

**ISCHAEMIC HEART DISEASE: RISKS AND
NITRATE THERAPY**

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Introduction

Diseases of the cardiovascular system and in particular those falling within the definition of ischaemic heart disease (IHD, coronary heart disease) covering a group of clinical syndromes that include angina pectoris, acute myocardial infarction (AMI), asymptomatic myocardial ischaemia and sudden ischaemic death, are together the commonest cause of death in Western society.

Research into the detailed pathophysiology of IHD reveals more and more about the links between the mechanisms and the personal and environmental factors associated with such events as myocardial infarction and sudden ischaemic death. Malta, together with the UK, share the dubious distinction of having one of the highest mortality rates for cardiovascular diseases in Europe - 26.5% of the registered deaths in Malta were due to IHD. This high mortality is matched by a high prevalence of IHD, and the estimated risk factors (cigarette smoking, diabetes mellitus, raised serum total cholesterol concentration and blood pressure) are common in the Maltese archipelago.

The treatment of patients with IHD is primarily focused on symptomatic relief i.e. reduction or abolition of angina pectoris (and its equivalents) and life prolongation. Nitrates are highly effective both in terminating acute attacks of angina pectoris and in the prophylaxis of symptomatic and asymptomatic myocardial ischaemia.

Aims and Methodology

Survey 1

Prevalence of major risk factors in Maltese myocardial infarct patients

To determine the importance of blood cholesterol, smoking, hypertension, diabetes mellitus, alcohol consumption, family history, age, sex and social class as coronary risk factors, a study was made of admissions to the Coronary Care Unit of St Luke's Hospital - Malta for non-fatal AMI. Reports of MI which included at least two of the following manifestations:

- a) preceded by severe prolonged chest pain (>30 minutes)
- b) electrocardiographic evidence of myocardial infarction

- c) cardiac enzyme changes (CPK, AST) associated with MI only were investigated.

Categorization of diabetes mellitus, blood pressure and cholesterol levels were based on WHO diagnostic criteria.

Statistical analysis: Where applicable, the chi-squared test for trend was used. Other t-tests lacked sufficient data.

Survey 2

Maltese medical practitioners' approach and views to nitrate therapy

In this postal survey, Maltese medical practitioners were questioned about their prescribing practices of nitrates as compared to other antianginals and newer nitrate formulations. Amongst other questions reviewed were:

- a) the clinical efficacy of nitrates
- b) incidence of nitrate side-effects
- c) main causes of nitrate therapy failure
- d) strategies for prevention of nitrate tolerance
- e) practitioner views regarding the nitrate controversy, mass screening for detection of ischaemia, and the pharmacists' role in treatment and prevention of ischaemia.

Survey 3

Maltese community pharmacists' role in nitrate therapy

Practicing Maltese community pharmacists' (n=155) all over Malta and Gozo were questioned on the major advice sought by anginal/post-infarction patients in the pharmacy setting, the nitrate formulations most commonly dispensed, any changes in prescribing practices of antianginals vis-a-vis newer nitrate delivery systems and calcium antagonists and whether the pharmacist considers himself to have an active role in the primary and secondary prevention of IHD.

Results and Discussion

Survey 1

Prevalence of major risk factors in Maltese myocardial infarction patients

Table 1 shows the distribution of risk factors among the male patients studied. Since there were only 2 female cases, sex was not investigated. Men over 60 years were 2.75 more likely to suffer a non-fatal AMI event than men aged 50-59 years; and 6.60 times more likely than man aged 40-49.

Raised serum cholesterol levels ($>5.2\text{mmol/l}$) constituted 64.1% of cases, with borderline cholesterol levels taking a 51.3% share. The high prevalence of smokers (82.3%), ex or current, indicated that the effect of heavy smoking on IHD progression is long-term (31.4% previous and 33.3% current heavy), and constitutes a major risk factor in AMI cases.

