Markers of β-Cell Failure Predict Poor Glycemic Response to GLP-1 Receptor Agonist Therapy in Type 2 Diabetes

DOI: 10.2337/dc15-0258

OBJECTIVE
To assess whether clinical characteristics and simple biomarkers of β-cell failure are associated with individual variation in glycemic response to GLP-1 receptor agonist (GLP-1RA) therapy in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS
We prospectively studied 620 participants with type 2 diabetes and HbA1c ≥58 mmol/mol (7.5%) commencing GLP-1RA therapy as part of their usual diabetes care and assessed response to therapy over 6 months. We assessed the association between baseline clinical measurements associated with β-cell failure and glycemic response (primary outcome HbA1c change 0–6 months) with change in weight (0–6 months) as a secondary outcome using linear regression and ANOVA with adjustment for baseline HbA1c and cotreatment change.

RESULTS
Reduced glycemic response to GLP-1RAs was associated with longer duration diabetes, insulin cotreatment, lower fasting C-peptide, lower postmeal urine C-peptide–to–creatinine ratio, and positive GAD or IA2 islet autoantibodies (P ≤ 0.01 for all). Participants with positive autoantibodies or severe insulin deficiency (fasting C-peptide ≤0.25 nmol/L) had markedly reduced glycemic response to GLP-1RA therapy (autoantibodies, mean HbA1c change −5.2 vs. −15.2 mmol/mol (−0.5 vs. −1.4%), P = 0.005; C-peptide <0.25 nmol/L, mean change −2.1 vs. −15.3 mmol/mol (−0.2 vs. −1.4%), P = 0.002). These markers were predominantly present in insulin-treated participants and were not associated with weight change.

CONCLUSIONS
Clinical markers of low β-cell function are associated with reduced glycemic response to GLP-1RA therapy. C-peptide and islet autoantibodies represent potential biomarkers for the stratification of GLP-1RA therapy in insulin-treated diabetes.

The glucagon-like peptide 1 (GLP-1) receptor agonists (GLP-1RAs) are effective glucose-lowering therapies commonly prescribed for patients with type 2 diabetes, typically as second- or third-line agents in combination with metformin and/or other oral therapy or in combination with insulin (1–3). These treatments are associated with weight loss and have a low risk of hypoglycemia in comparison with older therapies (4). However, in the absence of clear a difference in effectiveness and

1National Institute for Health Research Exeter Clinical Research Facility, University of Exeter Medical School and Royal Devon and Exeter National Health Service Foundation Trust, Exeter, U.K.
2Institute of Health Research, University of Exeter Medical School, Exeter, U.K.
Corresponding author: Angus G. Jones, angus.jones@exeter.ac.uk.
Received 4 February 2015 and accepted 4 July 2015.
Clinical trial reg. no. NCT01503112, clinicaltrials.gov.
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc15-0258/-/DC1.
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long-term outcome, the choice of second- and third-line therapy in type 2 diabetes remains a subject of considerable debate (2,5).

The glycemic response to GLP-1RAs is highly variable, with some individuals achieving very marked response but others achieving no improvement in HbA1c (3,6,7). While some of this variability will relate to lifestyle change, medication adherence, and measurement imprecision, it is likely that there will also be biological mechanisms contributing to this treatment response variation. Type 2 diabetes is a highly heterogeneous disease likely with different pathologies (8), and biomarker predictors of response to glucose-lowering therapies have been identified (9). Identifying clinical features or biomarkers predictive of response may help target treatment to those most likely to benefit; this would be particularly beneficial for the incretin therapies given their relatively high cost and frequency of short-term side effects (10).

A major mechanism of action of GLP-1RAs is potentiation of β-cell insulin secretion (4). We hypothesized that patients with more marked β-cell failure will be unable to substantially increase insulin secretion in response to GLP-1RAs and therefore will have reduced glycemic response.

