

## ORIGINAL ARTICLE

## Rosiglitazone Evaluated for Cardiovascular Outcomes — An Interim Analysis

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## ABSTRACT

**BACKGROUND**

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A recent meta-analysis raised concern regarding an increased risk of myocardial infarction and death from cardiovascular causes associated with rosiglitazone treatment of type 2 diabetes.

**METHODS**

We conducted an unplanned interim analysis of a randomized, multicenter, open-label, noninferiority trial involving 4447 patients with type 2 diabetes who had inadequate glycemic control while receiving metformin or sulfonylurea, in which 2220 patients were assigned to receive add-on rosiglitazone (rosiglitazone group), and 2227 to receive a combination of metformin plus sulfonylurea (control group). The primary end point was hospitalization or death from cardiovascular causes.

**RESULTS**

Because the mean follow-up was only 3.75 years, our interim analysis had limited statistical power to detect treatment differences. A total of 217 patients in the rosiglitazone group and 202 patients in the control group had the adjudicated primary end point (hazard ratio, 1.08; 95% confidence interval [CI], 0.89 to 1.31). After the inclusion of end points pending adjudication, the hazard ratio was 1.11 (95% CI, 0.93 to 1.32). There were no statistically significant differences between the rosiglitazone group and the control group regarding myocardial infarction and death from cardiovascular causes or any cause. There were more patients with heart failure in the rosiglitazone group than in the control group (hazard ratio, 2.15; 95% CI, 1.30 to 3.57).

**CONCLUSIONS**

Our interim findings from this ongoing study were inconclusive regarding the effect of rosiglitazone on the overall risk of hospitalization or death from cardiovascular causes. There was no evidence of any increase in death from either cardiovascular causes or all causes. Rosiglitazone was associated with an increased risk of heart failure. The data were insufficient to determine whether the drug was associated with an increase in the risk of myocardial infarction. (ClinicalTrials.gov number, NCT00379769.)

\*Investigators for the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study group are listed in the Appendix.

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FOR PATIENTS WITH TYPE 2 DIABETES, cardiovascular disease is the leading cause of death and the major cause of morbidity.<sup>1</sup> In such patients, cardiovascular risk is considerably elevated,<sup>2</sup> although recent reports have moderated this concern.<sup>3,4</sup> Factors that are implicated in the development of atherosclerosis include dyslipidemia, obesity, hypertension, hyperglycemia, and hyperinsulinemia.<sup>5</sup>

Type 2 diabetes is a progressive disease and its prevalence in the population is increasing. Since there is greater attention to glycemic targets, more patients are receiving combination therapies. Clinical trials comparing monotherapies are common, but comparisons of new dual-agent combinations with the standard of metformin plus sulfonylurea are rare. The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial is a long-term, multicenter, randomized, open-label study<sup>6</sup> that compares cardiovascular outcomes in patients with type 2 diabetes treated with rosiglitazone (Avandia) plus metformin or sulfonylurea (rosiglitazone group) with outcomes in patients treated with metformin plus sulfonylurea (control group). The results of the United Kingdom Prospective Diabetes Study (UKPDS) suggest that the comparators metformin and sulfonylurea used in the RECORD trial reduce myocardial infarction by 39% and 16%, respectively, as compared with conventional treatment and diet.<sup>7,8</sup>

After a recent meta-analysis by Nissen and Wolski<sup>9</sup> raised concern about the cardiovascular safety of rosiglitazone, the current totality of evidence needs to be made available. Accordingly, this interim report presents the outcomes and deaths from cardiovascular causes so far in the RECORD study.

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## METHODS

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### PATIENTS

The RECORD study has been described in detail previously.<sup>6</sup> We recruited patients for the study from April 2001 through April 2003. Eligible patients had type 2 diabetes, as defined by criteria of the World Health Organization<sup>10</sup>; were between the ages of 40 and 75 years; had a body-mass index (the weight in kilograms divided by the square of the height in meters) of more than 25.0; and had a glycated hemoglobin level of more than 7.0% and less than or equal to 9.0% while receiving max-

imum doses of metformin or a sulfonylurea. Exclusion criteria were the current use of other glucose-lowering agents, hospitalization for a major cardiovascular event in the previous 3 months, a planned cardiovascular intervention, heart failure, clinically significant hepatic disease, renal impairment, and uncontrolled hypertension. The study protocol was approved by ethics review committees or institutional review boards in accordance with the laws and customs of each country participating in the study.<sup>6</sup> Written informed consent was obtained from all patients.

### STUDY DESIGN

The study is being conducted at 338 centers in 23 countries in Europe and Australasia. After a 4-week run-in period, patients who were already taking a sulfonylurea were randomly assigned to receive either additional rosiglitazone or metformin; those taking metformin were assigned to receive either additional rosiglitazone or a sulfonylurea (glyburide, gliclazide, or glimepiride, according to local practice). Random allocation was performed by telephone, with random permuted blocks stratified according to background medication.

Throughout the study, the target glycated hemoglobin level was 7.0% or less. The starting dose of rosiglitazone (Avandia, GlaxoSmithKline) was 4 mg per day. The starting doses of metformin and sulfonylurea were determined according to local practice. If the glycated hemoglobin level exceeded 7.0% after 8 weeks of treatment, the doses of study drugs were increased to a maximum daily dose of 8 mg of rosiglitazone, 2550 mg of metformin, 15 mg of glyburide, 240 mg of gliclazide, and 4 mg of glimepiride. If the glycated hemoglobin level exceeded 8.5% while patients were receiving the maximum tolerated dose, a third agent was added for patients in the rosiglitazone group or insulin was initiated for patients in the control group. If patients receiving triple therapy in the rosiglitazone group had glycated hemoglobin levels of more than 8.5%, the study protocol recommended that rosiglitazone be stopped and insulin therapy started.

