European Heart Journal (1997) **18**, 1718–1724

Compliance and adverse event withdrawal:

their impact on the West of Scotland Coronary Prevention Study

The West of Scotland Coronary Prevention Study Group

Aims To assess the additional benefit gained from high compliance in the West of Scotland Coronary Prevention Study and to examine cases where withdrawal from trial medication was due to an adverse event.

Methods The incidence of definite coronary heart disease or non-fatal myocardial infarction, cardiovascular mortality, definite or suspect coronary heart disease death or non-fatal myocardial infarction, the need for coronary revascularization procedures, all-cause mortality and incident cancers were measured in the entire cohort and compared with the high compliance group. The adverse events associated with withdrawal were coded by body system.

Results In subjects with compliance $\geq 75\%$, treatment with pravastatin resulted in a 38% risk reduction for definite coronary heart disease death or non-fatal myocardial infarction and for cardiovascular mortality, a 46% reduction in risk or coronary revascularization and a 32% risk reduction ($P=0{\cdot}015$) for all-cause mortality.

Conclusions The analysis of the effect of pravastatin in the subgroup of high compliers to randomized medication demonstrated a substantial increase in the estimated risk reductions in comparison with that achieved in the intention-to-treat analysis. This result has significant implications for the motivation of high compliance among patients and for the assessment of the cost-effectiveness of treatment.

(Eur Heart J 1997; 18: 1718–1724)

Key Words: Primary prevention, compliance, withdrawals, on-treatment analysis, coronary heart disease, all cause mortality, pravastatin.

Introduction

The West of Scotland Prevention Study (WOSCOPS) was a double-blind randomized placebo-controlled trial of pravastatin in 6595 middle-aged men with moderately raised cholesterol levels who had no evidence of previous myocardial infarction[1]. It is well known that poor compliance is a major problem in the primary prevention context[2]. Patients who do not have overt symptoms of the condition for which they are being treated are less well motivated to comply with long-term therapy and may be less willing to tolerate minor side effects which could be associated with medication. There is a greater tendency for adverse events which develop after the initiation of therapy to be linked, rightly or wrongly, with the medication being taken. Hence, although it is appropriate that the primary analysis of any randomized trial is based on the intention-to-treat principle, some form of on treatment analysis is of great interest in the context of primary prevention, both to provide a true picture of the benefits of therapy in subjects who are good compliers and to motivate future patients to optimize their compliance. At the same time, it should be acknowledged that analyses, which adjust for on-treatment measures such as compliance, are no longer based on truly randomized comparisons and hence should be interpreted cautiously.

The level of non-compliance in the West of Scotland Coronary Prevention Study, with approximately 30% of subjects withdrawn from randomized therapy at 5 years, was similar to that of previous primary prevention trials of cholesterol lowering drugs[2]. This was, in part, due to the causes outlined above and was considerably exacerbated by the cholesterol controversy[3–6], which received a high media profile throughout the study, providing a very difficult climate within which to conduct a trial of this nature. The aim of this paper is to provide a more accurate estimation of the effect of treatment in subjects with a high rate of compliance.

Methods

Study design and subjects

The design of the study has been described in detail elsewhere[7]. Briefly, subjects were identified by

Revision submitted 10 March 1997, and accepted 14 March 1997.

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0195-668X/97/111718+07 $18.00/0

population screening in primary care. Men aged 45–64 years old were invited to be screened by their general practitioner and eventually 6595 subjects satisfied the entry criteria, including low density lipoprotein cholesterol levels $\geq 4{\cdot}0$ mmol . l^{-1}, with at least one $\geq 4{\cdot}5$ mmol . l^{-1} and at least one $\leq 6{\cdot}0$ mmol . l^{-1}. Follow-up involved four visits per annum for an average of 4·9 years (range 3·5–6·1 years), giving a total of 32216 subject years of follow-up.

End-points

End-points were identified from information received at routine trial visits, by analysis of annual electrocardiograms, by scrutiny of hospitalization and death reports and by computer record linkage[8]. Potential end-points were reviewed and classified by an End-points Committee[7]. The primary end-point of the study was definite coronary heart disease death or non-fatal myocardial infarction. Other important efficacy end-points considered in this paper include definite or suspect coronary heart disease death, or non-fatal myocardial infarction, cardiovascular mortality, the need for coronary revascularization procedures (coronary artery bypass graft or percutaneous transluminal coronary angioplasty) and all-cause mortality. Incident cancers, fatal or non-fatal but excluding minor skin cancers, were considered to be of particular importance in the assessment of safety.