We aimed to determine whether clinical characteristics and simple biomarkers associated with β-cell failure are associated with glycemic response to GLP-1RAs in patients with a clinical diagnosis of type 2 diabetes.

RESEARCH DESIGN AND METHODS
Study hypothesis and outcomes were pre-specified and registered with clinicaltrials.gov (https://clinicaltrials.gov/show/NCT01503112).

Study Setting and Participants
We prospectively studied 620 participants with a clinical diagnosis of type 2 diabetes, HbA1c ≥58 mmol/mol (7.5%), and estimated glomerular filtration rate >30 ml/min/1.73 m² commencing GLP-1RA therapy as part of their usual diabetes care and assessed response to therapy over 6 months. Participants were identified from National Health Service primary and secondary care and recruited at 17 participating sites in England between April 2011 and October 2013. Ethics approval was granted by the South West National Research Ethics committee, and all participants gave written informed consent.

Assessment
At baseline, prior to commencing treatment, we assessed HbA1c and clinical markers of β-cell failure (fasting C-peptide [11], post–largest home meal urine C-peptide–to–creatinine ratio [UCPCR] (12), GAD and IA2 autoantibodies [13], diabetes duration, and insulin co-treatment [14]). At 3 months (10–14 weeks) and 6 months (22–26 weeks) after commencing GLP-1RA therapy, we assessed HbA1c and adherence (self-reported over the 2 weeks prior to HbA1c measurement). Concurrent treatment was recorded at all visits.

The primary outcome measure was change in HbA1c in the first 6 months of GLP-1RA therapy. Change in weight (baseline to 6 months) was assessed as a secondary outcome.

To minimize confounding by adherence or treatment change, we excluded a follow-up visit from analysis where participants had stopped therapy ≥7 days prior to HbA1c assessment, had <75% self-reported adherence, had commenced any additional glucose-lowering therapies, or had stopped one or more concurrent oral hypoglycemic agent (OHA). Treatment response was based on the most recent eligible HbA1c, with the 3-month result used if the 6-month result did not meet the above criteria. Analysis of weight change was restricted to those who met the above criteria at 6 months (n = 443, w at 3 months was not assessed).

Statistical Analysis
Continuous Analysis
We assessed the relationship between baseline clinical markers of β-cell function and treatment response (HbA1c change post–GLP-1RA therapy) using least squares linear regression with adjustment for baseline HbA1c and co-treatment change (discontinuation of OHA and % change in insulin dose). Results were not adjusted for OHA dose change owing to lack of association with response (P = 0.3).

For determination of whether biomarkers added to knowledge of insulin treatment status, this analysis was repeated in subgroups defined by presence or absence of insulin co-treatment, with the inclusion of HOMA estimates of β-cell function (HOMA2%B) in non-insulin-treated participants. For determination of independence of autoantibody status and fasting C-peptide, this model was repeated with both C-peptide and autoantibody status as covariates. We assessed the relationship between clinical markers of β-cell function and weight loss post–GLP-1RA therapy using the same model with weight change (6 months – baseline) as the outcome variable.

Categorical Analysis
We assessed differences in adjusted mean change in HbA1c, weight, and insulin dose across subgroups defined by autoantibody and C-peptide status using univariate ANOVA with baseline HbA1c and treatment change as covariates. Fasting C-peptide subgroups were defined using previously reported thresholds for insulin requirement/type 1 diabetes (=0.25 nmol/L) and absence of “clinically significant” endogenous insulin secretion (≈0.08 nmol/L) (15).

Additional Analysis
Differences in HbA1c change at 3 and 6 months’ follow-up were assessed with the related-samples t test, with analysis restricted to those on treatment at both visits with >75% adherence and no change in glucose-lowering co-treatments.

Statistical analysis was performed using Stata Statistical Software: Release 13 (StataCorp, College Station, TX).