The majority of male patients (54.9%) did not have IHD prior to infarction, possibly underlying the role of silent (asymptomatic) myocardial ischaemia (SMI) in atherosclerotic progression. SMI episodes are documented to be more frequent in diabetic and elderly subjects; 35.3% of the patients were diabetic, while 29.4% had impaired glucose tolerance.

The higher the social standing of a person, the more likely one is conscious of, and has, positive attitudes to a healthy lifestyle. Such a trend was in fact seen to be the case in this study, with 47.9% of the patients being unskilled, this % decreasing with higher social class.

Hypertension, especially elevated diastolic blood pressure (BP), accelerates existing atherosclerosis and initiates IHD in highly susceptible communities. Previous diagnosis of hypertension prior to the acute event constituted 35.3% of patients. However, it was not investigated whether the patients received antihypertensive treatment. Antihypertensive drugs (thiazides, propranolol) affect serum concentration of lipids.

It is widely accepted that a "bad" family history of IHD in a first-degree relative, constitutes an important risk factor for IHD, and may multiply the risk up to 2-4 fold. 35.9% of the patients were found to have

SURVEY : PREVALENCE OF MAJOR RISK FACTORS IN MALTESE MYOCARDIAL INFARCT PATIENTS
RESULTS:

| PARAMETER | VARIABLE | TOTAL NO. OF PATIENTS | % FREQUENCY OF OCCURRENCE | COMMENTS |
|-----------------------|--|-----------------------|---------------------------|--|
| 1. AGE | 30-39 | 1 | 1.96 | n = 51 |
| | 40-49 | 5 | 9.80 | |
| | 50-59 | 12 | 23.53 | |
| | 60+ | 33 | 64.71 | |
| 2. BLOOD CHOLESTEROL | NORMAL <5.2 mmol/l | 14 | 35.80 | n = 39 since cholesterol levels of 12 patients were not available |
| | BORDERLINE 5.2-6.7 mmol/l | 20 | 51.28 | |
| | HYPERCHOLESTEROL >6.7 mmol/l | 5 | 12.82 | |
| 3. BLOOD PRESSURE | NORMAL <140/90 mmHg | 29 | 56.86 | n = 51 |
| | BORDERLINE 140/90-160/95 mmHg | 2 | 3.92 | |
| | HYPERTENSION >160/95 mmHg | 20 | 39.22 | |
| 4. BLOOD GLUCOSE | NORMAL <6 mmol/l | 18 | 35.29 | n = 51 |
| | IMPAIRED GLUCOSE TOLERANCE =>6-<11 mmol/l | 15 | 29.42 | |
| | DIABETES =>11 mmol/l | 18 | 35.29 | |
| 5. SOCIAL CLASS | I UPPER AND MIDDLE | 4 | 7.83 | n = 48 since occupation of 3 patients were not available |
| | II INTERMEDIATE | 8 | 16.67 | |
| | III SKILLED AND CLERICAL WORKERS | 13 | 27.08 | |
| | IV INTERMEDIATE | 23 | 47.92 | |
| | V UNSKILLED | 23 | 47.92 | |
| 6. DRINKING HABITS | NONE | 20 | 50.00 | n = 50 since 1 patient gave different accounts of his alcohol intake |
| | OCCASIONAL | 8 | 16.00 | |
| | MODERATE (<30g alcohol/day) | 5 | 10.00 | |
| | HEAVY (>30g alcohol/day) | 9 | 18.00 | |
| 7. SMOKING HABITS | NONE | 9 | 17.65 | n = 51 Moderate smoking was defined as <20gms tobacco/day. Heavy as >20gms/day |
| | PREVIOUS MODERATE | 4 | 7.84 | |
| | PREVIOUS HEAVY | 16 | 31.37 | |
| | CURRENT MODERATE | 5 | 9.80 | |
| | CURRENT HEAVY | 17 | 33.33 | |
| 8. FAMILY DISPOSITION | NONE | 25 | 64.10 | n = 39 12 patients either did not know whether a history existed (5) or gave a vague account (7) |
| | FAMILY HISTORY OF IHD | 14 | 35.90 | |
| 9. PREVIOUS IHD EVENT | NONE | 29 | 54.90 | n = 51 patients were grouped according to worst event point. 2 previous AMI had previous angina |
| | ANGINA | 8 | 15.69 | |
| | MYO. INFARCTION | 14 | 27.45 | |
| | OTHER IHD. (not defined) | 1 | 1.96 | |