The documentation of withdrawals due to the adverse events was examined. A definitive body system was assigned to each of these adverse events.

Analysis strategy and statistical methods

The logrank test was used to compare survival curves, and risk reductions were calculated from the hazard ratio estimated from Cox proportional hazards models. To assess the relationship between overall compliance and the risk reduction due to treatment with pravastatin, subjects were divided into categories on the basis of their compliance prior to the occurrence of an event or up to their follow-up time as appropriate. It has been assumed that most of the information in the compliance data is contained in the records of a subject's attendance for each trial visit and the issue or not of a supply of trial medication. Hence, in this analysis, a subject who attended and had pills issued at every visit either until he had an event or the study finished is considered to be 100% compliant. A subject who had apparently missed just one visit prior to his censoring or event date was still considered to be 100% compliant (a wide margin for attendance was permitted around the target visit date). Otherwise, percentage compliance in this paper is based on the relative frequency of potential visits at which trial medication was issued. For subjects who attended the visit after pills were issued, more detailed compliance information could be calculated from a pill count. Analysis of these data showed that once established on medication, pill counts were very high (>93% on average), reinforcing the validity of the simpler and more robust approach we have taken.

The aim of this analysis is not to build a mathematical model of the relationship between compliance and outcome in the study. Clearly, subjects who did not take any medication at all during the trial cannot be expected to have gained any benefit. The intention-to-treat analysis of the trial[1] demonstrated conclusively that treatment with pravastatin substantially reduced the risk of the combined end-point of coronary heart disease or non-fatal myocardial infarction. The purpose of this paper is to focus on the subgroup of subjects who achieved a level of compliance which might be considered to be typical of good compliers. We have tried to be pragmatic, acknowledging that not all subjects will be 100% compliant over a long period of time. With this in mind, we have taken the conservative view that subjects who are greater than or equal to 75% compliant should be considered to be high compliers and attention is focused on this subgroup. Data for the subgroups corresponding to 100% compliance and compliance between 75% and 100% are also presented for illustration as are the data for those subjects with compliance below 75%. Note that the method of computing compliance for subjects who have had an event results in varying numbers of subjects in the compliance categories across different endpoints.

As noted previously, analyses conditional on compliance during the course of the study are no longer truly randomized analyses and there is a possibility of imbalance among the treatment groups due to differences in the compliance profiles for the medications being compared. For this reason, estimates of the treatment effect in the high compliance group were recalculated for each end-point using the Cox proportional hazards model, adjusting for baseline risk factors which have previously been identified as being of prognostic value. The variables used to adjust for each outcome were selected in a previous analysis of the full dataset by stepwise regression analysis. The covariates used were current smoker (yes/no), diabetes (yes/no), taking nitrates (yes/no), minor electrocardiogram abnormality (yes/no), positive Rose questionnaire for angina (yes/no), family history of coronary heart disease (father died before the age of 55 years or mother before the age of 60, yes/no), age (years), history of hypertension (yes/no), diastolic blood pressure (mmHg), LDL/HDL cholesterol ratio.

Results

Compliance and withdrawals

Figure 1(a) shows that approximately 15% of subjects in both treatment groups had withdrawn from trial medication by the end of the first year of follow-up and