Laboratory Analysis
HbA1c and fasting glucose were measured in recruitment centers’ local laboratories (all are accredited National Health Service blood science laboratories). HbA1c measurement was standardized to the International Federation of Clinical Chemistry and Laboratory Medicine reference method procedure, and all repeated measurements within the same individual were analyzed within the same laboratory. C-peptide (blood and urine), urine creatinine (for UCPCR), and GAD/IA2 autoantibodies were measured in the Blood Sciences Department at the Royal Devon and Exeter Hospital, Exeter, U.K. C-peptide was measured using the E170 immuno- analyser from Roche Diagnostics (Manheim, Germany). GAD and IA2 were measured using commercial ELISA assays (RSR Limited, Cardiff, U.K.) and a Dynex
DSX automated ELISA system (Launch Diagnostics, Longfield, U.K.) and were considered positive if ≥97.5th centile of 500 adult control subjects (GAD >11 World Health Organization units/mL, IA2 >15 World Health Organization units/mL) as previously reported (16).

HOMA2%B and HOMA estimates of insulin sensitivity (HOMA2%S) were calculated in non-insulin-treated participants from fasting glucose and C-peptide using the HOMA2 calculator available from http://www.dtu.ox.ac.uk/homacalculator/ and are reported in electronic supplementary materials.

RESULTS
Participant Characteristics and Response to Therapy
Participant characteristics are shown in Table 1, and participant flow is detailed in Fig. 1. Mean (SD) reduction in HbA1c and weight was 14.9 (17.2) mmol/mol (1.4 [1.6%]) and 4.5 (5.6) kg. A total of 546 participants met criteria for inclusion in analysis (analysis on treatment HbA1c at 6 months n = 443 and at 3 months n = 103). HbA1c change at 3 and 6 months posttreatment was not different (mean change −15.7 vs. −15.1 mmol/mol, respectively, P = 0.2). Of participants, 64% were treated with liraglutide, 27% exenatide twice daily, and 9% exenatide once weekly.

Markers of Low Insulin Secretion Are Associated With Reduced Glycemic Response to GLP-1RAs
Markers of reduced insulin secretion were consistently associated with reduced glycemic response to GLP-1RA therapy (Table 2). Less response was seen in those with lower C-peptide, lower UCPCR, positive GAD or IA2 islet autoantibodies, longer duration of diabetes, and insulin cotreatment (P ≤ 0.01 for all). A 1 nmol/L decrease in fasting C-peptide was associated with 3.2 mmol/mol (0.3%) less HbA1c reduction post-GLP-1RA therapy (Supplementary Fig. 1); the presence of insulin cotreatment or islet autoantibodies was associated with an 8.5 and 10.0 mmol/mol (0.8 and 0.9%) reduction in glycemic response, respectively.

Baseline measurements associated with glycemic response were not associated with change in weight (P > 0.2 for all).

Participants With Severe Insulin Deficiency Had Markedly Reduced Glycemic Response to GLP-1RA Therapy
Participants with C-peptide <0.25 nmol/L (a previously reported threshold for insulin requirement and type 1 diabetes [15]) had markedly reduced glycemic response (Fig. 2A) (mean adjusted HbA1c change −2.1 [95% CI −10.2, 6.0] vs. −15.3 [−16.5, −14.0] mmol/mol [−0.2 vs. −1.4%], P = 0.002). Prevalence of C-peptide ≤0.25 nmol/L was low, with this characteristic predominantly found in insulin-treated participants (6.1% and 0.3% of insulin and non-insulin-treated participants, respectively).

A lower C-peptide threshold of ≤0.08 nmol/L (absence of “clinically significant” endogenous insulin [15]) identified fewer participants (3.4% of those insulin treated) with more marked lack of response to therapy (adjusted mean change 3.7 mmol/mol [95% CI −6.6, 14.0] vs. −15.2 mmol/mol [−16.4, −14.0] [0.3 vs. −1.4%], P = 0.0004).

