PRACTICE OBSERVED

Nifedipine and atenolol singly and combined for treatment of essential hypertension: comparative multicentre study in general practice in the United Kingdom

NIFEDIPINE-ATENOLOL STUDY REVIEW COMMITTEE

Abstract

A randomised double blind parallel group study was performed to compare the efficacy and acceptability of slow release nifedipine (maximum dose 40 mg twice a day) with those of atenolol (maximum dose 100 mg once a day) as single agents for the treatment of essential hypertension. Of 410 patients recruited almost exclusively from general practices in 22 centres in the United Kingdom 210 received nifedipine and 200 atenolol. Both drugs significantly reduced blood pressure, and control—a reduction of the diastolic pressure to less than 95 mm Hg—was obtained in about 65% of patients. Those who received nifedipine had more pronounced reductions in systolic pressure than those who received atenolol. One hundred and forty nine patients who failed to respond adequately to either atenolol or nifedipine in low doses were given both drugs once daily for eight weeks in a fixed combination capsule that contained atenolol 50 mg and nifedipine 20 mg. All patients showed further reductions in blood pressure, although those who were taking β atenolol before the combination capsule had more pronounced reductions in systolic pressures. Twenty six patients (12%) were withdrawn because of adverse effects while taking nifedipine compared with 19 (10%) taking atenolol. Flushing and oedema were more common after the calcium antagonist, whereas diarrhoea and dyspepsia were

more common after atenolol. The frequencies of headaches, dizziness, fatigue, and dyspnoea were equally distributed between the two groups. When the fixed combination capsule was taken side effects such as flushing and oedema continued.

Nifedipine was more effective than atenolol in lowering systolic blood pressure, although neither drug used alone controlled the pressure of more than two thirds of the patients studied. When used in a fixed combination slightly better control of blood pressure was achieved with a lower dose of each drug.

Introduction

The treatment of essential hypertension using a "stepped care" approach has been advocated for some time.¹ There has, however, been a radical change because of the increase in the number of drugs such as calcium channel blockers and angiotensin converting enzyme inhibitors that were not included in the original stepped care regimens. In addition, doctors have realised that treatment with several drugs increases the incidence of both non-compliance and side effects.^{2,3} The tendency therefore has been to keep the number of drugs and the number of doses required to the minimum needed to lower the blood pressure. The cardioselective β adrenergic blocking drug atenolol has been extensively used as a first line single drug for the treatment of mild to moderate hypertension. The introduction of the calcium channel antagonist nifedipine in a slow release preparation provided another useful antihypertensive drug used both alone⁴ and in combination with other agents such as β blockers.⁵ Both atenolol and nifedipine have side effects and may be unsuitable for, or poorly tolerated by, some patients. No study of suitable statistical power, however, has addressed the issue of whether one of these agents might be better than the other as a single treatment of hypertension or whether a combination offers distinct advantages.

Atenolol and nifedipine were therefore evaluated both for their ability to control blood pressure and for the incidence of side effects. In addition the two drugs were combined in one capsule to see if this would produce an additive effect in reducing blood pressure and decrease the incidence of side effects that occurred when the drugs were given singly. To secure adequate statistical power a much larger clinical study was carried out than is normally used.

Department of Medicine, Leicester Royal Infirmary, Leicester LE2 7LX

A M HEAGERTY, MD, MRCP, senior lecturer

J SWALES, MD, FRCP, professor

St Mary's Hospital, Newport, Isle of Wight

A BAKSI, MB, FRCP, consultant

Department of Clinical Pharmacology, Ninewells Hospital, Dundee

D MACLEAN, MB, FRCP, consultant

Department of Cardiology, Royal Liverpool Hospital, Liverpool L7 8XP

S SALTISSE, MSc, MD, consultant

Applied Statistics Research Unit, University of Kent, Canterbury

J B CURRAM, MSc, statistician

P M NORTH, PhD, director

Correspondence to: Dr Heagerty.

