	51
1-14/day	41	34	23
15-24/day	32	23	19
⩾25/day	15	3	7

OTHER FACTORS

Premature Menopause.—Menstruation had stopped in 29 (20%) of these women. The estimated prevalence in women aged 40 of a premature menopause is 3%-5%. Amenorrhoea resulted from operative or radiation treatment for ovarian conditions in 18 and was spontaneous in 11. Most of those with a premature menopause had hyperlipidaemia.

Oral Contraceptives.—Most of these women were first seen before the widespread introduction of oral contraceptives, and at the time of their presentation with I.H.D. only 12 (8%)—10 of whom presented with myocardial infarction—had been taking oral contraceptives.

An analysis has been made of the characteristics of all women admitted to the intensive coronary care unit in the Royal Infirmary during the period 1964-72 (Oliver, 1970; Radford and Oliver, 1973). Of those under 45 years admitted routinely during these years 52% were taking oral contraceptives (table XI). This figure should be contrasted with that (10%-15%) estimated for the normal population of the same age (Radford and Oliver, 1973). There was no difference in the prevalence of the major risk factors in those women taking oral contraceptives compared with those who were not.

TABLE XI—*Prevalence of Major Risk Factors in 31 Women admitted with Myocardial Infarction to coronary care unit from 1964-72. Results are Numbers of Patients*

	Patients on Oral Contraceptives (n=16)	Patients not on Oral Contraceptives (n=15)
No major risk factors	2	0
One major risk factor	5	3
Two major risk factors	7	10
Three major risk factors	2	2

Parity.—There was no significant difference in the numbers of children born to these women when compared with the expected, nor was there an excess miscarriage rate. Twelve spontaneous miscarriages occurred in the 108 married women who could recall clearly their gynaecological experiences.

Menarche.—The age of the onset of menstruation was recorded in 122 of the 145 women. The median was 13.9 years with a mean of 14.4 years and a range of 11-17 years. This was not different from the expected.

Family history of I.H.D.—A history of I.H.D. in first degree relatives was recorded in about half of these women. It is difficult to quantify this and in table XII only three subanalyses are shown: of patients with a family history of I.H.D. in one parent 50-70 years, one parent aged less than 50 or two parents or one sibling aged 50-70, or in many first degree relations. There was no significant difference in the importance of family history between patients with myocardial infarction and those with angina. A family history of I.H.D. was present in 16 (11%) of those without a major risk factor (table III) and in 92 (64%) of those with one or more major risk factors.

TABLE XII—*Prevalence of a Family History of I.H.D. in 81 Patients with Myocardial Infarction and 64 with Angina*

	Myocardial Infarction Patients (%)	Angina Patients (%)	Total (%)
No family history	30	36	33
Family history:	49	48	48
1 parent 50-70 yrs	25	27	25
1 parent <50 or 2 parents or 1 sibling 50-70 yrs	19	16	18
Many first degree relations	5	5	5
Not known	21	16	19

Obesity.—While 21% of all patients with I.H.D. under 45 were obese to an extent of 15% or more above their standard weight obesity alone—that is, without other associated risk factors—occurred in only 5% of the whole group.

Hirsutism.—Six of these young women had excess hair on the upper lip or below the chin and one shaved regularly.

Radiology.—Screening for calcification in the coronary arteries (Oliver *et al.*, 1964) was undertaken in 94 women and calcification was evident in 21 patients. Coronary angiograms were not done in most of the women since the technique was developed several years after most women were admitted to the study and after some had died. Coronary angiograms were made in only 12 women; four had triple vessel disease, three had two coronary arteries with extensive atheroma, and five had more than 75% stenosis of one coronary artery.

PROGNOSIS

Life tables were constructed to determine prognosis, and the mortality over a 12-year period is shown in figs. 2-5. The follow up was conducted at annual or occasionally biennial intervals. At each examination, a clinical history was taken and an electrocardiogram and radiological examination of the heart were made.