Presence of Raised GAD and/or IA2 Islet Autoantibodies Is Independently Associated With Reduced Response to GLP-1RA Therapy
Glycemic response to GLP-1RA was also markedly lower in those who were GAD or IA2 antibody–positive (adjusted mean HbA1c change −4.6 mmol/mol [95% CI −10.3, 1.1] vs. −15.5 mmol/mol [−16.8, −14.2] [−0.4 vs. −1.4%], P = 0.0003) (Fig. 2B). The relationship between autoantibody status and response was not fully explained by differences in fasting insulin secretion: after adjustment for fasting C-peptide, autoantibodies were associated with an 8.1 mmol/mol (0.7%) reduction in glycemic response to GLP-1RA (P = 0.02). Eight percent of insulin-treated participants and 0.9% of non-insulin-treated participants were GAD or IA2 positive.

When analysis was restricted to autoantibody-negative participants, diabetes duration, insulin cotreatment, and fasting C-peptide remained associated with glycemic response (Supplementary Table 1).

Biomarkers of β-Cell Failure Remained Associated With Glycemic Response in Patients Receiving Insulin Treatment
Insulin treatment was strongly associated with other markers of β-cell failure, with longer diabetes duration, lower C-peptide–based measures, and higher proportion of positive autoantibodies seen in insulin-treated patients (P < 0.001 for all) (Supplementary Table 2). In those treated with insulin, C-peptide–based measures and autoantibodies remained predictive of glycemic response (Supplementary Table 3): a 1 nmol/L decrease in fasting C-peptide was associated with a 4.3 mmol/mol (0.4%) reduction in glycemic response (P = 0.01), and positive autoantibodies were associated with an 8.1 mmol/mol (0.7%) reduction in response (P = 0.03). However, these characteristics were not associated with response in non-insulin-treated participants (P for all >0.18) (Supplementary Table 4).

Insulin-Treated Patients With Low C-peptide or Positive Autoantibodies Have Reduced Response to GLP-1RA Therapy
Eleven percent of insulin-treated participants had either positive autoantibodies or low C-peptide (≤0.25 nmol/L).

Table 1—Participant baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (mmol/mol)</td>
<td>83 (17)</td>
<td>9.7 (1.6)</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>11.9 (3.7)</td>
<td>54</td>
</tr>
<tr>
<td>% male</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>% insulin treated</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>56 (10.4)</td>
<td>10.0 (6.6)</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>39.7 (7.5)</td>
<td>1.2 (0.6)</td>
</tr>
<tr>
<td>Fasting C-peptide (nmol/L) (n = 532)</td>
<td>3.6 (3.1)</td>
<td>3.7 (GAD only 3.1%, GAD and IA2 0.6%, IA2 only 0%)</td>
</tr>
</tbody>
</table>

Data are means (SD) unless otherwise indicated. N = 546 except where otherwise specified.
These participants had mean change in HbA1c after GLP-1RA therapy of 2.3 mmol/mol (95% CI −8.4, 3.7) (−0.2%) compared with −10.9 mmol/mol (−12.9, −8.8) (−1.0%) in other insulin-treated participants (Fig. 3). Antibody-positive/low C-peptide participants also had less reduction in insulin dose (17% vs. 40%, \( P = 0.006 \)), however, weight loss was similar (weight change at 6 months −4.2 vs. −5.0 kg, \( P = 0.05 \)) (Fig. 3). The clinical characteristics of insulin-treated participants with and without low C-peptide and/or positive autoantibodies were similar: mean BMI 36.6 vs. 39.7 kg/m\(^2\) (\( P = 0.07 \)), age at diagnosis 42.2 vs. 44.3 years (\( P =0 . 4 \)), diabetes duration 14.5 vs. 12.8 years (\( P = 0.3 \)), and time to insulin 5.8 vs. 5.9 years (\( P = 0.9 \)).

**CONCLUSIONS**

This study demonstrates that markers of \( \beta \)-cell failure are associated with reduced glycemic response to GLP-1 receptor analogs. Insulin-treated patients and those who have positive islet autoantibodies and/or low C-peptide have markedly reduced glycemic response to this treatment. Participants with these markers of \( \beta \)-cell failure had reduced glycemic response without additional weight loss, suggesting that they will derive less overall benefit from GLP-1RA treatment.

