Ivabradine — a selective and specific $I_f$ inhibitor: efficacy and safety in stable angina

K. Fox

Royal Brompton Hospital, London, U.K.

Aims To assess the antianginal and anti-ischaemic efficacy and safety of ivabradine in patients with stable angina.

Methods and results A total of 360 patients with stable angina were randomly assigned, in a double-blind fashion, to receive placebo or ivabradine 2.5 mg twice daily, 5 mg twice daily or 10 mg twice daily for 2 weeks. Patients voluntarily continued treatment (ivabradine 10 mg twice daily) in a 2- to 3-month, open-label extension period; this was followed by a randomized withdrawal period in which patients received ivabradine 10 mg twice daily or placebo for 1 week. Ivabradine was well tolerated, and no rebound phenomena were observed on treatment withdrawal. Dose-dependent significant reductions in heart rate were achieved at all dose levels ($P < 0.05$). Ivabradine 5 and 10 mg twice daily significantly increased time to 1-mm ST-segment depression ($P < 0.005$) and time to limiting angina on exercise tolerance testing. Patients continuing on ivabradine during the withdrawal period maintained the improvements in exercise tolerance test criteria, whereas those who received placebo showed significant deterioration.

Conclusion Ivabradine (Procoralan®, Servier, Neuilly-sur-Seine, France) — a selective and specific inhibitor of the $I_f$ (cardiac pacemaker, or 'funny') current — is a well-tolerated heart rate lowering agent with antianginal and anti-ischaemic efficacy in patients with stable angina. Results from the present study suggest that ivabradine could be a valuable alternative to current angina therapies.

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Introduction

Stable angina is a common clinical condition that is associated with significant morbidity and mortality. In the U.K., 2 million people currently experience angina pectoris and the annual incidence is 0.83 per 1000 of the population aged 31–70 years. In the U.S.A. over 7 million adults are affected by stable angina, with an estimated 350,000 new cases per year.

Angina is the result of myocardial ischaemia caused by an imbalance between myocardial blood supply and oxygen demands. Patients experiencing angina are unable to increase their coronary blood flow during stress to meet the increased myocardial metabolic demand. Cardiac muscle, unlike skeletal muscle, cannot develop appreciable oxygen debt during stress and repay it later; consequently, characteristic anginal chest pain develops. Angina is typically precipitated by exertion, eating, exposure to cold and emotional stress, and the intensity does not change with respiration, coughing or change in position.
The objectives of treatment are to reduce the severity and frequency of angina attacks during everyday activities, increase exercise tolerance and consequently improve quality of life; this can be achieved by reducing myocardial demands. Reducing the heart rate improves endocardial blood supply and decreases myocardial oxygen demand by allowing an increase in diastolic perfusion time during the heart cycle. Agents that reduce the heart rate would therefore be predicted to exert a beneficial effect on both elements of the imbalance that occurs during angina.

Ivabradine (Procoralan®, Servier, Neuilly-sur-Seine, France) is a new heart rate lowering agent that selectively inhibits the primary pacemaker If (or ‘funny’) current in the sinoatrial node of the heart. The If current is a hyperpolarization-activated mixed Na+/K+ inward current and is probably the most important pacemaker current of the sinoatrial node.3—6 Ivabradine has been shown to reduce heart rate at rest and during exercise in experimental animals7—9 and in healthy human volunteers.10 The aim of the present study was to investigate the efficacy and safety of different doses of ivabradine in patients with stable angina, including the effects on time to 1-mm ST-segment depression and time to limiting angina during exercise.11

Methods

Patient population

Inclusion criteria
Patients eligible for inclusion in the study were men or women of non-child-bearing potential, aged 18 years or over, with at least a 3-month history of stable chronic angina triggered by physical activity and relieved by rest or nitroglycerine. A positive and stable exercise tolerance test (ETT) was required at selection (day −7) and inclusion (day 0); a positive ETT was defined as the occurrence of both limiting angina and ST-segment depression of at least 1 mm as compared with resting ECG. The stability of ETT performance between selection and inclusion into the study was assessed by time to 1-mm ST-segment depression and could not differ by more than 20% or 1 min.