TABLE 1: Distribution of variables (Risk-factors) included in analysis of AMI patients (d). All patients parameters as on first episode of Myocardial infarction except previous IHD event.

| PARAMETER | BRHS * | MALTA STUDY (1) | MALTA STUDY (2) |
|-------------------------------------|---------|-----------------|-------------------------|
| A. MALES | 428 | 51 | 17 |
| B. AGE RANGE (yr) | 40 - 59 | 39 - 88 | 40 - 59 |
| C. MEAN AGE (yr) | 53.3 | 63.1 | 51.4 |
| D. SMOKING: | | | |
| (%) NEVER | 13.0 | 17.7 | 11.8 |
| (%) CURRENT | 46.0 | 43.1 | 64.7 |
| E. NO HISTORY OF ANGINA PECTORIS | 50.0% | 54.9% | 52.9 50.2 |
| F. SYSTOLIC BP % >161mmHg | 24.3 | 39.2 | 11.8 |

TABLE 2: Comparison of statistics obtained from the British Regional Heart Study (BRHS) for men with a previous definite MI according to ECG compared with those obtained in the Malta Study. Malta Study (2) corrected analysis when taking the 40 - 59 age group for better comparison.

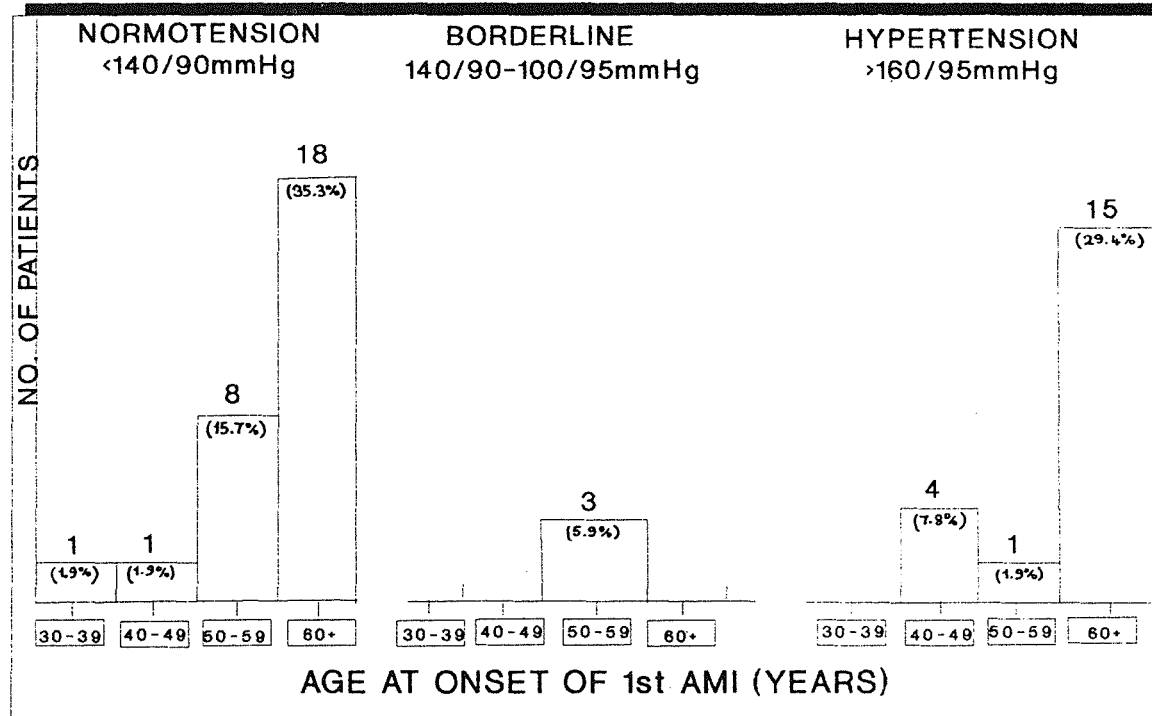


Figure 1. Hypertension as a risk factor: No. of patients plotted against age at 1st AMI (years), by blood-pressure category. Values in brackets denote percentage (%) out of total No. of patients. n = 51

a family disposition of IHD, determined by patient recall on prolective investigation.

Epidemiological studies have consistently shown an apparent protective association between light to moderate alcohol consumption and IHD. In this study, male infarct patients were more likely to have been non-drinkers (56.0%) than drinkers. Heavy drinkers were 1.8 more prevalent than moderate drinkers, while moderate drinkers were 5.6-fold less prevalent when compared to non-drinkers. On average, heavy drinkers have higher BP levels than others; this interrelation was not investigated.

Table 2 shows results obtained in this study with those of the British Regional Heart Study, a prospective study aimed to determine the personal and environmental risk factors for IHD in Great Britain.

Hypertension was 3 times more likely to be present in patients over 60 years (Fig. 1) and 1.3 times more likely to be present in patients with no family history of IHD. The trend of an increasing proportion of infarct men who had no family history with increasing blood pressure was 0.05 significant.

Current heavy smoking constituted a major risk (33.3%) when compared to current and previous moderate smoking (9.8% and 7.8% respectively), and non-smokers (17.7%). The effect of cessation did not have an effect on the infarct outcome (Fig. 2), in that the years since cessation of smoking did not show an inverse relationship to the number of patients. Heavy smoking habits were more predominant in the 50-59 year age group (7/12 patients). 22/33 patients over 60 years had current (8) or previous (14) heavy tobacco consumption. The trend of an increasing proportion of infarct men who had a family history with increasing tobacco consumption was 0.1 significant.

The predominant number of borderline cholesterol cases were aged over 60 years (13/20 patients), while half of the patients aged 50-59 years (6/12 patients) were borderline cases (Fig. 3). The majority of raised serum cholesterol (SCh) cases occurred in the 5th social class (12/24 patients investigated). The trend of an increasing proportion of infarct men who had high SCh levels with decreasing social class was 0.5 significant.

69.7% of patients aged over 60 years had raised serum glucose (sG) levels (23/33 investigated), with 30.4% of this category having diabetes (Fig.