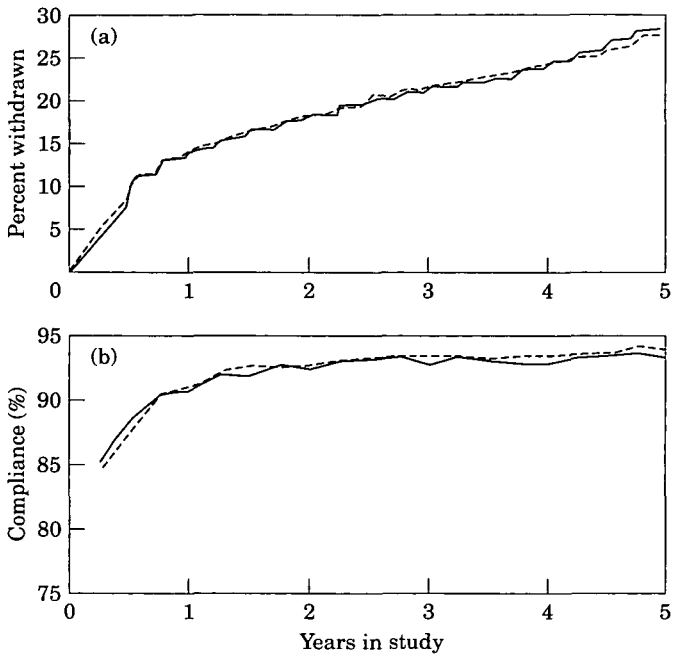

Figure 1 **(a) Percentage of randomized subjects permanently withdrawn (excluding deaths) from trial medication by year in study and split by treatment group. (b) Compliance as measured by pill count among those subjects attending trial visits and having medication issued, by year in study and split by treatment group. ——=placebo; – – –=pravastatin.**

approximately 30% had withdrawn by the end of 5 years. For subjects who attended trial visits and had their compliance assessed by pill count, the mean percentage compliance since the previous visit is plotted in Fig. 1(b). At the first trial visit, the mean compliance in the two treatment groups is approximately 85%, rising to approximately 93% at the end of the first year and remaining stable until the end of the study. Once participants were established on medication, their compliance was very high. There is no evidence of any difference between the treatments in the percentage of pills consumed or in time to withdrawal. Time to withdrawal curves are given in Fig. 2 separately for voluntary and adverse event associated withdrawals. There are no statistically significant differences between the patterns of withdrawal for the two treatments. As a simple overall assessment of compliance, subjects attended and received trial medication at 77% of possible trial visits.

Table 1 contains the means (standard deviation) (continuous variables) and percentages with risk factors (categorical variables) for each of the three compliance groups for a variety of risk factors which were found to be predictors of outcome. It can be seen that small and probably trivial increases in age or systolic blood pressure are present in the 100% compliance group. In the categorical measurements, a history of taking regular medication (nitrates, in diabetics and in hypertensives) significantly increases the rate of compliance. The converse is true of the smoking group. This may represent the compliance in a lower socio-economic group or a lack of interest in preventative measures in smokers.

In Table 2, the numbers of adverse event withdrawals are shown by treatment group and body system. The group treated with pravastatin show less cardiovascular withdrawals, as expected. The differences in the endocrine/metabolic numbers are accounted for by six cases of withdrawal because of a raised cholesterol in the placebo group and none in the treated group. This demonstrates unblinding either intentionally by individuals or by their medical advisors. Also within this body system sexual dysfunction was split 12 (placebo) and eight (pravastatin). In the general body system, fatigue, lethargy and malaise were split nine (placebo) and 13 (pravastatin) and weight loss one (placebo) and four (pravastatin) with no other specific condition appearing more than four times. In the special senses group, three cases of entirely separate eye conditions appeared in the pravastatin group and cases of Menieres, labarynthitis and tinnitus are grouped one (placebo) and four (pravastatin).

The details of all adverse events will be examined in a later paper.

Treatment effect in the high compliers

In Table 3, it can be seen that there is little evidence of any difference between the treatments in the low compliance group (compliance <75%). The two groups with

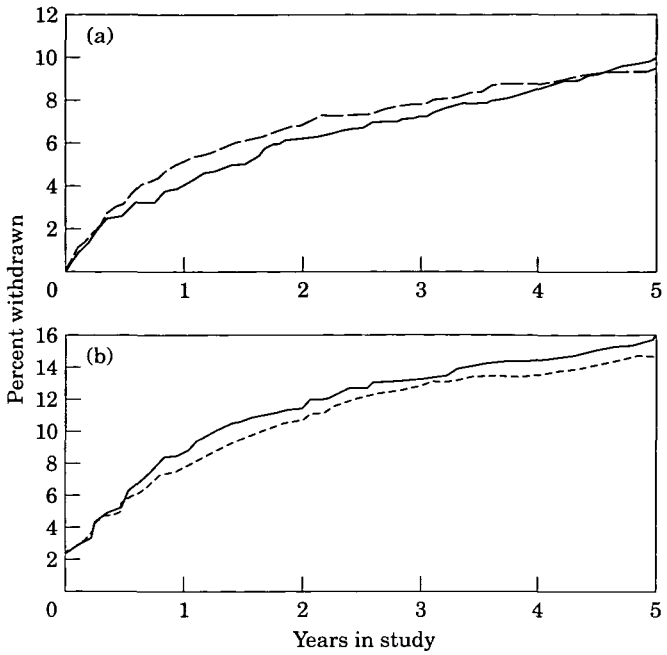

Figure 2 **Percentage of subjects permanently withdrawn from trial medication for reasons categorised as (a) Adverse event related and (b) Voluntary reasons, plotted against time in study. ——=placebo; – – –=pravastatin.**