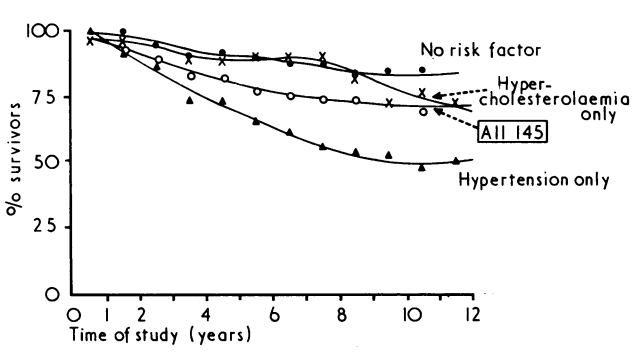


FIG. 2—Prognosis of 145 women with I.H.D. under 45 years and of those with no risk factors, hypercholesterolaemia only, and hypertension only. There were too few deaths in cigarette smokers to plot a survival curve for this as single risk factor.

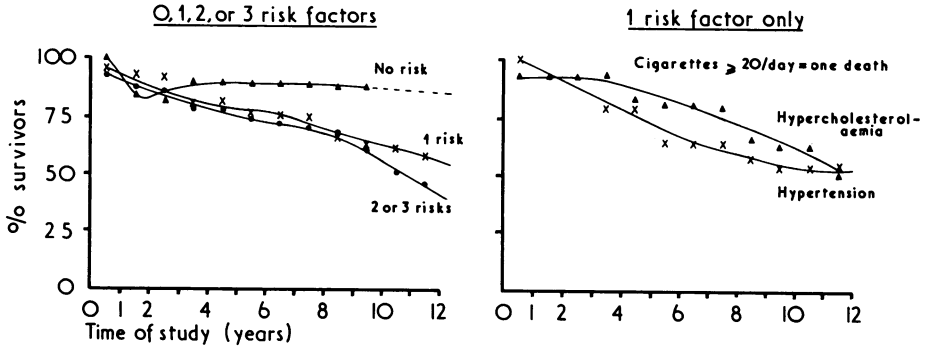


FIG. 3—Prognosis of 81 young women with myocardial infarction according to presence of risk factors.

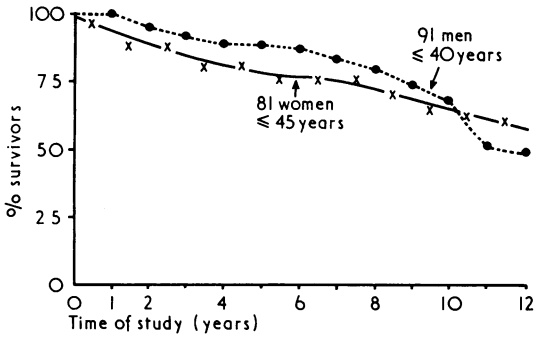


FIG. 4—Prognosis of 81 young women, disregarding risk factors, in contrast to that reported for 91 young men (Gertler *et al.*, 1964).

The overall prognosis for these 145 young women with angina or myocardial infarction was that 75% survived 12 years (fig. 2). When there was hypertension the survival rate was worse, with only 50% surviving 12 years. The presence of hypercholesterolaemia did not worsen prognosis. It was impossible to relate excessive cigarette smoking to prognosis because too few women continued to smoke after the initial presentation with I.H.D.

The prognosis for the young women with myocardial infarction was best if there were no associated major risk factors (fig. 3). The presence of hypertension carried a worse prognosis than that of hypercholesterolaemia. It is possible to compare the prognosis of young women with myocardial infarction with that of young men with myocardial infarction and in fig. 4 the 12-year survival figures reported for 91 men under the age of 40 are contrasted with the findings of this study from 81 women with myocardial infarction under the age of 45 (Gertler *et al.*, 1964). Disregarding the presence of risk factors the overall prognosis of both sexes is similar, though perhaps a little worse for young women.

The prognosis of the 64 young women with angina pectoris is shown for the 12-year period of study in fig. 5. The presence of one risk factor makes the survival curve less good than when there are no risk factors. Hypertension is the risk factor of most importance in determining the poor prognosis in patients with angina pectoris. There were no deaths over the 12-year period in the 28 women with associated hypercholesterolaemia, and only one death in the 13 women who smoked 20 or more cigarettes daily.