### OUTCOME MEASURES

The primary end point was hospitalization (for acute myocardial infarction, congestive heart failure, stroke, unstable angina pectoris, transient ischemic attack, unplanned cardiovascular revascularization, amputation of extremities, or any

other definite cardiovascular reason) or death from cardiovascular causes (including heart failure, acute myocardial infarction, sudden death, and death caused by acute vascular events including stroke); the outcome was analyzed as the time to first occurrence. Members of an independent committee evaluating clinical end points (five cardiologists, a neurologist, and a diabetologist) were unaware of study-group assignments and used prespecified criteria to adjudicate all potential outcomes reported by investigators. Evaluators in the trial's contract organization (Quintiles) were unaware of study-group assignments in screening all serious adverse events for potential end points.

This interim report evaluated data that were available as of March 30, 2007. Secondary end points were death from cardiovascular causes and from any cause, myocardial infarction (resulting in either hospitalization or death), congestive heart failure (hospitalization or death), and the composite of death from cardiovascular causes, myocardial infarction, and stroke. Some events were pending adjudication while this report was being written. Analyses are reported both for adjudicated events only and for adjudicated events plus events pending adjudication. For 19 cardiovascular deaths pending adjudication, we cannot determine yet whether any were due to acute myocardial infarction or congestive heart failure.

#### STUDY OVERSIGHT

An independent data and safety monitoring board meets twice annually to review unblinded safety data for the ongoing study; the most recent meeting took place on May 24, 2007. Members of the steering committee (seven academic investigators and one representative of the sponsor) developed the study design, had full access to the interim data, were responsible for the decision to publish the results, and wrote the manuscript. The committee members vouch for the accuracy and completeness of the data reported. Study committees and investigators are listed in the Appendix.

#### STATISTICAL ANALYSIS

The RECORD study was designed as a noninferiority trial. The rosiglitazone group was defined as noninferior to the control group if the upper limit of the two-sided 95% confidence interval for the hazard ratio for the primary end point comparing the rosiglitazone group with the control group was below 1.20 on completion of the study. A total of 4000 patients to be followed for a median of 6 years

would give a power of 99% to detect such noninferiority when the control group had an event rate of 11% per year (3% with deaths from cardiovascular causes and 8% with hospitalizations), allowing for a 2% annual loss to follow-up.

This interim report follows a prespecified plan for statistical analysis. All analyses were performed according to the intention-to-treat principle, with the exclusion of 11 patients who received no study medication. The time from randomization to the event was derived for each end point, with follow-up censored at the cutoff date of March 30, 2007, for patients who did not have an event. Cumulative incidence was estimated with the use of the Kaplan–Meier method. The relative risk comparing the rosiglitazone group with the control group was estimated as a hazard ratio and 95% confidence interval on the basis of Cox proportional-hazards regression stratified according to background medication. Two-sided P values were calculated with the use of log-rank tests, unadjusted for multiple testing.

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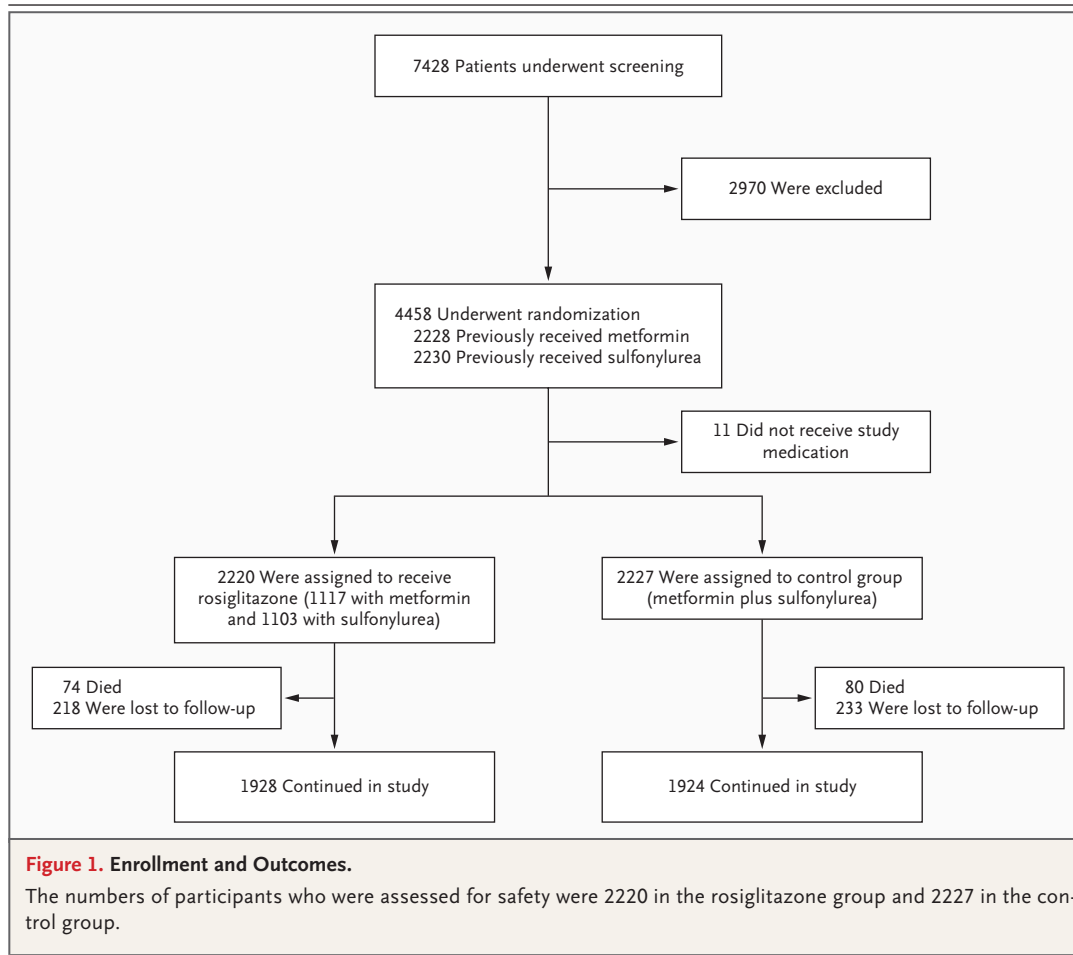
## RESULTS

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#### PATIENTS

Of 7428 patients who underwent screening, 4458 were randomly assigned to study groups (Fig. 1). No study medication was received by 11 patients (6 in the rosiglitazone group and 5 in the control group), who were excluded from the analysis. At baseline, 2222 patients who were receiving metformin monotherapy were assigned to receive either rosiglitazone plus metformin (1117 patients) or metformin plus sulfonylurea (1105 patients); 2225 patients receiving sulfonylurea monotherapy were assigned to receive rosiglitazone plus sulfonylurea (1103) or metformin plus sulfonylurea (1122). Results presented here are for all patients who were randomly assigned to receive rosiglitazone combinations (2220), as compared with all patients assigned to receive metformin plus sulfonylurea (2227).