Table 1 Distribution of baseline covariates by compliance category in the 6595 randomised subjects

	Compliance category[1]			
	<75%	(75%, 100%)	100%	*P*-value
(a) Continuous measurements (mean, standard deviation)				
Age (years)	54·7 (5·46)	54·7 (5·49)	55·5 (5·53)	<0·0001
Systolic blood pressure (mmHg)	134 (17·7)	135 (17·1)	136 (17·1)	0·0001
Diastolic blood pressure (mmHg)	83·3 (10·4)	83·6 (10·5)	84·3 (10·2)	0·0049
HDL (mmol . l^{-1})	1·14 (0·25)	1·14 (0·24)	1·14 (0·24)	0·77
LDL (mmol . l^{-1})	4·97 (0·46)	4·97 (0·44)	4·96 (0·45)	0·43
LDL:HDL	4·56 (1·01)	4·53 (1·03)	4·54 (1·01)	0·85
(b) Categorical measurements (% with condition)				
Family history[2]	5·7%	5·5%	5·8%	0·98
Taking nitrates	1·8%	1·2%	2·5%	0·022
Positive Rose/Angina questionnaire	5·1%	5·2%	5·1%	0·98
Diabetes	0·6%	1·0%	1·4%	0·038
Hypertension[3]	13·5%	13·3%	17·3%	0·0001
Minor electrocardiogram abnormality	8·0%	7·1%	8·4%	0·43
Current smoker	50·1%	50·1%	40·1%	<0·0001

[1]There were 1693 (25·7%), 941 (14·3%) and 3961 (60%) subjects in the <75%, (75%, 100%) and fully 100% categories respectively.
[2]Family history: mother <60, or father <55 years who died of coronary heart disease.
[3]Hypertension: self-reported.

compliance equal to or greater than 75% showed similar trends in the benefit of active treatment. It can also be seen that end-point rates are not independent of compliance levels, with cardiovascular end-point rates typically being lowest in the low compliance group. No strong trends are evident in the incident cancers, while a comparison of the cardiovascular deaths and all deaths reveals a very low rate of non-cardiovascular mortality in the 100% compliance group.

Table 4 shows the estimated treatment effects in the high compliance group. For the cardiovascular end-point categories and all-cause mortality, the estimated

Table 2 Numbers of adverse event withdrawals shown by body system and treatment group

Body system	Placebo	Pravastatin	Total
Cardiovascular	40	24	64
Dermatological	10	14	24
Drug interactive	1	1	2
Endocrine/metabolic	22	10	32
Gastrointestinal	67	76	143
General	18	26	44
Haematopoietic	2	2	4
Hepatic/biliary	7	8	15
Immunology/sensitivity	1	0	1
Musculoskeletal	32	37	69
Nervous system	66	66	132
Renal/genitourinary	14	11	25
Respiratory	19	23	42
Special senses	1	7	8
Total	300	305	605

risk reduction associated with pravastatin treatment increased when moving from the entire cohort to the high compliers (unadjusted) and then further but to a lesser extent after adjustment for the baseline covariates. The adjusted estimates are arguably the most relevant. In comparison to the whole cohort, adjusted rates for high compliers showed changes in the estimated risk reductions due to treatment with pravastatin in the range of 5%–9% for the cardiovascular end-points, reaching a 38% risk reduction for the primary end-point of definite coronary heart disease death or non-fatal myocardial infarction, and with the most dramatic improvements being seen for coronary revascularization (37% rising to 46% for high compliers) and all-cause mortality where the risk reduction increased by 10% to 32% (P=0·015). There were no significant differences among the three analyses for incident cancers.