Other inclusion criteria included the following: documented coronary artery disease [coronary angiography showing 50% stenosis in the proximal two-thirds of at least one major coronary artery or (for males) being on a waiting list for coronary angiography and having a previous positive exercise thallium scan; or previous dipyridamole, dobutamine or exercise echocardiography test showing a hypokinetic or akinetic segment during exercise]; or previous myocardial infarction at least 3 months before randomization; or typical angina pain >3 months after a coronary artery bypass graft or >6 months after a coronary angioplasty procedure; and compliance with placebo during the run-in period of ≥75%.

Exclusion criteria

Exclusion criteria included acute myocardial infarction or coronary artery bypass graft within the previous 3 months; coronary angioplasty within the previous 6 months; unstable angina; Prinzmetal angina or microvascular angina; significant valvular disease; atrial fibrillation, atrial flutter or indwelling pacemaker; contraindication to ivabradine [second- and third-degree atrioventricular block, resting bradycardia (<50 beats/min) or sick sinus syndrome]; or inability to perform exercise tests.

The study was conducted in accordance with the Declaration of Helsinki (1964) as revised in Hong Kong (1989). All patients gave their written, informed consent and their participation was approved by an independent ethics committee in each participating country.

Study design

The study protocol is shown in Fig. 1. After an initial wash-out period on placebo lasting 2–7 days (depending on the half-life of previous antianginal medication), a 1-week single-blind, placebo run-in period was used to assess the stability of ETT performance and protocol compliance. Then, in a double-blind fashion, patients were randomly assigned to receive placebo or one of three doses of ivabradine (2.5, 5 or 10 mg twice daily) for 2 weeks, followed by a 2- or 3-month open-label extension phase (participation voluntary, depending on administrative constraints in different countries) during which all patients received ivabradine 10 mg twice daily, in order to assess safety and maintenance of efficacy. Finally, patients in the open-label extension were randomly assigned in a double-blind fashion to continue on ivabradine 10 mg twice daily or to be withdrawn to placebo for 1 additional week in order to confirm the persistence of efficacy, assess disease evolution and check for rebound phenomena after treatment withdrawal.
Treatment

Treatment was assigned to patients by random permutation blocks and chronological order of inclusion in the study. Treatment was administered orally, twice a day (morning and evening). For the double-blind periods, the different doses of ivabradine and placebo were supplied in blister packs as tablets of identical shape, taste and appearance. Boxes containing the blister packs were labelled with study period number and the patient’s randomization number.

Efficacy criteria

The primary efficacy criteria were time to 1-mm ST-segment depression (horizontal or down-sloping for more than 0.08 s after the J point) and time to limiting angina during ETT at the trough of drug activity (12 h post-dose).

Secondary efficacy criteria included the following: heart rate at rest and maximal heart rate, rate pressure product (RPP) at rest and peak of exercise, and time to angina onset at trough of drug activity; all ECG parameters at the peak of drug activity (4 h post-dose); and angina attack frequency and short-acting nitrate consumption as recorded in patients’ diaries.

Exercise tolerance test

ETTs were performed at the trough of drug activity on days −7, 0 and 14, and at the peak of drug activity on day 14. The ETT was performed on an ergometric bicycle; the initial workload was set at 30 W and was increased by 30 W every 2 min. ECGs recorded during ETTs were reanalyzed centrally by a physician who was independent of study recruitment (Professor A. Cohen-Solal, Beaujon Hospital, Clichy, France). The central reading was performed blindly and retrospectively, and the results obtained centrally were used for efficacy evaluation.

Safety

Safety was assessed by reference to adverse events, vital signs, cardiovascular events (blood pressure during ETT, ECG at rest and 24-h Holter monitoring in a subset of 75 patients equally distributed between the treatment groups) and laboratory tests.

Statistical analysis

Between-group comparisons were performed using the Kruskal–Wallis test and a one-way analysis of variance. In case of a significant group effect, the three ivabradine groups were compared with placebo using the two-tailed Dunnett’s test and the equivalent non-parametric approach. In case of a significant treatment effect, with at least one ivabradine dose different from placebo, the dose–effect relationship was studied using linear regression.