Approximately 10% of patients (218 in the rosiglitazone group and 223 in the control group) were lost to follow-up. This fact, along with the much lower overall event rate than we had predicted, substantially lowered the statistical power of our analysis. A total of 140 patients in the rosiglitazone group and 244 patients in the control group began to receive insulin. At the latest visit, 1626 patients in the rosiglitazone group and 1476 patients in the control group were receiving their



allocated treatment. In total, 675 patients (263 in the rosiglitazone group and 412 in the control group) withdrew from receiving study drugs but were still in follow-up.

Baseline characteristics were well balanced between the groups (Table 1). Table 2 shows by group the numbers of patients with the primary end point (hospitalization or death from cardiovascular causes) and several secondary end points over a mean follow-up of 3.75 years (3.77 years for the rosiglitazone group and 3.73 years for the control group). Results are reported for adjudicated events and for events adjudicated plus those pending adjudication. Kaplan–Meier plots are shown in Figures 2 and 3.

For adjudicated primary end points (217 in the rosiglitazone group and 202 in the control group), the hazard ratio was 1.08 (95% confidence interval [CI], 0.89 to 1.31). An additional 91 patients (50 in the rosiglitazone group and 41 in the control group) had potential primary events reported

by investigators, but these events were pending adjudication. The inclusion of these events resulted in a hazard ratio of 1.11 (95% CI, 0.93 to 1.32). A subgroup analysis of patients who were classified according to previous monotherapy with metformin or sulfonylurea revealed no evidence of a treatment-by-stratum interaction (interaction test,  $P=0.41$ ). The time-to-event curves in Figure 2 may suggest possible divergence between groups, with more events in the rosiglitazone group after 2.5 years of follow-up. However, data after 4 years involve small numbers of patients, and further follow-up will be necessary.

There was no statistically significant difference between the rosiglitazone group and the control group for the following secondary end points: acute myocardial infarction, death from cardiovascular causes or any cause, or the composite of cardiovascular death, myocardial infarction, and stroke (both for adjudicated events and adjudicated plus pending events). However, the power to detect

**Table 1. Baseline Characteristics of the Patients.\***

Variable	Rosiglitazone Group (N=2220)	Control Group (N=2227)
Previous medication — no. (%)		
Metformin only	1117 (50.3)	1105 (49.6)
Sulfonylurea only	1103 (49.7)	1122 (50.4)
Age — yr	58.4±8.3	58.5±8.3
Male sex — no. (%)	1142 (51.4)	1152 (51.7)
White race — no. (%)†	2200 (99.1)	2199 (98.7)
Time since diagnosis — yr	7.0±5.0	7.1±4.9
Body-mass index	31.6±4.7	31.5±4.9
Glycated hemoglobin — %	7.9±0.7	7.9±0.7
Fasting plasma glucose — mg/dl	177±43	177±40
Hypertension — no. (%)‡	1754 (79.0)	1774 (79.7)
Ischemic heart disease — no. (%)		
Any disease	359 (16.2)	374 (16.8)
Stable angina	222 (10.0)	228 (10.2)
Myocardial infarction	102 (4.6)	114 (5.1)
Unstable angina	20 (0.9)	30 (1.3)
Cerebrovascular disease — no. (%)		
Any disease	100 (4.5)	97 (4.4)
Stroke	54 (2.4)	54 (2.4)
Transient ischemic attack	50 (2.3)	47 (2.1)
Peripheral arterial disease — no. (%)	124 (5.6)	131 (5.9)
Congestive heart failure — no. (%)	12 (0.5)	6 (0.3)
Lipid disorder — no. (%)§	2123 (95.6)	2100 (94.3)
Smoking history — no. (%)		
Current smoker	363 (16.4)	343 (15.4)
Former smoker	565 (25.5)	539 (24.2)

\* Plus-minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters.

† Race was determined by the investigators.

‡ Hypertension was defined as a systolic blood pressure of more than 130 mm Hg or a diastolic blood pressure of more than 80 mm Hg.

§ A lipid disorder was defined by investigator-reported diagnosis or as a low-density lipoprotein cholesterol level of 100 mg per deciliter or more, a triglyceride level of 200 mg per deciliter or more, or a high-density lipoprotein cholesterol level of less than 40 mg per deciliter for men or less than 50 mg per deciliter for women.

significant differences was low, as reflected by the wide 95% confidence intervals (Table 2). The hazard ratio for death from cardiovascular causes for adjudicated plus pending events was 0.80 (95% CI, 0.52 to 1.24). For myocardial infarction, the hazard ratio for adjudicated plus pending events was 1.23 (95% CI, 0.81 to 1.86).

Patients in the rosiglitazone group had a sig-

nificantly higher risk of congestive heart failure than did patients in the control group, with 38 versus 17 adjudicated events (hazard ratio, 2.24; 95% CI, 1.27 to 3.97). The inclusion of events pending adjudication increased the number of events to 47 and 22, respectively (hazard ratio, 2.15; 95% CI, 1.30 to 3.57), resulting in an excess risk of heart failure in the rosiglitazone group of 3.0 (95% CI, 1.0 to 5.0) per 1000 patient-years of follow-up.

## DISCUSSION

Since patients with type 2 diabetes have a high risk of cardiovascular disease, any hypoglycemic agent the patient receives should not worsen that risk and preferably should lower it. Although the RECORD study is ongoing, we believe the exceptional circumstances surrounding a recent safety concern regarding rosiglitazone make it important to publish interim data.