Discussion

On treatment, analyses of clinical trials must be interpreted cautiously[9–16]. Compliance may be a predictor of outcome. For instance, it is possible that subjects from deprived areas are likely to have higher risk and to be poorer compliers. Conversely, those who are taking medication for other reasons and hence may be at high risk, may be better compliers because they have already accepted the concept of taking medication on a long-term basis. This argument is supported by the data in Table 1. Differences in compliance may be a result of the treatments themselves as well as due to social and other factors. Adverse effects of medication may reduce compliance, while the benefits of therapy may improve compliance. Most importantly, poor compliance may be directly associated with an end-point itself in the sense that the deteriorating condition of the patient prior to the occurrence of an end-point may lead to poor compliance. For instance, most cancer deaths will be preceded by a long period of illness, while many cardiovascular deaths, particularly in younger subjects, will not. Hence, the selection of subjects who are high compliers for a composite end-point such as all-cause mortality could disproportionately select events of a particular type.

In the West of Scotland Coronary Prevention Study there was no evidence of any treatment-related patterns of withdrawal from trial medication. It might be hoped that adjustment of analyses for baseline risk

Table 3 For various end-points, percentage with event (numbers of subjects with/without end-points) for placebo (Pl) and pravastatin (Pr) and P*-values (in parentheses), for the logrank test comparing time-to-event curves between the treatment groups*

	Compliance category		
	<75%	(75%, 100%)	100%
Definite coronary heart disease death or non-fatal myocardial infarction	Pl: 4·8% (40/801) Pr: 4·8% (41/811) (0·99)	Pl: 8·0% (38/437) Pr: 5·0% (23/440) (0·042)	Pl: 8·6% (170/1807) Pr: 5·5% (110/1877) (0·0002)
Definite or suspect coronary heart disease death or non-fatal myocardial infarction	Pl: 6·1% (51/788) Pr: 5·8% (49/802) (0·76)	Pl: 8·1% (38/434) Pr: 6 1% (28/430) (0·19)	Pl: 10·4% (206/1776) Pr: 6·9% (138/1855) (0·0001)
Coronary artery bypass graft or percutaneous transluminal coronary angioplasty	Pl: 1·8% (16/862) Pr: 1·8% (16/863) (0·98)	Pl: 3·0% (15/490) Pr: 1·3% (6/467) (0·057)	Pl: 2·5% (49/1892) Pr: 1·5% (29/1943) (0·017)
Cardiovascular death	Pl: 1·7% (15/858) Pr: 1·4% (12/855) (0·57)	Pl: 3·2% (16/488) Pr: 1·5% (7/470) (0·066)	Pl: 2·2% (42/1874) Pr: 1·6% (31/1927) (0·16)
All deaths	Pl: 4·6% (40/833) Pr: 4·6% (40/827) (0·98)	Pl: 8·2% (42/471) Pr: 6·0% (29/457) (0·14)	Pl: 2·8% (53/1854) Pr: 1·9% (37/1912) (0·07)
Incident cancers	Pl: 2·7% (23/826) Pr: 4·1% (35/812) (0·12)	Pl: 4·9% (24/469) Pr: 2·8% (13/449) (0·09)	Pl: 3 0% (59/1892) Pr: 3·4% (68/1925) (0·52)

Table 4 **P** *values and estimated risk reductions [associated 95% confidence intervals] for various end-points, for the entire randomized cohort and for the high compliance group (compliance greater than or equal to 75%), with and without adjustment for covariates*

	Entire cohort	High compliers (unadjusted)	High compliers (adjusted for covariates)
Definite coronary heart disease or non-fatal myocardial infarction	0·0001 31% [17,43]	0·0001 37% [22,50]	0·0001 38% [23,50]
Definite or suspect coronary heart disease death or non-fatal myocardial infarction	0·0001 29% [15,40]	0·0001 33% [19,45]	0·0001 34% [19,46]
Coronary artery bypass graft or percutaneous transluminal coronary angioplasty	0·009 37% [11,56]	0·0026 46% [19,64]	0·0031 46% [19,64]
Cardiovascular death	0·033 32% [3,53]	0·035 35% [3,57]	0·029 37% [5,58]
All deaths	0·051 22% [0,40]	0·017 32% [6,50]	0·015 32% [7,51]
Incident cancers	0·55 − 8% [− 41,17]	0·81 4% [− 31,29]	0·72 6% [− 30,28]