Efficacy analyses were conducted in the per-protocol (PP) population and then in the intention-to-treat populations. The PP population comprised patients who completed the study with no major protocol violations, and who had trough ETT results at the end of the study with an evaluable time to 1-mm ST-segment depression at baseline. Values are expressed as mean ± standard deviation.
for the PP population, unless otherwise stated. Quoted \( P \) values are from parametric analyses; \( P < 0.05 \) was considered statistically significant. The safety population comprised all patients randomized to the study who received at least one treatment dose. Safety variables were analyzed using descriptive statistics.

### Results

Of 529 patients screened for eligibility, 400 were selected; the main reason for non-selection was a negative ETT at day —7 (100 patients). Of the selected patients, 40 were not included in the randomized population, most commonly due to a negative ETT at day 0. A total of 360 patients were randomized in the double-blind, placebo-controlled period. There were no clinically relevant differences between the treatment groups with regard to any of the baseline characteristics (Table 1).

### Primary efficacy criteria

#### Time to 1-mm ST-segment depression at trough of drug activity

During the double-blind phase, ivabradine 5 and 10 mg twice daily significantly increased the time to 1-mm ST-segment depression in the PP population by 44 s and 46 s, respectively, as compared with 9 s for placebo \( (P < 0.05; \text{Fig. 2a}) \). There was also a significant dose effect \( (P = 0.005) \). Ivabradine 2.5 mg twice daily also increased time to 1-mm ST-segment depression, but this effect was not significantly different from placebo.

#### Time to limiting angina at trough of drug activity

There was a significant treatment group effect with respect to changes in time to limiting angina. Ivabradine increased time to limiting angina; the 10 mg twice daily dose achieved statistical significance as compared with placebo \( (\text{Fig. 2b}) \), and a significant dose—effect relationship was observed \( (P = 0.005) \).

### Secondary efficacy criteria

#### Time to 1-mm ST-segment depression at peak of drug activity

A significant treatment effect was observed, with increases in time to 1-mm ST-segment depression of between 33 and 70 s occurring in the active treatment groups as compared with an increase of 10 s in the placebo group. The highest two doses (ivabradine 5 and 10 mg twice daily) induced a statistically significant increase in time to 1-mm ST-segment depression \( \) (Fig. 3a). The results were similar to the effects at trough of drug activity, except that the effects were larger.

#### Time to limiting angina at peak of drug activity

Ivabradine increased the time to limiting angina at the peak of drug activity. The observed effects were more pronounced at peak than at the trough of drug activity; a significant effect was obtained with 5 and 10 mg twice daily ivabradine \( \) (Fig. 3b).

### Heart rate

There were significant reductions in resting heart rate relative to placebo, at both peak and trough

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**Table 1** Baseline characteristics of the randomized and per-protocol populations in the double-blind, dose-ranging period

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Randomized population ( (n = 360) )</th>
<th>Per-protocol population ( (n = 257) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>323/37</td>
<td>233/24</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.5 ± 9.2</td>
<td>58.1 ± 8.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.0 ± 11.2</td>
<td>79.6 ± 11.1</td>
</tr>
<tr>
<td>Clinical data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine heart rate (beats/min)</td>
<td>69.7 ± 10.3</td>
<td>69.1 ± 9.7</td>
</tr>
<tr>
<td>Standing heart rate (beats/min)</td>
<td>74.6 ± 11.1</td>
<td>74.9 ± 11.0</td>
</tr>
<tr>
<td>Supine blood pressure (systolic/diastolic; mmHg)</td>
<td>133.7 ± 16.3/81.3 ± 8.2</td>
<td>132.7 ± 16.3/81.2 ± 7.9</td>
</tr>
<tr>
<td>Standing blood pressure (systolic/diastolic; mmHg)</td>
<td>133.0 ± 17.0/82.1 ± 8.2</td>
<td>131.6 ± 16.2/82.1 ± 7.8</td>
</tr>
<tr>
<td>Disease factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of coronary artery disease (months)</td>
<td>68.1 ± 63.9</td>
<td>69.7 ± 61.2</td>
</tr>
<tr>
<td>Previous myocardial infarction (%)</td>
<td>60.7</td>
<td>59.1</td>
</tr>
<tr>
<td>Previous coronary artery bypass graft (%)</td>
<td>16.4</td>
<td>16.7</td>
</tr>
<tr>
<td>Previous percutaneous transluminal coronary angioplasty (%)</td>
<td>18.3</td>
<td>15.2</td>
</tr>
<tr>
<td>Mean frequency of angina attacks (number per week)</td>
<td>5.3 ± 7.9</td>
<td>5.4 ± 8.2</td>
</tr>
<tr>
<td>Mean consumption of short-acting nitrates (units per week)</td>
<td>3.4 ± 7.6</td>
<td>3.4 ± 7.9</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation.
of drug activity, with all doses of ivabradine (Table 2). Maximal heart rate during exercise decreased in a similar manner. The heart rate lowering effects of ivabradine increased significantly with increases in dose ($P < 0.0001$).