A recent meta-analysis by Nissen and Wolski raised concern that rosiglitazone was associated with an increased risk of myocardial infarction and death from cardiovascular causes.<sup>9</sup> The limitations of the meta-analysis have been pointed out by its authors and by others.<sup>11</sup> Many contributing studies were small-scale and short-term, were designed to evaluate glycemic control, had no event adjudication, and had an imbalance in follow-up (with more patients in the control group withdrawing owing to hyperglycemia). Trials with no myocardial infarctions and no deaths from cardiovascular causes were excluded, and rates of myocardial infarction were low.<sup>12</sup>

The RECORD trial is a large, randomized, long-term study involving patients with type 2 diabetes that was designed to assess the cardiovascular safety of rosiglitazone combined with metformin or sulfonylurea, as compared with the combination of metformin and sulfonylurea, medications with previous evidence of a reduction in cardiovascular risk.<sup>7,8</sup> All cardiovascular end points that are reported by investigators in the trial undergo independent blinded adjudication to enhance the quality of the data. A wide variety of patients with type 2 diabetes, with and without previous cardiovascular disease, are included in the study.

This interim report is based on data for 4447 participants with a mean follow-up of 3.75 years, representing 16,675 patient-years of follow-up — almost two thirds of the follow-up that was in-

**Table 2. Hospitalization or Death from Cardiovascular Causes.\***

Variable	Rosiglitazone Group (N=2220) <i>no. of patients</i>	Control Group (N=2227) <i>no. of patients</i>	Hazard Ratio (95% CI)	P Value
<b>Adjudicated events</b>				
Primary end point	217	202	1.08 (0.89–1.31)	0.43
Death				
From cardiovascular causes†	29	35	0.83 (0.51–1.36)	0.46
From any cause	74	80	0.93 (0.67–1.27)	0.63
Acute myocardial infarction‡	43	37	1.16 (0.75–1.81)	0.50
Congestive heart failure‡	38	17	2.24 (1.27–3.97)	0.006
Death from cardiovascular causes, myocardial infarction, and stroke	93	96	0.97 (0.73–1.29)	0.83
<b>Events adjudicated and pending adjudication</b>				
Primary end point	267	243	1.11 (0.93–1.32)	0.26
Death				
From cardiovascular causes†	37	46	0.80 (0.52–1.24)	0.32
Acute myocardial infarction‡	49	40	1.23 (0.81–1.86)	0.34
Congestive heart failure‡	47	22	2.15 (1.30–3.57)	0.003
Death from cardiovascular causes, myocardial infarction, and stroke	109	114	0.96 (0.74–1.24)	0.74

\* Each patient was counted only once for each category. The primary end point was the first occurrence of a hospitalization or death from cardiovascular causes.

† Of the adjudicated deaths from cardiovascular causes, 38 (16 in the rosiglitazone group and 22 in the control group) were primary end points. The remainder occurred after the patient had already been hospitalized for a cardiovascular event. For deaths from cardiovascular causes that were adjudicated or pending adjudication, 47 (20 in the rosiglitazone group and 27 in the control group) were primary end points.

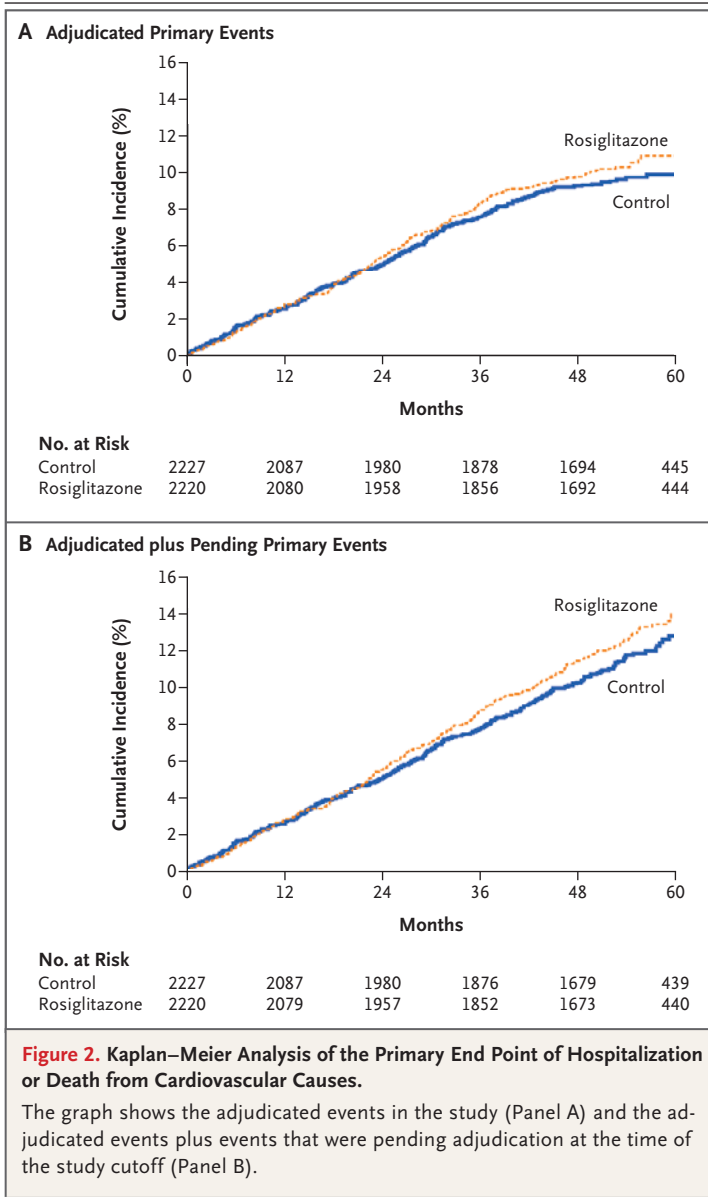
‡ This category included both hospitalizations and deaths. Some of the 19 deaths from cardiovascular causes (8 patients in the rosiglitazone group and 11 in the control group) that were pending adjudication may have been due to acute myocardial infarction or congestive heart failure, but these data were not available at the time of the study cutoff.