Patients and methods

TRIAL DESIGN

Seventy four general practitioners in 22 centres took part in a randomised double blind parallel group study. At each centre a consultant physician was appointed to oversee the study and to advise on clinical problems. Men and women aged 18-75 years whose blood pressures taken at rest on two separate occasions were within the ranges 160/95 and 220/120 mm Hg (those under 65) and 180/100 and 240/130 mm Hg (those aged 65 and over) were eligible for the study. They were recruited to the study if they were newly diagnosed or if their blood pressure rose to within those ranges after the withdrawal of their pre-existing medication. Patients with malignant hypertension; those who had had a myocardial infarction or a cerebrovascular accident within the previous three months; those with obstructive airways disease, peripheral vascular disease, or cardiac failure were excluded; women of childbearing age were ineligible. All patients gave fully informed consent and the study had the approval of the ethical committee.

and how acceptable they found their treatment during each period of the trial.

STATISTICAL ANALYSIS

The power of the study was calculated using the measurement of diastolic blood pressure taken when the patient was sitting down. From previous studies it was assumed that in this position there was a standard deviation of 10 mm Hg on this element of blood pressure measurement.⁶ In order therefore to detect a true difference in treatment of 3 mm Hg with a probability of 80% at the 5% level of significance we calculated that 176 patients would be required in each arm of the trial.

All data were recorded in confidential patient record folders; completed files were forwarded to the applied statistics research unit, University of Kent at Canterbury, and stored on a computer. Changes in blood pressures and heart rates from week 4 to week 12 were compared between groups for all patients who had completed the study at this point by Student's two

FIG 1—Designs of the study.

STUDY PROTOCOL

Patients were recruited at week 0, assigned a trial number, and given a course of a placebo drug (one tablet twice a day) for four weeks (fig 1). The trial number determined the eventual treatment group to which the patient was allocated. If a patient had been taking antihypertensive drugs they were withdrawn on recruitment. At week 4 any patient whose blood pressure remained within the preset ranges received either slow release nifedipine 20 mg orally twice a day or atenolol 50 mg orally once a day for four weeks. At week 8 blood pressures were measured again; any patient who had a diastolic blood pressure of 95 mm Hg or more or who had been entered at week 4 with a diastolic pressure of 95-104 mm Hg and who had failed to attain a fall of 10 mm Hg was termed a non-responder. Responders continued the study with their drugs unchanged. Non-responders were given either nifedipine 40 mg orally twice a day or atenolol 100 mg orally once a day for the next four weeks. Patients who had been responders at week 8 finished the study at week 12. Patients who had been non-responders at week 8 were then given a fixed combination capsule containing nifedipine slow release 20 mg and atenolol 50 mg once a day for a further eight weeks. Patients returned at week 16, and the study was completed at week 20.

The trial drugs were packed in a double dummy manner using matching placebos so that both physician and patient were unaware of the treatment during the double blind phase—that is, up to week 12.

Blood pressures and heart rates were recorded at each visit. Blood pressure was measured with a bias free semiautomatic sphygmomanometer (Copol, Japan) or a Hawksley random zero sphygmomanometer. Two readings were taken with the patient sitting down after a five minute rest, and the mean value plus the heart rate were noted. Patients were then asked to stand for one minute, after which the blood pressure and pulse rate were again recorded twice and the average readings noted. In addition side effects, concurrent illnesses, other drugs being taken, and weight were recorded at each visit. Patients were withdrawn from the study if at any time there were intolerable side effects or if additional antihypertensive drugs were needed. The reasons for all withdrawals were recorded. Compliance was assessed by counting the tablets at each visit, and the acceptability of the treatment was assessed by tabulating the patients' answers to questions about how they felt

sample *t* test as the data were normally distributed. For data on the study of the fixed dose combination capsule, the blood pressures and pulse rates were compared for all patients who had completed the study at week 20 with their values at week 12 by Student's paired *t* test. Patients were labelled as withdrawn if they had died or had serious side effects from the drugs, or if they had severe concurrent illnesses or failed to attend for follow up. A *p* value of <0.01 was considered significant for reasons given in the discussion. Where interval estimates were appropriate a 99% confidence interval is given.