**Time to onset of angina**
There were significant increases in time to angina onset, with ivabradine 10 mg twice daily producing a 45-s improvement as compared with placebo at trough of drug activity. The observed effect was greater at peak of drug activity; both 5 and 10 mg twice daily doses of ivabradine produced a significant increase in time to onset of angina: 43 s and 66 s, respectively, as compared with placebo.

**Rate pressure product**
Angina and ischaemia reduction was associated with significant, dose-dependent reductions in RPP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>2.5 mg twice daily</th>
<th>5 mg twice daily</th>
<th>10 mg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting heart rate (beats/min)</td>
<td>0.4 ± 10.9</td>
<td>−4.5 ± 10.6*</td>
<td>−9.5 ± 12.0*</td>
<td>−14.2 ± 10.0*</td>
</tr>
<tr>
<td>At peak of drug activity</td>
<td>2.8 ± 12.7</td>
<td>−6.5 ± 11.0*</td>
<td>−12.0 ± 13.1*</td>
<td>−18.7 ± 10.4*</td>
</tr>
<tr>
<td>Maximal heart rate (beats/min)</td>
<td>1.6 ± 9.1</td>
<td>−5.5 ± 9.8*</td>
<td>−8.3 ± 8.9*</td>
<td>−13.4 ± 10.5*</td>
</tr>
<tr>
<td>At peak of drug activity</td>
<td>3.7 ± 9.8</td>
<td>−6.5 ± 11.8*</td>
<td>−11.1 ± 11.5*</td>
<td>−17.7 ± 11.7*</td>
</tr>
</tbody>
</table>

Values are expressed as value on day 14 minus that on day 0; mean ± standard deviation. *Significantly different from placebo in pairwise comparison.
(heart rate × systolic blood pressure) in patients receiving ivabradine, both at rest and at peak of exercise ($P < 0.001$ and $P = 0.011$, respectively). At trough of drug activity, RPP at rest decreased by an average of 509, 1366 and 1909 bpm/mmHg with ivabradine 2.5, 5 and 10 mg twice daily, respectively, as compared with an increase of 178 bpm/mmHg with placebo. The changes were greater at peak of drug activity; RPP at rest decreased by an average of 740, 1740 and 2621 bpm/mmHg with ivabradine 2.5, 5 and 10 mg twice daily, respectively, as compared with an increase of 167 bpm/mmHg with placebo.

**Open-label extension period**

Patients who continued in the open-label extension period maintained the improvements in time to 1-mm ST-segment depression that were shown by patients receiving ivabradine in the dose-ranging phase (Fig. 4). Patients who had received placebo in the dose-ranging phase showed a reduction in angina and ischaemia when they were switched to ivabradine. Time to 1-mm ST-segment depression improved by more than 1 min from baseline to the end of the open-label extension period ($P < 0.001$). The time to limiting angina was also significantly increased in the patient population as a whole ($P < 0.001$).

**Withdrawal period**

Patients who received placebo during the randomized withdrawal period of the study showed significant deterioration in all major ETT parameters measured. Patients who continued on ivabradine 10 mg twice daily during the withdrawal phase maintained improvements in ETT parameters, including reductions in heart rate, increased time to 1-mm ST-segment depression and increased time to limiting angina (Fig. 5a and b).