tended by the end of the study. The study design calls for targeting similar glycemic control in the rosiglitazone group and the control group to assess cardiovascular safety independent of glycemia. Patients and investigators are encouraged to follow a carefully planned treatment algorithm. A recent report on the first 1122 patients showed that patients in the rosiglitazone group and the control group had similar glycemic control after 18 months of treatment.<sup>13</sup>

Overall, the rate of primary end points (hospitalization or death from cardiovascular causes) was low: 3.1% per year for adjudicated plus pending events. The protocol excluded some high-risk patients (e.g., those with heart failure, hospitalization for cardiovascular causes during the previous 3 months, and pending cardiovascular intervention). Targeting treatment toward current management guidelines for dyslipidemia, hypertension,

and improved glucose control may also contribute to the low event rate. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD, ISRCTN number 64783481) study reported an increase from 0 to 36% in the use of lipid-lowering therapy in its control group during 1998–2005.<sup>14</sup> This finding reflects guidelines that patients should be actively treated to reduce cardiovascular risk, notably with glucose-lowering drugs, statins, aspirin, and more intensive use of blood-pressure-lowering agents.<sup>15</sup> Moreover, event rates in recent similar trials involving patients with diabetes — the Collaborative Atorvastatin Diabetes Study (CARDS,<sup>4</sup> NCT00327418), Heart Protection Study (HPS,<sup>3</sup> ISRCTN 48489393), and FIELD<sup>14</sup> — are similar to those in the RECORD trial.

The interim results for the primary end point were inconclusive, with a hazard ratio of 1.08 (95% CI, 0.89 to 1.31) on the basis of events ad-



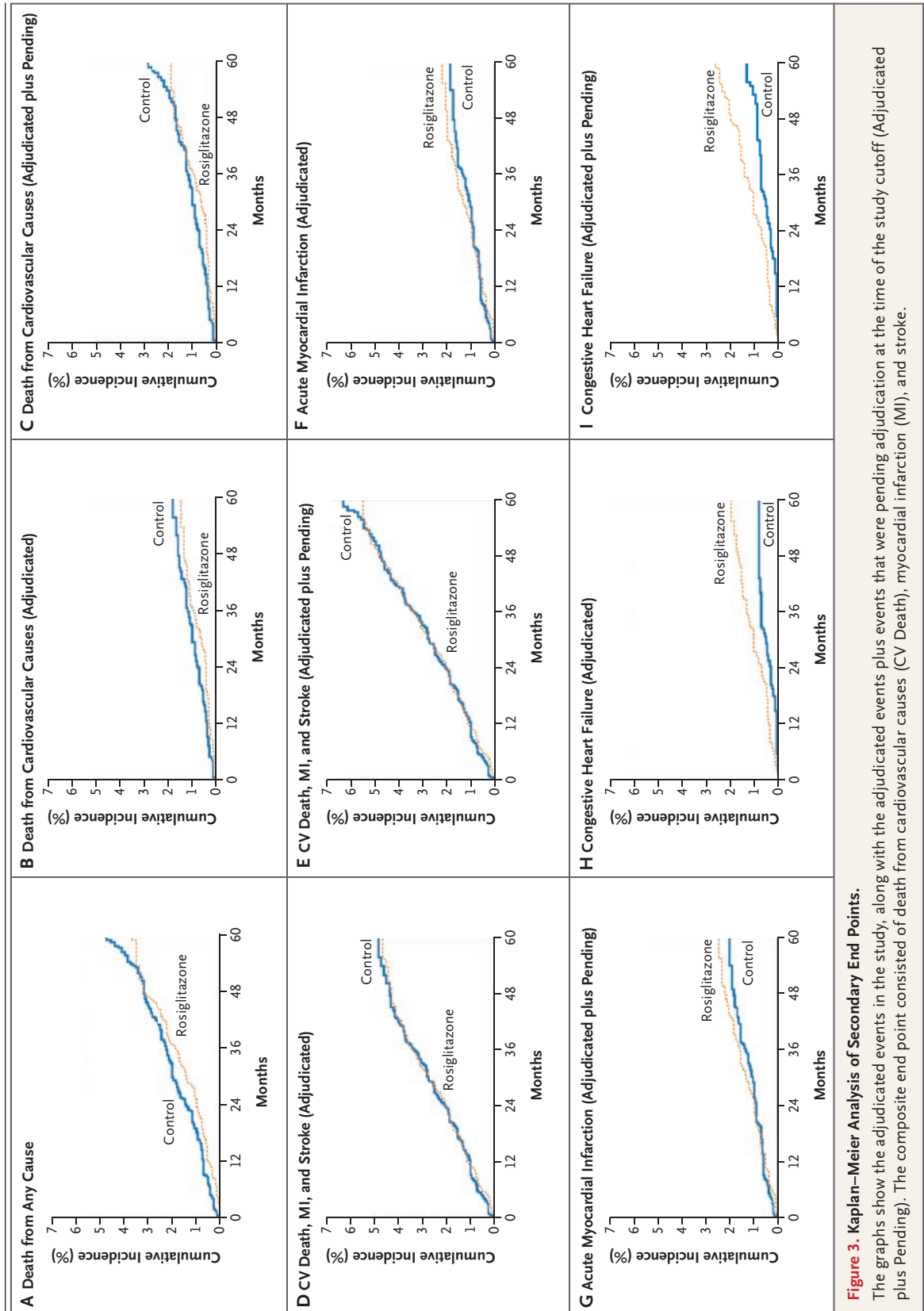
judicated by the committee reviewing clinical end points. In any interim trial report, there are inevitably some potential primary events pending adjudication. Adding in these pending events increased the hazard ratio to 1.11 (95% CI, 0.93 to 1.32). Thus, the data for the primary end point are compatible with as much as a 7% improvement, or as much as a 32% worsening, in cardiovascular risk. The study lost statistical power because of the withdrawal of patients from their assigned treatment and losses to follow-up, although patients in the rosiglitazone group fared better in these respects than did patients in the control

group. We cannot determine whether some consequent bias in end-point ascertainment occurred. All serious adverse events were screened for possible end points.