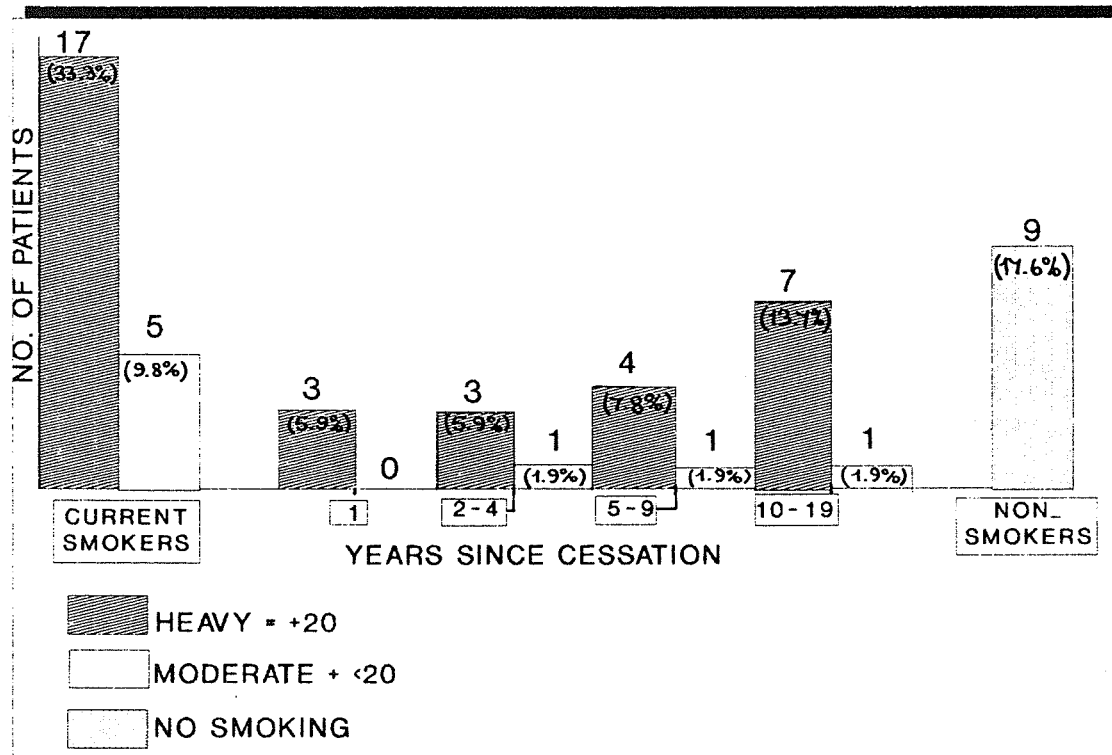


Figure 2. Effect of smoking and years since cessation as Prevalence in myocardial infarct patients. Smoking habits as on 1st AMI. A comparison between light to heavy smokers is also seen. Values in brackets denote percentage (%) out of total No. of patients. n = 51