Results

A total of 459 patients entered the study of whom 232 were assigned to receive nifedipine and 227 to take atenolol. At week 4, 410 patients still had blood pressures sufficiently raised to continue in the study and 210 received nifedipine and 200 atenolol. The demographic data for the two groups at week 4 (table 1) show that they were well matched for age, sex, weight, smoking habits, previous treatment, pulse rate, and blood pressure. The fate of all patients during the double blind phase of the study is shown in figure 2. Forty nine patients were withdrawn before week 4 because of adverse reactions to placebo (11), hypotensive response to the placebo (23), and non-attendance (15). These patients were equally distributed between the two groups. One patient had a non-fatal stroke while taking placebo, and one had severe hypertension. One hundred and eighty one of the 210 patients taking nifedipine (86%) and 174 of the 200 taking atenolol (87%) completed the study at week 12 and it is on the results from these subjects that statistical analyses of pulse rates and blood pressure measurements are based. Fifty five patients were withdrawn between weeks 4 and 12 for the reasons given below. Of those patients who had been randomised and not withdrawn 87 taking nifedipine (36%) and 86 taking atenolol (43%) were non-responders at week 8 and continued in the study beyond week 12 taking the fixed combination capsule. At week 20, 149 (86%) of this group were still receiving treatment, and it is in this group that comparisons of pulse rates and blood pressure were made between weeks 12 and 20.

COMPLIANCE

The compliance of each patient was taken as the number of tablets taken $\times 100\div$ the number of tablets that should have been taken. This was calculated from the number of tablets the patient should have been given according to the trial design minus the number returned according to the patient's record forms. In the entire study group 93% of patients achieved a compliance of greater than or equal to 80%, and 68% achieved a compliance of greater than or equal to 95%. The 80% compliance rates of those taking nifedipine and those taking atenolol were 92% and 94%, respectively.

SIDE EFFECTS

One hundred and twenty one patients experienced side effects while they were taking placebo tablets. The commonest problems were headache (28) and dizziness (17). In addition, 11 patients felt tired and 10 complained of dyspepsia. Eleven patients had such severe reactions while they were taking the placebo tablets that they were withdrawn. These included dizziness (2), oedema (1), chest pain (1), aching legs (1), gastritis (1), and diarrhoea (1); two complaints were not specified. One patient developed severe hypertension and one had a mild cerebrovascular accident during this phase and both were withdrawn. The patients withdrawn were equally distributed between the two groups, six being randomised to have nifedipine and five to have atenolol.

One patient died from a myocardial infarction while taking atenolol, and 150 patients had complained of side effects by week 8 and 103 by week 12. After all data had been obtained the incidence of expected effects was analysed for nifedipine and similarly a separate group was documented for atenolol. For nifedipine headache, flushing, dizziness, tachycardia or palpitations, and oedema (either general or local) were recorded. For atenolol fatigue and lassitude, bradycardia, gastrointestinal upset, peripheral ischaemia or pain, and wheezing or dyspnoea were recorded. Table II shows the expected side effects of nifedipine and the number of patients who were taking atenolol yet reported them. Headache and dizziness were surprisingly reported just as often by patients taking atenolol as by those taking nifedipine. Flushing, oedema, and tachycardia or palpitations, however, were most commonly reported by patients taking nifedipine. Table III shows the expected side effects of a β blocking agent; again, fatigue and lassitude were reported by those taking nifedipine, and wheezing or dyspnoea were reported equally by both groups of patients. The most common side effects reported by patients taking atenolol were dyspepsia and diarrhoea, although these were problems also reported by those taking