The low rate of the primary end point, along with the notable loss to follow-up, meant that the study has less statistical power than was originally planned. Assuming a continued primary-event rate of 3.1% per year, we project that 750 patients will have a primary end point by study completion. Under the hypothesis of no true treatment difference, this estimate would provide a power of 70% to claim noninferiority relative to a noninferiority margin of 1.20 for the hazard ratio. However, we already have 510 patients with a primary event (adjudicated plus pending events) and an observed hazard ratio of 1.11, which means that the conditional power to claim noninferiority on study completion is somewhat less.

As compared with the control group, the rosiglitazone group had no evidence of an increased risk of death, either from any cause (hazard ratio, 0.93; 95% CI, 0.67 to 1.27) or from cardiovascular causes (hazard ratio, 0.80, 95% CI, 0.52 to 1.24). The primary end point included all first hospitalizations or deaths from cardiovascular causes and as such included myocardial infarction and congestive heart failure. Our study showed that the risk of heart failure in the rosiglitazone group was more than twice that in the control group. This finding is consistent with previous evidence regarding heart failure and the thiazolidinediones.<sup>16,17</sup> Although the absolute excess risk was relatively small, this finding is of concern and reinforces advice that patients should be warned of the risk and that thiazolidinediones should not be started or continued in patients with heart failure.

For acute myocardial infarction, the difference between the rosiglitazone group and the control group was not statistically significant (hazard ratio for adjudicated events, 1.16; 95% CI, 0.75 to 1.81; hazard ratio for adjudicated plus pending events, 1.23; 95% CI, 0.81 to 1.86). These estimates are somewhat lower than those reported in the meta-analysis by Nissen and Wolski.<sup>9</sup> They are consistent with as much as a 19% improvement, and as much as an 86% worsening, in risk. For the composite end point of death from cardiovascular causes, myocardial infarction, and stroke, the rosiglitazone group did not differ significantly from the control group.



**Figure 3. Kaplan-Meier Analysis of Secondary End Points.**

The graphs show the adjudicated events in the study, along with the adjudicated events plus events that were pending adjudication at the time of the study cutoff (Adjudicated plus Pending). The composite end point consisted of death from cardiovascular causes (CV Death), myocardial infarction (MI), and stroke.



A significant limitation of our study was that it was an open-label trial. The allocation of drugs was nonblinded owing to the number of preparations and dosing schedules and because the time for the introduction of insulin therapy differed between groups. Monitoring staff checked site records for missing events, and all serious adverse events underwent blinded screening for potential cardiovascular end points; in addition, the adjudication of events was blinded. These procedures and the choice of end points reduce, but do not remove, the risk of ascertainment bias.

The primary composite end point reflects the study objective — an assessment of overall cardiovascular safety — but therefore includes some hospitalizations (e.g., for valvular disease) that no observer would consider potentially related to treatment. The inclusion of such events tends to favor the achievement of noninferiority. Hence, sensitivity analyses will be performed at the end of the study that include only events related to atherosclerotic arterial disease.

We made the decision to publish our interim findings because in their absence, concern raised by the meta-analysis by Nissen and Wolski could well compromise the study's integrity through an increase in the dropout rate and potential biases in reporting events. At present, every effort is being made to maintain follow-up until study completion in 2 years. Extra inquiries to investigators, to identify any end points previously missed,<sup>18</sup> are expected to reduce substantially the extent of loss to follow-up by the end of the study.

This interim analysis is restricted to a limited amount of information. The statistical plan was predefined. The intent was primarily to estimate treatment differences, with no planned action regarding study continuation, so the significance level of the final analysis was not affected. The final report will be more extensive, with data presented for different background medications and other subgroups and examining possible imbalances across treatment groups for concomitant medications and other possible confounders.

In conclusion, our interim findings from a large, prospective trial are inconclusive with respect to the primary end point of hospitalization or death from cardiovascular causes and are as yet insufficient to claim noninferiority. There is no evidence of any increased mortality, either from any cause or from cardiovascular causes. There is a significant increase in the risk of heart failure. The data do not allow a conclusion as to whether treatment with rosiglitazone results in a higher rate of myocardial infarction than does therapy with metformin or a sulfonylurea. The study's data and safety monitoring board, which is charged with safeguarding the study patients, has recommended continuation of the trial. Study completion will enable a clearer determination of the long-term cardiovascular effects of treatment with rosiglitazone and thus help determine the most appropriate combination therapies for patients with type 2 diabetes.

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Dr. Home reports being involved in research, consulting, health care development, and teaching activities for all major pharmaceutical companies active in diabetes research (including GlaxoSmithKline), but all consulting and lecture fees he receives are donated to the institutions with which he is associated (Newcastle University, Worldwide Initiative for Diabetes Education, and the International Diabetes Federation); Dr. Pocock, receiving consulting fees and grant support from GlaxoSmithKline; Dr. Beck-Nielsen, receiving consulting fees from GlaxoSmithKline, Merck, and Novartis and grant support and lecture fees from GlaxoSmithKline and Novo Nordisk; Dr. Gomis, receiving consulting and lecture fees from GlaxoSmithKline, Novartis, Pfizer, Merck, and Sanofi-Aventis; Dr. Hanefeld, receiving consulting fees from GlaxoSmithKline, Novo Nordisk, and Sanofi-Aventis and lecture fees from Bayer-AG, Sanofi-Aventis, Hoffmann-La Roche, Takeda, and Eli Lilly; Mr. Jones, being an employee of and holding stock in GlaxoSmithKline; Dr. Komajda, receiving consulting fees from GlaxoSmithKline and Servier and lecture fees from GlaxoSmithKline and Takeda; and Dr. McMurray, receiving consulting fees from GlaxoSmithKline and Amgen and grant support from GlaxoSmithKline, Novartis, and Amgen. No other potential conflict of interest relevant to this article was reported.

We thank the study patients for their time and continued commitment; members of the data and safety monitoring board and clinical end-points committee for their diligent activity; Professor Henry Dargie for important and material contributions to the design and direction of the study; Dr. Duolao Wang for conducting confirmatory statistical analyses; and the GlaxoSmithKline and Quintiles RECORD teams for their quality input.