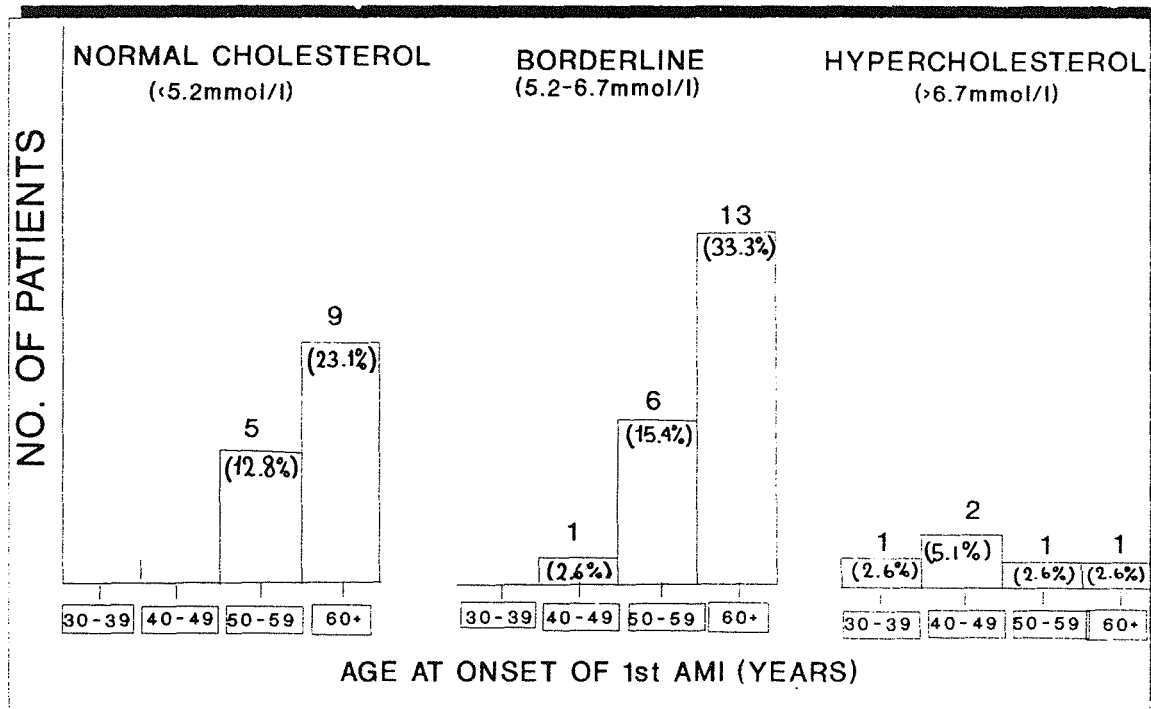


Figure 3: Cholesterol (Serum) as a risk factor: No. of patients plotted against age at 1st AMI (Years) by blood Cholesterol level categories. Values in brackets show percentage out of total No. of patients (n = 39)

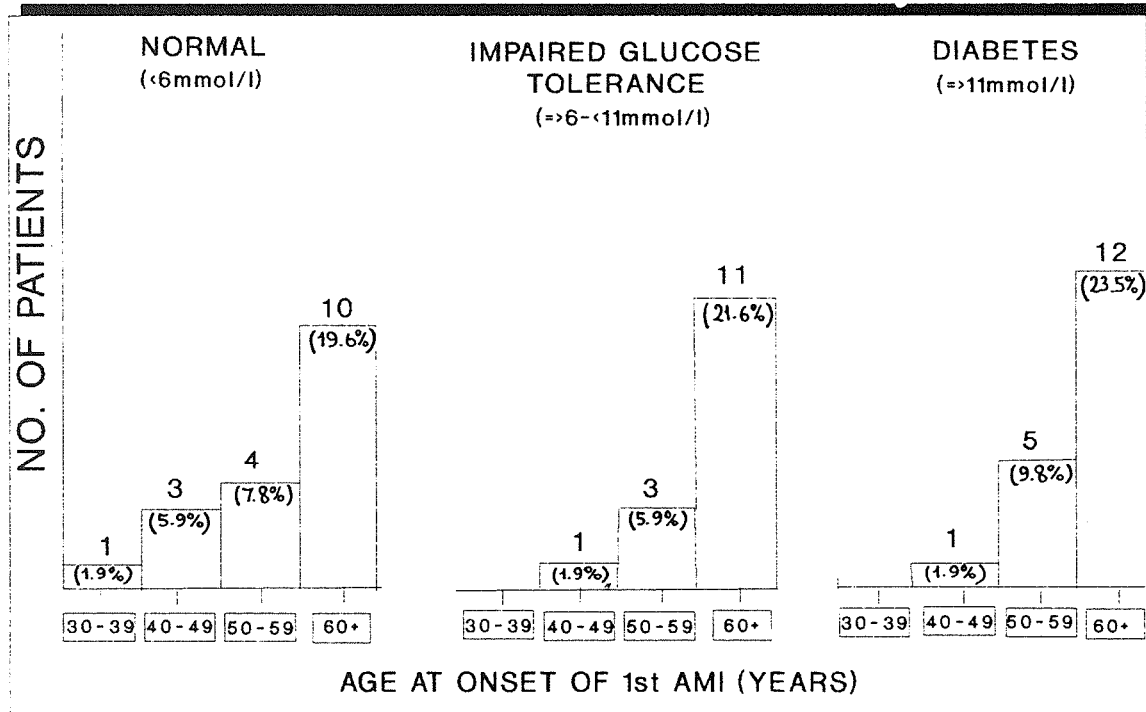


Figure 4: Serum glucose levels as a risk factor: No. of patients plotted against age at 1st AMI (Years) by serum glucose level categories etc. Values in brackets show percentage out of total No. of patients (n = 51)

4). 8/12 patients investigated between the age group 50-59 years also had raised SG levels, with diabetes taking a 41.7% share in this age group. Diabetes was more common in the lower fifth class (12/23 patients investigated). The trend of an increasing proportion of infarct men who had a family history of IHD with increasing glucose levels was 0.5 significant.