Discussion

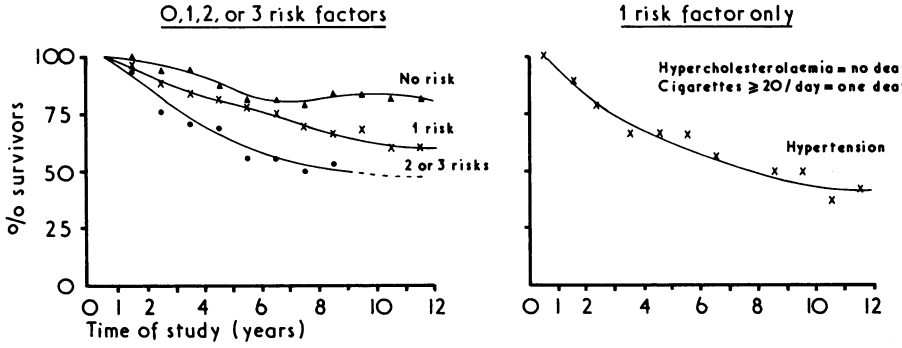
There are several inherent difficulties in reporting this series of 150 women under 45 years who developed I.H.D. It only represents the experience of one cardiologist working for 20 years in a major university hospital serving a city of 450,000 with a surrounding population of about 1 million.

No conclusions can be reached concerning the prevalence of I.H.D. in young women since unknown selection factors may have operated to provide such a large individual experience. Nor can reliance be given to the relative proportions presenting with angina or myocardial infarction. The Edinburgh Community Study (Armstrong *et al.*, 1972) of I.H.D. provides reliable figures of incidence, however, and these were realanysed to provide some perspective (table I).

Some of these women may have been referred to the department of cardiology in the Royal Infirmary because physicians in the community knew of my interest in I.H.D. and some bias may have operated to refer to me patients with an unrepresentative prevalence of risk factors. This is unlikely to have been a major influence, however, since all the women (96 patients) who were referred during the years 1953-64 by general practitioners were referred for a consultative opinion and not specifically to me though they were all seen by me either initially or within a few months of referral. There were 52 women with myocardial infarction and 44 with angina before 1965 and 33 and 21 respectively during 1965-70. The slight proportionate increase in those with myocardial infarction was probably due to the establishment in 1964 of a coronary care unit in the Royal Infirmary. Selective referral of patients from a distance can be excluded since only one lived outside a 50-mile radius from the centre of the city of Edinburgh.

The duration of the survey also led to problems since diagnostic methods change over a period of 18 years. Thus, lipoprotein typing was done in only one-third of patients and coronary

FIG. 5—Prognosis of 64 young women with angina according to presence of risk factors.



arteriograms were undertaken in only 12 women. On the other hand, a smaller number studied more intensively would not necessarily have yielded more information.

A further weakness is that the prevalence in the same community of the major risk factors is not known. A survey of prevalence of risk factors in the west of Scotland, however, where the incidence of I.H.D. is actually higher than in Edinburgh, shows that hyperlipidaemia and hypertension are very much less common in healthy young women than in these women with I.H.D. (V. M. Hawthorne, personal communication).

The diagnosis of angina in young women is not always easy to make. Changes suggestive of myocardial ischaemia can occur in the post-exercise electrocardiogram in 10%-26% of apparently normal women (Cumming *et al.*, 1973). Taking this into account, an error in diagnosis might have been introduced into this series though it is likely to have been less since the women reported here also had symptoms of angina. Angina with electrocardiographic evidence of myocardial ischaemia may occur in some young women in the absence of demonstrable atherosclerotic occlusion of large coronary arteries (Eliot and Bratt, 1969; Glancy *et al.*, 1971). There is insufficient data to allow any conclusions about the incidence of this and much depends on the adequacy of the coronary angiograms. Most of the women reported in this series did not have coronary angiograms and so no comment can be made about the proportion that might have little or no disease in their coronary arteries. An ischaemic basis for pain is not excluded by a negative coronary angiogram, however, since infarction has occurred in such patients (Eliot and Bratt, 1969) and increased lactate concentrations can occur in the coronary sinus blood (Kemp *et al.*, 1967). There is no satisfactory explanation for the occurrence in these women of myocardial ischaemia in the absence of coronary artery disease, though it could be due to undetectable small-vessel disease, a major thrombotic tendency (Glancy *et al.*, 1971), or an abnormal haemoglobin-oxygen dissociation curve (Eliot and Bratt, 1969).