TABLE I—Study groups at week 4

	Nifedipine (n=210)	Atenolol (n=200)
No of men	111	95
No of smokers	61	48
No who had previously received treatment	108	105
Age (years)*	55.6 (10.7)	57.6 (9.7)
Weight (kg)*	75.7 (14.6)	75.5 (14.0)
Systolic blood pressure (mm Hg)*:		
Measured when patient sitting	175.8 (20.9)	174.4 (19.5)
Measured when patient standing	173.4 (20.3)	172.1 (20.0)
Diastolic blood pressure (mm Hg)*:		
Measured when patient sitting	104.9 (8.9)	104.1 (7.7)
Measured when patient standing	106.5 (9.2)	105.8 (9.2)
Pulse rate (beats/minute)*:		
Measured when patient sitting	81.1 (10.7)	79.6 (8.4)
Measured when patient standing	83.2 (10.7)	81.6 (8.8)

*Results expressed as mean (SD).

TABLE II—Incidence of expected side effects of nifedipine. Results are expressed as number of patients affected* (number withdrawn from treatment)

Study group	Headache	Flushing	Dizziness	Tachycardia or palpitations	Oedema (general or local)
Patients taking nifedipine 20 mg daily	24 (8)	21 (9)	7 (3)	5 (1)	19 (4)
Patients taking nifedipine 40 mg daily	7 (0)	7 (1)	5 (0)	2 (0)	12 (1)
All patients taking nifedipine	28 (8)*	27 (10)*	12 (3)	5 (1)*	26 (5)*
Patients taking atenolol 50 mg daily	20 (3)	2 (1)	7 (4)	1 (1)	2 (1)
Patients taking atenolol 100 mg daily	3 (0)	1 (0)	2 (1)	0 (0)	0 (0)
All patients taking atenolol	21 (3)*	3 (1)	8 (5)*	1 (1)	2 (1)
Patients taking the combination capsule after nifedipine alone	8 (1)	3 (0)	1 (0)	1 (1)	4 (0)
Patients taking the combination capsule after atenolol alone	10 (1)	6 (1)	3 (1)	2 (0)	5 (0)
All patients taking the combination capsule	18 (2)	9 (1)	4 (1)	3 (1)	9 (0)

*In some cases numbers total more than those for the overall group because some patients complained of the same side effect on both low dose and high dose treatment.

FIG 2—Flow diagram showing the fate of all patients recruited to the double blind phase of the study (weeks 0-12).

nifedipine. Fifty five patients (13%) were withdrawn between weeks 5 and 12, of whom 48 had unacceptable side effects from the drug they were taking, six failed to attend for follow up, and there was one death.

One hundred and seventy three patients (42% of the total number entered) received the fixed combination capsule. Side effects were reported by 45 patients (26%) at week 16 and 33 (22%) at week 20. Twenty four patients were withdrawn during this phase of the study; one patient had a mild cerebrovascular accident, and one had poorly controlled blood pressure. A further nine were withdrawn because of intolerable side effects—headache (2), palpitations (1), flushing (1), depression (1), wheeziness (1), dizziness (1), hypotension (1), and unspecified (1). Three patients failed to attend for follow up, and 10 patients were withdrawn at week 16 owing to misinterpretation of the protocol by the doctor. The addition of atenolol in the fixed combination capsule did not appear to reduce the incidence of side effects caused by the calcium antagonist in patients taking nifedipine.

BLOOD PRESSURE AND PULSE RATE

Two hundred and eighty seven (63%) of the patients admitted were reviewed on consecutive visits in clinics during the middle or late morning, and 172 (37%) were reviewed in the afternoon, up to a maximum of 12 hours after taking the last oral dose of treatment. The nifedipine and atenolol subgroups were well balanced for the timing of their blood pressure measurements.