**Angina attacks and consumption of short-acting nitrates**

There were reductions in both the number of angina attacks recorded and in the consumption of short-acting nitrates during the initial double-blind period by those patients receiving ivabradine, although these changes did not reach statistical significance. During the open-label extension period, during which all patients received ivabradine 10 mg twice daily, the consumption of short-acting nitrates was reduced from a mean of $2.28 \pm 3.74$ units per week at baseline to $0.50 \pm 1.14$ units per week ($P < 0.001$). The number of angina attacks was also significantly reduced during this period from a mean of $4.14 \pm 5.59$ attacks per week at baseline to $0.95 \pm 2.24$ attacks per week ($P < 0.001$). Patients who continued with ivabradine treatment during the randomized withdrawal period showed no change in the frequency of angina attacks, but in patients receiving placebo the frequency increased by $0.74 \pm 1.95$ attacks per week, although the difference between groups did not reach statistical significance ($P = 0.067$).

**Safety/tolerability**

Overall, the incidence of adverse events in patients receiving ivabradine was low and generally similar to that in patients receiving placebo during the first double-blind, dose-ranging period. Only visual symptoms (commonly associated with changes in light intensity) were higher in those receiving ivabradine [2.5 mg ($n = 1$), 5 mg ($n = 1$) and 10 mg ($n = 13$)] than in those receiving placebo ($n = 0$). A similar pattern of adverse events was observed during the open-label extension period; 31 patients (17.9%) experienced visual symptoms (graded as mild in 29 patients). During the randomized withdrawal period, visual symptoms were experienced by only one patient receiving ivabradine. All visual symptoms resolved spontaneously during or after
drug discontinuation. Only three patients withdrew from the study due to visual symptoms, and all of these were voluntary withdrawals and not at the investigators' insistence because of safety concerns.

There were no serious cardiac events reported after treatment withdrawal, suggesting the absence of any rebound phenomena.

Discussion

In this double-blind, placebo-controlled, dose-ranging study, the novel selective and specific $I_f$ inhibitor ivabradine demonstrated antianginal and anti-ischaemic efficacy in the treatment of patients with stable angina pectoris. Ivabradine significantly improved exercise tolerance (increased time to 1-mm ST-segment depression and time to limiting angina), reduced the frequency of angina attacks and reduced the consumption of short-acting nitrates. In patients receiving ivabradine, the improvements in measured ETT criteria were maintained for the duration of the trial. In patients receiving placebo during the withdrawal period, the measured ETT criteria deteriorated significantly.

The clinical benefits observed in the present study were closely related to the heart rate lowering effects of ivabradine. Significant dose-dependent reductions in heart rate at rest and at peak of exercise, measured at either peak or trough of drug activity, were achieved in all ivabradine treatment groups during the double-blind, dose-ranging period. The extent of heart rate reduction observed with ivabradine 10 mg twice daily in the this study is similar to that reported with repeated doses of ivabradine 10 mg twice daily in healthy volunteers. There is evidence to suggest that a high heart rate is associated with increased cardiovascular morbidity and mortality. It is therefore possible that the heart rate lowering effects of ivabradine could help to reduce morbidity and mortality in patients with cardiovascular diseases.

Ivabradine is a selective and specific inhibitor of one of the most important pacemaker currents in the sinoatrial node — the hyperpolarization-activated $I_f$ current. Ivabradine, unlike other heart rate lowering agents, has been shown to have little or no effect on other cardiac ion currents or cardiac action potential shape at therapeutic concentrations in animal studies, and has no significant effect on myocardial contractility.

The cardiovascular tolerability of ivabradine could be attributed to the highly specific and selective mode of action on the $I_f$ channel. In the present study, ivabradine exhibited excellent general tolerability and, in contrast to beta-blockers, exhibited no rebound phenomena on withdrawal. The only adverse effects related to treatment were visual symptoms reported by some patients receiving ivabradine 10 mg twice daily. Reports of visual symptoms were expected because they occurred during an earlier study with ivabradine in healthy volunteers. Visual symptoms associated with ivabradine are usually of mild to moderate intensity, resolve spontaneously and do not affect the general or cardiovascular tolerability of the drug.
channels similar to \( I_f \) channels have been found in the retina and could be linked to the visual symptoms experienced with the higher doses of ivabradine in some patients.\(^{19-21}\)