A similar series of young women with I.H.D. has not previously been reported. The most striking feature was that 89% of the 145 women with myocardial ischaemia or infarction had an evident predisposing factor: 74% either had hypercholesterolaemia, diastolic hypertension, or smoked more than 20 cigarettes daily and one-third showed two or more of these major risk factors. In other words, young women who developed I.H.D. usually manifested one of the risk factors commonly associated with its premature development in men.

Hypercholesterolaemia was more common than hypertriglyceridaemia and type IIa hyperlipoproteinaemia was the commonest of the abnormal phenotypes. While the numbers were small it is surprising that type IIa should have occurred more often than type IV though this same preponderance has been reported previously in women aged 40-49 (Wood *et al.*, 1972). A preponderance of type IIa has also been observed in older women with I.H.D. (Brown and Daudiss, 1973; Lorimer *et al.*, 1974) and presumably reflects a major genetic component in the development of premature I.H.D. in these young women. It did not seem to be due to greater success in treating type IV patients. The pattern differs from that observed in men.

The occurrence of left ventricular hypertrophy in most women with diastolic hypertension indicated its serious nature. Pregnancy hypertension or toxaemia were common precursors in those with hypertension. It has proved impossible to record with any consistency whether the blood pressure remained raised between the time of the pregnancy or of pre-eclamptic toxaemia and the onset of I.H.D.

A history of ischaemic heart disease was recorded frequently in first degree relatives of those who presented with hyperlipidemia and in those with hypertension. This is consistent with the familial expression of hyperlipidaemia (Slack, 1969) and hypertension (Pickering, 1968).

There were fewer non-smokers among those with myocardial infarction compared with those who presented with angina pectoris and with the reported prevalence in the U.K. population (Todd, 1972), and those with myocardial infarction smoked more than those with angina pectoris and the general population. These results are in keeping with those recently reported by Bengtsson (1973) for 47 women under the age of 60 years and those earlier observed in older women (Kannel *et al.*, 1968). A similar difference in cigarette smoking habits between patients who develop myocardial infarction and those who have angina has previously been reported in men (Doyle *et al.*, 1964). The rapid rise in mortality from I.H.D. in young women during recent years may be related in part to the striking increase in cigarette smoking which has occurred in women in their 20s and 30s over much the same period (Todd, 1972).

The relationship between premature cessation of ovarian function and the premature onset of I.H.D. has been described previously on the basis of surveys of women who developed a spontaneous premature menopause or had bilateral oophorectomy (Oliver and Boyd, 1959; Sznajderman and Oliver, 1963). The finding in this series that 20% of all women with I.H.D. under 44 years had already had a menopause confirms this association, and an additional 16% of women had had infrequent or very irregular menstruation during three months before the onset of angina or myocardial infarction. Further support can be derived from a recent Swedish survey (Bengtsson, 1973).

During the years of this survey when the oral contraceptive has been available in Britain, 31 women presented in the coronary care unit with myocardial infarction and 16 (52%) had been taking an oral contraceptive. This should be contrasted with an expected prevalence of between 12%-15% of oral contraceptive takers in the general population (Radford and Oliver, 1973). Only two of these 16 women had no major risk factor and nine of the 16 had two or more major risk factors (hypercholesterolaemia, hypertension, or excess cigarette smoking). This suggests that oral contraceptives increase the risk of myocardial infarction only in those women who already have a high risk for the development of I.H.D. Some of the women admitted with myocardial infarction to the coronary care unit had been receiving high dosage oestrogens for a number of years. Now that these have been withdrawn it is possible that the risk of developing I.H.D. will be less. The relation of oral contraceptives to myocardial infarction has been considered in greater detail in a recent paper (Radford and Oliver, 1973) and it has been concluded that the incidence of myocardial infarction is greater in women who take the oral contraceptive though most of these women already have a predisposing risk factor for the development of myocardial infarction. It is not suggested that oral contraceptives alone increase the risk of myocardial infarction.