At week 4 the treatment groups were similar with respect to measurements of blood pressures and heart rates (table I). Both groups of patients showed significant reductions in blood pressures measured when they were sitting and standing at week 12 (tables IV and V). Mean heart rates also fell significantly as expected in the group taking atenolol (fig 3), but there was no change in the group taking nifedipine when compared with results when taking placebo (fig 3). At week 12 there was no significant difference between the two groups in the mean measurements of diastolic blood pressure taken when patients were sitting or when they were standing (tables IV and V). Patients on nifedipine, however, showed greater reductions in mean systolic pressures than those taking atenolol (table V).

One hundred and forty nine patients received the fixed combination capsule from week 12 to week 20. There were further significant reductions in all components of blood pressures and heart rates measured at 20 weeks when patients were sitting and standing (table VI). The greatest reductions

TABLE III—Incidence of expected side effects of atenolol. Results are expressed as number of patients affected (number withdrawn from treatment)

Study group	Fatigue or lassitude	Bradycardia	Gastrointestinal upset	Peripheral ischaemia or pain	Wheezing or dyspnoea
Patients taking nifedipine 20 mg daily	9 (1)	0 (0)	12 (4)	1 (0)	3 (0)
Patients taking nifedipine 40 mg daily	3 (0)	0 (0)	4 (1)	0 (0)	0 (0)
All patients taking nifedipine	10 (1)*	0 (0)	16 (5)	1 (0)	3 (0)
Patients taking atenolol 50 mg daily	13 (3)	2 (0)	18 (1)	3 (0)	4 (0)
Patients taking atenolol 100 mg daily	3 (0)	0 (0)	3 (0)	0 (0)	1 (0)
All patients taking atenolol	14 (3)*	2 (0)	21 (1)	3 (0)	5 (0)
Patients taking the combination capsule after nifedipine alone	2 (0)	0 (0)	3 (0)	0 (0)	1 (0)
Patients taking the combination capsule after atenolol alone	5 (0)	0 (0)	1 (0)	0 (0)	0 (0)
All patients taking the combination capsule	7 (0)	0 (0)	4 (0)	0 (0)	1 (0)

*In some cases numbers total more than those for the overall group because some patients complained of the same side effects on both low dose and high dose treatment.

TABLE IV—Mean (SD) measurements of blood pressure (mm Hg) in patients taking nifedipine or atenolol alone, weeks 4, 8, and 12

	Nifedipine alone				Atenolol alone			
	Measured with patient standing (n=171)		Measured with patient sitting (n=174)		Measured with patient standing (n=170)		Measured with patient sitting (n=172)	
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
Week 4	174.0 (19.9)	106.6 (8.8)	176.8 (20.3)	105.1 (7.6)	173.0 (20.2)	106.3 (9.4)	175.1 (19.9)	104.6 (7.7)
Week 8	155.1 (18.9)	96.2 (10.4)	157.3 (18.7)	94.0 (9.8)	159.6 (23.0)	97.0 (10.6)	161.9 (22.6)	94.9 (10.2)
Week 12	150.5 (18.8)	92.4 (10.3)	153.5 (17.8)	90.4 (9.3)	157.2 (24.2)	94.9 (11.0)	158.8 (23.4)	91.8 (8.9)

TABLE V—Mean (SD) reductions in blood pressures (mm Hg) between weeks 4 and 12 and comparison of the effects of nifedipine alone and atenolol alone

Blood pressure	Nifedipine alone	Atenolol alone	Mean of difference	99% Confidence interval	p Value
Diastolic pressure:					
Measured when patient sitting	14.6 (10.4)	12.8 (9.9)	1.8	-1.0 to 4.6	0.100
Measured when patient standing	14.2 (10.9)	11.4 (11.6)	2.8	-0.4 to 5.9	0.023
Systolic pressure:					
Measured when patient sitting	23.3 (19.1)	16.3 (18.2)	7.0	1.9 to 12.2	<0.001
Measured when patient standing	23.5 (20.7)	15.7 (19.2)	7.7	2.2 to 13.3	<0.001