#### APPENDIX

The following were participants in the RECORD study: **Steering Committee:** P.D. Home (chair), H. Beck-Nielsen, R. Gomis, M. Hanefeld, N.P. Jones, M. Komajda, J.J.V. McMurray, S.J. Pocock. **Data and Safety Monitoring Board:** I. Campbell (chair), I. Ford, P. Hildebrandt, R. Landgraf, F. Verheugt. **Clinical End Point Committee:** M. Komajda (chair), M. Böhm, A. Gavazzi, K. Lees, M. Marre, P. Ponikowski, M. Syväne. **Investigators (numbers in parentheses after country indicate number of randomized patients):** *Australia (51)* — G. Jerums, Heidelberg West; A. Lang, Malvern; R. Watts, Port Lincoln; F. De Looze, Sherwood; S. Colagiuri, Randwick; R. Moses, Wollongong; V. Heazlewood, Kippa Ring; M. McKeirnan, Carina Heights; A. Lowy, Miranda; T. Roberts, Keswick. *Belgium (104)* — E. Weber, Arlon; F. Coucke, Sint-Gillis-Waas; J. Tits, Genk; B. Keymeulen, Brussels; M. Giri, Gent; J. Mortelmans, Oostham; A. Hutsebaut, Moerkerke; W. Denier, Genk. *Bulgaria (204)* — A. Borissova, N. Ovcharova, V. Hristov, N. Veleva, Sofia; L. Koeva, Varna; M. Mitkov,