Diabetes mellitus was uncommon and only four out of 94 women had an abnormal glucose tolerance test result. Diabetes has frequently been suggested as an important explanation of the premature development of I.H.D. (Herman and Gorlin, 1965). While this may be so in women who are older it is not my experience, and it was not more common in those with myocardial infarction than in those with angina.

In contrast to the findings of a previous report of I.H.D. in older women (Oliver, 1970) there was no greater parity in these younger women with I.H.D. than that expected in the general population. Furthermore, there was the same proportion of single to unmarried women. This contrasts with the recent Swedish study (Bengtsson, 1973) where parity was reported to be greater in women with I.H.D. There was also no increase in the incidence of spontaneous abortion in the series reported here though this has previously been associated with the premature development of I.H.D. (Winkelstein *et al.*, 1958).

A contribution to our knowledge about I.H.D. in women is made by this study as a result of the long follow up. Many of the women were seen annually over periods of 15 or even 20 years, and 50% of the survivors were followed for 12 years. The prognosis of young patients with angina pectoris is better than that for those with myocardial infarction, the prognosis of whom is comparable to that reported previously for men with myocardial infarction under the age of 40. In both forms of I.H.D. co-existent hypertension carried a worse prognosis.

The good prognosis of young women with angina should be noted with regard to the current uncertainty about the benefit which saphenous vein by-pass surgery may have on prognosis.

In conclusion, the incidence of I.H.D. in young women seems to be on the increase, but the cause of the rise in mortality in the years 1958-70 is unexplained. The striking increase in the percentage of young women who smoke cigarettes and the increase in the number of cigarettes smoked may be a major contributor (Todd, 1972). If so, we can expect a steady increase in myocardial infarction in young women. This survey should be useful since it outlines many of the characteristics of women who develop angina or myocardial infarction at a young age, estimates prognosis, and might act as a reference with which to compare future studies of I.H.D. in young women.

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Effect of Clofibrate on Blood Viscosity in Intermittent Claudication

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Summary

Sixty-two patients with intermittent claudication associated with peripheral arterial diseases were treated with clofibrate, 2 g daily, for a minimum of six months. Progress was compared with that in a similar pretreatment period and also with that of a matched untreated control group of 27 patients. The most striking effect of clofibrate was a steep and sustained fall in whole-blood viscosity measured over a wide range of shear rates. This was associated with a significant fall in abnormally raised initial plasma-fibrinogen levels. An increased proportion of patients on treatment showed evidence of clinical improvement. Clofibrate had no effect on the susceptibility of red blood cells to autoxidation but it led to a significant shift in the red cell fatty acid pattern.

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Introduction

Three considerations prompted a preliminary trial of clofibrate in intermittent claudication. Firstly, despite many technical advances vascular surgery can benefit only a few of these patients. For the rest no consistently successful treatment is available. Secondly, clofibrate has been shown to lower a raised plasma fibrinogen level (Cotton *et al.*, 1963), and significant interrelations have now been established between plasma fibrinogen, whole-blood viscosity, blood flow, and the clinical manifestations and prognosis of the disease (Wells *et al.*, 1964; Weaver *et al.*, 1969; Merrill, 1969; Dormandy *et al.*, 1973 a, b). Thirdly, clofibrate seems to benefit patients with angina pectoris independently of its action of lowering blood lipids (Physicians of the Newcastle upon Tyne Region, 1971; Research Committee of the Scottish Society of Physicians, 1971), and in some respects the two types of ischaemic pain are similar. It was felt, moreover, that a detailed study of the red cell fatty acids might clarify the striking but still unexplained relation between the susceptibility of red cells to oxidative damage (two-hour malonyldialdehyde) on the one hand and the symptoms, signs, and rheological abnormalities on the other (Dormandy *et al.*, 1973 a, b).

Patients

The patients were chosen mainly from the group of intermittent claudicants previously described (Dormandy *et al.*, 1973 a, b). Sixty-two patients were given clofibrate, 2 g daily, for a minimum of six months (mean 7·4 months). Their mean age (± S.D.) was 62 ± 8 years, and there was the usual preponderance of men (47)