TABLE VI—Mean (SD) reductions in blood pressures (mm Hg) and heart rates (beats/minute) at weeks 12 and 20 for the 149 subjects taking fixed combination capsule

Measurement	Week 12	Week 20	Mean of difference	99% Confidence interval	p Value
Diastolic pressure:					
Measured when patient sitting	94.8 (8.9)	91.1 (9.2)	3.7	1.7 to 5.7	<0.001
Measured when patient standing	97.4 (10.5)	93.8 (11.4)	3.6	1.4 to 5.8	<0.001
Systolic pressure:					
Measured when patient sitting	161.4 (22.3)	155.7 (22.6)	5.7	1.9 to 9.5	<0.001
Measured when patient standing	159.3 (23.1)	154.0 (22.9)	5.3	1.5 to 9.1	<0.001
Heart rate:					
Measured when patient sitting	74.7 (12.5)	69.8 (8.4)	5.0	2.5 to 7.5	<0.001
Measured when patient standing	76.5 (13.4)	71.4 (8.2)	5.1	2.3 to 7.9	<0.001

in pulse rates were in patients who initially took nifedipine alone and who took atenolol as the second drug, but there were greater reductions in blood pressures in patients who initially took atenolol alone and who took nifedipine as the additional drug in the fixed combination capsule.

A summary of the results from all patients randomised to take part in the study, including those withdrawn at intervals for whatever reason, showed that they were similar with regard to blood pressures and pulse rates compared with the summary of the results from those patients who completed the study.

Discussion

These data show that both nifedipine and atenolol when used singly can control the blood pressures and heart rates of about two thirds of patients with mild to moderate hypertension. While the type of side effects that occurred depended on which drug was used, the incidences of those effects did not differ. Thus careful selection

of patients before starting treatment with a β blocker can minimise the incidence of side effects associated with such drugs. Moreover, the fixed combination capsule of atenolol and nifedipine was useful in further reducing blood pressure, but the reported protective effect of β blockade against side effects caused by the calcium antagonist was not seen.⁷

The main purpose of this trial was to compare the activities of two of the leading types of drug for the treatment of hypertension. The chosen agents, slow release nifedipine and atenolol, have previously been studied alone and in combination in studies in hospitals with small numbers of patients,⁷ but they have never been compared in a large group of subjects with mild to moderate hypertension. The present study of over 400 such patients is one of the largest comparative controlled trials conducted in general practice where most mild to moderate hypertension is treated. The risks of hypertension have been correlated with the degree of increase in blood pressure and there is evidence to support the belief that

FIG 3—Effects of slow release nifedipine (x) and atenolol (●) on measurements of radial pulse. p Values refer to comparison of changes in heart rate between weeks 4 and 12 by Student's two sample *t* test. Bars represent one standard deviation from the mean. Standard deviations are given to indicate the spread of the data. With such large samples standard errors of the mean are very small.

reduction of diastolic blood pressure below 100 mm Hg will reduce the incidence of the vascular complications of hypertension.⁸ There are many antihypertensive drugs available, and it is important to choose the ones that suit patients best, because they are then more likely to take the drugs, the incidence of side effects will be reduced, and the drugs are more likely to be cost effective.

The number of patients randomised was calculated to show with 95% certainty that a difference of 3 mm Hg between the results of treatment with atenolol and nifedipine was significant. Tests of significance were carried out on several different variables at different times. This multiple testing increased the chance of detecting false positive results—that is, results which appeared significant only because of the inherent random variations in the data. To guard against this the 1% level of significance was used throughout the study rather than the customary 5% level. We hope therefore that we have achieved some protection against the possibility of identifying spurious results. Any formal attempt to determine the precise level of significance for carrying out the multiple tests was complicated by the correlations among different variables in the study and among the same variables over time.