Alcohol consumption was more predominant in the 60+yrs age group. The majority of drinkers lied in the lower fifth social class (10/22 drinkers investigated).

Age and family history. The trend of an increasing proportion of infarct men who had no family history of IHD with increasing age was 0.25 significant, underlying that there was a tendency of MI to become manifest at an early age in those with a family disposition.

Survey 2

The response rate was 49.1% (106 responses out of 216). The majority of practitioners view nitrates as first line treatment for stable angina (67.9%) and prefer them to calcium antagonists for prophylactic management of angina (57.3% vs 42.7%). 89.2% agreed that treatment should be targeted at both silent (asymptomatic) and symptomatic episodes of ischaemia, however 42.2% do not agree with mass population screening of IHD, although they indicated that screening of high risk groups is feasible. Surprisingly, 51.3% of practitioners do not take measures to prevent or circumvent tolerance. The main risk factor (besides sex and age) associated with anginal development according to respondents' experience was smoking.

The gross majority of medical practitioners (92.9%) supported other roles for the pharmacist besides patient referral.

Survey 3

The number of pharmacists responding was 30.3% (47 responses out of 155).

53.2% of pharmacists declared that ischaemic patients have never asked their advice on medical treatment of angina, while 46.8% answered in the affirmative. The most common advice sought regards correct usage of anti-anginals, followed by complaints re side-effects. Sublingual glyceryl trinitrate (GTN) was found to be the nitrate most dispensed for relief and prophylaxis of anginal pain (54.0%), while oral isosorbide dinitrate (ISDN) took the bigger share of the market for nitrates used for long-term prophylaxis (38.0%). The predominant change in prescribing practises, noted in 50.0% of respondents, was attributed to more calcium antagonists being prescribed as an alternative to nitrates. 87.2% of the pharmacists agree to more involvement, besides referral, in the treatment of angina, but only 29.8% agreed to participate in mass screening by non-complex diagnostic tools (e.g. Reflotron, BP monitoring). The majority (70.2%) supported the advisory and educational role of pharmacists.

Conclusion

Survey 1

The results obtained in this prolective study (except for hypertension) were comparable to the British Regional Heart Study (BRHS) suggesting similar lifestyles and environmental factors acting on myocardial infarct outcome in the Maltese and British populations. Both share amongst the highest mortality rates of IHD for Europe.

The four main risk factors were found to be raised serum cholesterol levels, age, high tobacco consumption and low social class, suggesting that if dietary and anti-smoking campaigns are targeted at older men of low social standing, the incidence of non-fatal AMI will be drastically reduced. This does not minimize the importance of educating younger generations against unhealthy lifestyles to prevent the generation and progression of IHD; a role which pharmacists are in a prime position to execute.

Survey 2 and 3

Medical respondents commonly felt that nitrate therapy is still the first-line therapy for angina. A positive mentality is being developed among practitioners regarding the importance of treating asymptomatic episodes, only recently proven effective, showing a clear interest of practitioners in the subject. Surprisingly, the majority do not agree with intermittent/pulse nitrate therapy, an important step in the

circumvention of nitrate tolerance, possibly denoting a possible role of pharmacists to inform practitioners better on this matter.

The results obtained in both surveys re-inforces the belief that pharmacists have an important role as primary health educators and in the screening and evaluation of drug interactions. Moreover, the pharmacist has an important role in the primary prevention of IHD, being in a prime position to identify high risk groups and refer them to the practitioner, besides giving educational advice about healthy lifestyles. The set-up of a cardiac unit established to screen any person, whether referred or not, who wishes to be checked for signs of ischaemia is proposed.

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