Current recommendations for patients with stable angina suggest that most patients should be treated with all three classes of antianginal drugs before medical therapy is judged to be a failure and angioplasty or surgery is considered.\(^{22-25}\) A meta-analysis of randomized trials comparing percutaneous transluminal coronary angioplasty with medical treatment concluded that coronary angioplasty should only be used for patients whose symptoms are not well controlled on pharmacotherapy.\(^{26}\) The main classes of drugs prescribed to reduce myocardial ischaemia and prevent angina are beta-blockers, nitrates and calcium channel blockers. Beta-blockers are the recommended first-line therapy for stable angina.\(^{24}\)

Beta-blockers are known to have antianginal effects and reduce ischaemia; there is evidence that their anti-ischaemic benefit is due to their heart rate lowering properties.\(^{27,28}\) The efficacy achieved by ivabradine in the present study is comparable to that achieved historically by beta-blockers. Although beta-blockers are recommended as initial treatment in patients with stable angina, they are not without their problems.\(^{22}\) The beneficial effects of beta-blockers on heart rate may be offset by their effects on myocardial contractility and vasocostriction. Beta-blockers have been shown to reduce myocardial contractility and can cause a paradoxical vasocostriction of large epicardial arteries, both at rest and during exercise, in experimental animals\(^{9,29}\) and humans.\(^{30}\) Anginal symptoms were reported to be poorly controlled in a study of primary care patients with stable angina, even though 64% of patients were taking more than one cardiovascular drug.\(^{31}\)

Beta-blockers are contraindicated in many patients, including those with peripheral vascular disease (which often coexists with coronary artery disease),\(^{32}\) those with obstructive airways disease\(^{33,34}\) and those with hypotension or higher than first-degree heart block.\(^{35}\) Lipid and carbohydrate metabolism may also be adversely affected by beta-blockers.\(^{36-41}\) There is therefore clearly a need for additional, more specific heart rate lowering agents with antianginal efficacy.

**Conclusion**

The randomized, double-blind period of the present study in patients with stable angina showed that ivabradine (Procoralan) — a selective and specific \( I_f \) inhibitor — produced dose-dependent reductions in heart rate, at rest and during exercise, and significant improvements in ergometric criteria during ETs. In the open-label extension period, ivabradine 10 mg twice daily also produced significant reductions in the frequency of reported angina attacks. The general and cardiovascular tolerability of ivabradine was excellent and no rebound phenomena were observed. These results suggest that ivabradine may be an effective and safe alternative to the range of options available for the medical treatment of stable angina and, potentially, other myocardial ischaemic conditions.

**References**


Appendix

European Ivabradine Late Phase II Investigators Group:

Belgium: G. Heyndrickx, Aalst; M. Vrolix, Genk.
Czech Republic: J. Bultas, Praha; J. Janousek, Beroun; O. Jerabek, Zdabor; V. Stanek, Praha; J. Vrany, Praha.
Germany: H. Becker, Hanau; U. Biermann, Altenkirchen; L. Hopf, Frankfurt; M. Keck, Bad Munster; G. Kober, Bad Nauheim; G. Rettig, Muenster; R. De Chatel, Budapest; A. Janosi, Budapest; L. Matos, Budapest; I. Preda, Budapest; K. Toth, Pecs.
Russian Federation: I. Chazov, Moscow; A. Golikov, Moscow; V. Makolkin, Moscow; V. Metelitsa, Moscow.
Spain: J. Bardaji, Cuenca; J. Bruguera, Barcelona; J. Cruz Fernandez, Sevilla; C. Fernandez Palomeque, Palma De Mallorca; J. Gonzalez Juanatey, Santiago De Compostela; C. Macaya, Madrid; C. Pagola, Jaen; L. Rodriguez Padial, Toledo.

U.K.: P. Bennett, Bath; J. Davies, Newport; K. Fox, London; D. Lindsay, Gloucester; W. Littler, Birmingham; B. Silke, Belfast; S. Singh, Birmingham; J. Stephens, Romford; G. Sutton, Uxbridge.