Plովdiv; T. Rusev, Pleven; I. Daskalova, Sofia. *Croatia* (274) — Z. Metelko, V. Rotvik, V. Goldoni, Zagreb; M. Jandric, Slavonski Brod; J. Rubes, Krapinske Toplice; Z. Beer, Varazdin; I. Aganovic, Zagreb; M. Persic, Rijeka. *Czech Republic* (145) — J. Janousek, Trutnov; F. Saudek, E. Valentova, Praha; M. Honka, Ostrava Poruba; V. Sobeslavská, Tábor; E. Mandakova, Rakovník; J. Belobradkova, Brno; P. Skala, Holice v Cechách; P. Weiner, Jindřichuv Hradec; M. Komrskova, Pisek; L. Dohnalova, Ceske Budejovice. *Denmark* (57) — H. Huhl, Slagelse; K. Kolendorf, Koge; S. Larsen, Glostrup; H. Lervang, Aalborg; A. Prange, Kolding; L. Ørskov, Silkeborg; O. Snorgaard, Hillerød; T. Storm, Næstved; H. Perrild, København. *Estonia* (220) — A. Kork, Tallinn; H. Tupits, Tallinn; M. Kunder, Tallinn; L. Viitas, Pärnu; T. Toomsoo, Tallinn; H. Vides, Viljandi; B. Adojaan, Tartu; I. Last, Paide; K. Veidrik, Rakvere; R. Lanno, Tallinn; K. Arbeiter, Tallinn; M. Stern, Saku. *Finland* (193) — J. Eriksson, Helsinki; J. Hopsu, Espoo; R. Siren, Helsinki; S. Sulosaari, Kerava; T. Piippo, Tampere; J. Saltevo, Jyväskylä; A. Latva-Nevala, Seinäjoki; T. Kaitila, Lappeenranta; P. Jarvinen, Hyvinkaa; A. Piironen, Rovaniemi; H. Pirttiäho, Oulun Kaupunki; P. Himanen, Turku; V. Ilvesmaki, Lahti; L. Juurinen, Riihimäki; R. Siren, Helsinki; M. Pietilä, Turku; S. Ruot-salainen, Kuopio. *France* (86) — O. Verier-Mine, Valenciennes; J. Brun, Dijon; G. Charpentier, Corbeil Essonne; C. Le Devehat, Nevers; M. Rieu, Paris; E. Verlet, Dunkerque; P. Triot, Arras; R. Fonteny, Chartres; J. Quadrelli, Nogent le Phaye; P. Poisson, Voves; P. Fournier, Chartres; J. Vogel, Husseren Wesserling; O. Decloux, Cernay; L. Goepfert, Mulhouse; M. Ruetsch, Dessenheim; J. Huberschwiller, Colmar; M. Gissler, Wittenheim; B. Michalak, Marseille; D. Obadia, Aubagne; M. Bourgoin, Gemenos; D. Cadinot, Broglie; C. Jouin, Saint Leger sur Yvelines; D. Sacareau, M. Bismuth, Labarthe-sur-Leze; T. Coeure, Champol; C. Fabie, Calmont; J. Reinard, Toulouse; P. Poinot, Carbonne; P. Galy, Pinsaguel; H. Vilarem, Castelnaudary; G. Binet, Salles sur l'Hers; B. Gay, Badens; P. Munck, Trebbes. *Germany* (178) — P. Ott, Dresden; M. Nauck, Bad Lauterberg; R. Paschke, Leipzig; H. Frick, Rhaunen; A. Sammler, Friedrichsthal; M. Morcos, Heidelberg; W. Stuermer, Wuerzburg; T. Segiet, Speyer; W. Schaffstein, Kronberg; U. Berek, Wetzlar; A. Schaffert, Stuttgart; C. Raddatz, Gau-Algesheim; D. Ayasse, Kallstadt; R. Naumann, Chemnitz; G. Scholz, Offenbach; P. Kirrbach, Burgstaedt; O. Mueller, Lambrecht. *Greece* (139) — S. Raptis, Athens; E. Pagkalos, Thessaloniki; S. Pappas, Piraeus; E. Giannoulaki, Patra; N. Katsilambros, A. Melidonis, G. Piaditis, C. Zoupas, Athens; K. Soulis, Thessaloniki; A. Vagenakis, Patra; D. Makriyannis, Ioannina; P. Kaldrimis, I. Migdalis, Athens. *Hungary* (400) — M. Baranyai, Szombathely; P. Faludi, Budapest; I. Foldesi, Szentes; B. Gachalyi, Budapest; M. Dudas, Gyula; T. Hidvegi, Győr; E. Juhasz, Eger; Z. Kerenyi, Budapest; G. Neuwirth, Debrecen; T. Oroszlan, Zalaegerszeg; J. Patkay, Dunaujvaros; K. Simon, Siófok; J. Szegedi, Nyiregyhaza; G. Tamas, Budapest; B. Valenta, Nyiregyhaza; G. Vandrofi, Veszprem; P. Voros, Budapest; G. Kurta, Berettyóújfalú. *Italy* (116) — C. Fossati, Milan; R. Uccioli, Rome; R. Pasquali, N. Melchionda, Bologna; M. Parenti, Rimini; A. Galluzzo, Palermo; L. Carboni, Cagliari; O. Giampietro, Pisa; M. Calderini, Parma; R. Giorgino, Bari; B. Ambrosi, San Donato Milanese; A. Arcangeli, Prato; A. Aiello, Campobasso; G. Ghirlanda, Rome; R. Carleo, Naples; U. Valentini, Brescia; P. Pozzilli, Rome; F. Orto, Salerno. *Latvia* (173) — I. Rezgale, Riga; L. Kokare, Riga; I. Andersone, Tukums; B. Vizina, Limbazi; D. Teterovska, Ogre; A. Eglite, Jekabpils; V. Pirags, Riga; L. Kudule, I. Sturis, Riga; I. Lagzdina, Liepaja. *Lithuania* (134) — J. Lasiene, Kaunas; J. Pluskys, Vilnius; N. Jakuboniene, E. Varanauskiene, Kaunas; B. Urbonaite, Klaipeda; J. Butkus, Vilnius; G. Gumbrevicius, Kaunas. *The Netherlands* (76) — W. de Backer, Rijswijk; V. van de Walle, Geleen; J. Jonker, Groningen; M. Janssen, Ridderkerk; F. Gulzar, Zwijndrecht; I. Ong, Hoogvliet; H. Ferguson, Rotterdam; W. Feis, Oude Pekela; H. Franssen, Musselkanaal; J. Snijders, Landgraaf; M. Osinga-Meek, 's-Hertogenbosch. *New Zealand* (36) — R. Cutfield, Auckland; R. Scott, Christchurch; J. Mann, Dunedin; B. Smith, Wellington; A. Dissanayake, Auckland; M. Khant, Tauranga; R. Leikis, Hastings; P. Dixon, Palmerston North. *Poland* (363) — I. Kinalska, Bialystok; B. Wierusz-Wysocka, Poznan; E. Semetkowska-Jurkiewicz, Gdansk; A. Stankiewicz, Cracow; D. Zytkeiwicz-Jaruga, Wroclaw; M. Polaszewska-Muszynska, Bydgoszcz; K. Jedynasty, Warsaw; Z. Szybinski, Cracow; K. Jusiak, Warsaw; A. Mikolajczyk-Swatko, Lodz; E. Bandurska-Stankiewicz, Olsztyn; M. Bojarska-Los, Lublin; E. Krzyzagoska, Poznan; A. Bochenek, Warsaw; J. Lopatynski, Lublin; H. Szczecinska, Warsaw; P. Kubalski, Grudziadz. *Romania* (157) — C. Ionescu-Tirgoviste, Bucharest; N. Hancu, Cluj-Napoca; V. Serban, Timisoara; M. Graur, Iasi; M. Mota, Craiova; A. Barnea, Bucharest; C. Dobjanschi, Bucharest. *Russia* (149) — A. Ametov, Moscow; A. Dreval, Moscow; L. Vedeneva, St. Petersburg; I. Demidova, Moscow; N. Vorokhobina, St. Petersburg; L. Subaeva, Moscow. *Slovakia* (325) — M. Macko, Presov; J. Fabry, Bratislava; I. Buganova, Zilina; L. Fabryova, Bratislava; L. Kalinova, Bratislava; J. DzuPONOVA, Prievidza; B. Krahulec, E. Toserova, Z. Nemethyova, Bratislava; J. Vozar, Samorin; A. Gabrisova, Trencin; I. Tkac, Kosice; J. Okapcova, Banska Bystrica; T. Kupcova, Lucenec; E. Nehajova; Kysucke Nove Mesto; P. Farkas, Sahy; E. Martinka, Lubochna. *Spain* (64) — M. Muñoz Torres, Granada; L. Escobar Jimenez, Cadiz; I. Conget, Barcelona; J. Herrera Pombo, Madrid; S. Gaztambide, Bilbao; J. Manzanares, Reus; A. Serrano, Vizcaya; C. Vazquez, Barcelona. *Sweden* (469) — M. Schönander, Göteborg; A. Norrby, Göteborg; R. Tengel, Skene; A. Nilsson, Helsingborg; I. Lager, Kristianstad; U. Mathiessen, Oskarshamn; P. Andersson, Eksjö; U. Adamsson, Danderyd; F. Sjöberg, Linköping; E. Forbes, Nacka; L. Nicol, Köping; S. Lindmark, Umeå; D. Aronsson, Mora; M. Dahl, Kungälv; M. Landin-Olsson, Lund; B. Polhem, Uddevalla; P. Hellke, Göteborg; J. Waller, Vadstena; B. Zethelius, Uppsala. *Ukraine* (103) — M. Tronko, P. Bodnar, O. Larin, Kiev; Y. Karachentsev, Kharkov; T. Pertseva, Dnepropetrovsk; A. Serhiyenko, Lvov; P. Prudius, Vinnitsa. *United Kingdom* (242) — P. O'Hare, Warwickshire; P. Allamby, Dronfield; M. Blagden, Derbyshire; M. Gumbley, Westbury, I. Grandison, Wiltshire; D. Keating, Sheffield; P. Maksimczyk, Somerset; M. Pimm, Weston-Super-Mare; I. Strawford, Somerset; T. Wall, Woking; A. Matthews, Chesterfield; M. Sampson, Colney; A. Adler, Cambridge; T. Cahill, Frome; C. Fox, Northampton; J. Ham, Rugby; A. Harrower, Airdrie; J. Hole, S. Rowlands, Wiltshire; P. 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