factors will adjust for undetected imbalances. The event rates in the West of Scotland Coronary Prevention Study placebo group suggest a trend to lower risk of all outcomes studied in the group with poorest compliance. This could be associated with health conscious individuals who were at low risk and who withdrew early because of media reports suggesting dangers of cholesterol lowering diets and treatments. The results for all-cause mortality must be interpreted cautiously. It can be seen from Table 4 that the majority of the deaths in the fully 100% compliant group are cardiovascular events, with increasing contributions from non-cardiovascular deaths with decreasing compliance, as predicted in the discussion above. However, the assignment of compliance rates as low as 75% to the high compliance group does result in the inclusion of a significant proportion of non-cardiovascular deaths in the all-cause mortality analysis. Risk reductions for all-cause mortality in one population cannot be extrapolated directly to another population without consideration of the relative incidences of cardiovascular and non-cardiovascular death. For instance, in a post-myocardial infarction population, all-cause mortality will be dominated by cardiovascular deaths. Hence, all cause mortality does not represent a fixed concept, independent of the characteristics of the population being studied.

The results of West of Scotland Coronary Prevention Study demonstrates that the treatment of hypercholesterolaemic men who have no previous evidence of myocardial infarction, with the 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor pravastatin, can substantially reduce the risk of coronary heart disease morbidity and mortality and can reduce all cause mortality. In addition, pravastatin was very well tolerated and there was no evidence of significant treatment related non-compliance. Treatment with pravastatin can offer significant benefits to the patient with high compliance; 38% risk reduction for definite coronary heart disease death or non-fatal myocardial infarction and for cardiovascular mortality and a 46% reduction in risk of coronary revascularization. Notwithstanding the caveat above, the results for all-cause mortality (32% risk reduction, $P=0{\cdot}015$) strongly reinforce and enhance the intention-to-treat analysis. In clinical practice, adherence to prescribed therapy is likely to be worse than in clinical trials[17]. From a public health viewpoint, the challenge now is to identify the high-risk patients who will benefit most from this form of therapy and to address the non-treatment specific factors which lead to poor compliance.

This study was supported by a research grant from The Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey.

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Appendix

West of Scotland Coronary Prevention Study Group

Executive Committee: Prof. James Shepherd (Chairman, Co- Principal Investigator), Prof. Stuart M. Cobbe (Co-Principal Investigator), Prof. A. Ross Lorimer, Prof. James H. McKillop, Prof. Ian Ford, Prof. Christopher J. Packard, Prof. Peter W. Macfarlane, Dr Chris Isles. All at Glasgow Royal Infirmary and Glasgow University, with the exceptions of IF (Robertson Centre for Biostatistics, Glasgow University) and CI (Department of Medicine, Dumfries & Galloway District General Hospital). (This committee also constitutes the Publication Committee for the study). *Data and Safety Monitoring Committee*: Prof. Michael F. Oliver (Chairman) (National Heart and Lung Institute, London, U.K.), Prof. Anthony F. Lever (Department of Medicine and Therapeutics, Western Infirmary, Glasgow, U.K.), Prof. Byron W. Brown (Stanford University, Stanford, California, U.S.A.), Prof. John G. G. Ledingham (Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Oxford, U.K.), Prof. Stuart J. Pocock (London School of Hygiene & Tropical Medicine, London, U.K.), Dr Basil M. Rifkind (National Institutes of Health, National Heart Lung & Blood Institute, Bethesda, Maryland, U.S.A.). *Cardiovascular End-points Committee*: Prof. Stuart M. Cobbe, Dr Barry D. Vallance (Department of Cardiology, Hairmyres Hospital, East Kilbride, U.K.), Prof. Peter W. Macfarlane. *Adverse Events Review Board*: Prof. A. Ross Lorimer, Prof. James H. McKillop, Dr David Ballantyne (Department of Cardiology, Victoria Infirmary, Glasgow, U.K.). *Data Centre Staff*: Liz Anderson, David Duncan, Sharon Kean, Audrey Lawrence, June McGrath, Dr Vivette Montgomery, John Norrie. *Population Screening*: Melvyn Percy (Minerva Medical plc). *Clinical Coordination, Monitoring and Administration*: Dr Elspeth Pomphrey, Dr Andrew Whitehouse, Patricia Cameron, Pamela Parker, Fiona Porteous, Leslie Fletcher, Christine Kilday. *Computerized ECG Analysis*: David Shoat (deceased), Shahid Latif, Julie Kennedy. *Laboratory Operations*: Margaret Bell, Robert Birrell. *Company liaison and general support*: Dr Margot Mellies, Dr Joseph Meyers, Mrs Wendy Campbell.