Nifedipine was significantly more effective in reducing systolic pressures. This finding may have been influenced by the criterion of a response to treatment, which was defined in the protocol and depended on reduction in the diastolic pressures, but it is consistent with the different modes of action of the two agents. Heart rates were significantly reduced in those patients taking atenolol, but there was little change among patients treated with nifedipine. Taken alone both nifedipine and atenolol reduced the blood pressure of 60-70% of patients to below 95 mm Hg, and some but not all of the remainder responded to a combination of the two drugs in low doses. The combination appeared to produce less additional benefit in patients who were first treated with nifedipine alone, perhaps because nifedipine had reduced the pressure further than atenolol alone would have done, or because the dose of nifedipine in

the combination capsule was lower than the dose that patients taking nifedipine alone had received previously.

The incidence of side effects with each drug must be interpreted with caution because patients with illnesses in which either drug was contraindicated were carefully excluded. The overall incidence of side effects was therefore low and the problems we expected with β blockers were kept to a minimum. In addition the exclusion of patients at high risk of developing side effects on the drugs probably influenced the low rate of withdrawal from treatment between weeks 4 and 12. Similarly, the incidences of deaths, non-fatal cerebrovascular accidents, and myocardial infarctions were extremely low although the study was relatively short.

Treatment with the fixed combination capsule resulted in further significant reductions in blood pressures despite the fact that the dosage of each drug was lower in the combination than the patients had received when taking the single drug. Again, the larger reductions seem to have occurred when patients already taking atenolol had nifedipine added to their treatment. This may, however, be due to the fact that the dose of nifedipine in the fixed combination was lower than that taken by patients receiving nifedipine alone. What was clear was that the addition of the β blocker to the calcium antagonist did not reduce the incidence of side effects of the vasodilator.

In summary, this study shows that nifedipine and atenolol were both effective singly in treating mild to moderate hypertension in most of the patients to whom they were given, and that careful selection of patients can keep the incidence of the side effects of the β blocker to a minimum. In addition, in a combination capsule taken once a day the two drugs were effective and taken in this way they may be a useful adjunct to treatment already available for mild to moderate hypertension.

Study group—Ashford: A Norris; Caerphilly: B Davies, P Harney, M Sabbuba, G Tayyebbi, Q Din; Cambridge: D Evans, P Williams; Canterbury: A Marshall, P Attwood; Cardiff: J Lazarus, S Chaudhuri, C Gibbs, S Shrivastava, M Thomas, D Ward; Dudley: M Bone, A Khan, M Kubik, J Mary, R Tandon; Chichester: R Simpson; Dundee: D Maclean, A Buchan, J Fletcher, A Jacob, J Locke, D Ritchie, K Sagar; Farnborough: C Wharton; Galashiels: J Gaddie; Glasgow: T Murray, F Ballantyne, D MacLachlan, L Smith, I Struthers; Isle of Wight: A Baksi, A Beale, D Biggs, J Brand, M Brooks, P Coleman, M Court, M Denman-Johnson, A Frame, G Gent, J Mackett, K Majumdar, N Reid, C Smith, D Turner; Leicester: J Swales, A Bennett, N Dudge, A Heagerty, T Khong, P Lazarus; Liverpool: S Saltissi, P Daensvang, S Desai, M Feld, G Goenka, S Goldthorpe, E Krasner, F McMillan; Londonderry: D Keegan, K Cosgrove, N Chughan, H Leitch, B McCartie; Maidstone: A Stevens, M Brook, C Gwyn-Jones; Central and South Manchester: G Howitt, M Ashworth, P Raftery, E Unwin; North east Manchester: M Husaini, G Hamlet, S Kokiet, K Malhotra, D Wickenden; Norwich: R Greenwood; Poole: Z Rana; Torquay: M Thorne, R Hyde, S Lansdowne, C Molan, E Southall. Department of Statistics, University of Kent: J Curram, P North, D Winskill. Bayer Research: J Edwards, K Goodier, K Leighton, J Snaith, K Young.

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