Our finding that markers of \( \beta \)-cell failure are associated with reduced response to GLP-1RA therapy is consistent with findings of previous studies. Research in smaller cohorts has suggested that those with lower blood C-peptide have less insulin secretion in response to GLP-1RA (17) and are less able to replace insulin with a GLP-1RA (18,19) and that low home postmeal urine C-peptide-to-creatinine ratio is associated with reduced glycemic response to liraglutide (20). Previous research demonstrating reduced response to GLP-1RA in those receiving insulin cotreatment or with longer diabetes duration is also consistent with our findings (3,21). In contrast, one study has demonstrated increased HbA1c reduction in insulin-treated patients with longer duration of diabetes, a finding principally driven by increased response to placebo in the short-duration comparator group (22).

To our knowledge, this is the first study to assess the relationship between islet autoantibodies and response to GLP-1RA therapy. The independence of autoantibody and C-peptide testing in our study may suggest that the mechanism, as well as the severity, of underlying \( \beta \)-cell failure is important to treatment response.

**Table 2** — The relationship between baseline markers of \( \beta \)-cell function and HbA\(_{1c}\) changes after GLP-1RA therapy

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Regression coefficient (95% CI)*</th>
<th>Standardized regression coefficient (95% CI)**</th>
<th>( T ) statistic***</th>
<th>Significance (( P ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes duration (years)</td>
<td>0.27 (0.08, 0.46)</td>
<td>0.10 (0.03, 0.18)</td>
<td>2.7</td>
<td>0.006</td>
</tr>
<tr>
<td>Insulin cotreatment</td>
<td>8.5 (5.3, 11.7)</td>
<td></td>
<td>5.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting C-peptide (nmol/L)</td>
<td>−3.2 (−5.2, −1.2)</td>
<td>−0.12 (−0.19, −0.04)</td>
<td>−3.1</td>
<td>0.002</td>
</tr>
<tr>
<td>UCPCR (nmol/mmol)</td>
<td>−0.56 (−1.0, −0.12)</td>
<td>−0.10 (−0.18, −0.02)</td>
<td>−2.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Autoantibody (GAD/IA2) positive</td>
<td>10.0 (3.1 − 16.8)</td>
<td></td>
<td>2.8</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*A negative regression coefficient denotes a greater HbA\(_{1c}\) reduction with a higher baseline value or presence of dichotomous state. **Number of SDs difference in HbA\(_{1c}\) change post–GLP-1RA for a 1-SD increase in baseline value. ***Regression coefficient/SE.
Further studies with more robust assessment of stimulated insulin secretion would be needed to test this hypothesis. The lack of glycemic response seen in this cohort where \( \beta \)-cell failure is marked is consistent with potentiation of \( \beta \)-cell insulin secretion being the major mechanism of glucose lowering by GLP-1RAs. These agents have additional non–\( \beta \)-cell dependent glucose-lowering effects on gastric emptying and suppression of glucagon; however, the relative contributions of these actions to glucose lowering remains unclear (23,24). While acute administration of GLP-1 markedly reduces meal-induced glucagon secretion, gastric emptying, and postprandial glucose even in C-peptide–negative type 1 diabetes (25), chronic treatment with GLP-1RAs appears to have only a small effect on plasma glucagon (26–30) and may have little effect on gastric emptying (31,32). This finding is consistent with poor glycemic effect of ongoing administration of GLP-1RAs in type 1 diabetes randomized controlled trials, where there appears to be a small reduction in insulin dose without improvement in glycemia (33,34).

**Strengths and Weaknesses**

A strength of this study is that we have prospectively examined a large number of participants in a real-world setting with detailed assessment at both baseline and follow-up. Our finding that many different markers of reduced \( \beta \)-cell function are consistently associated with reduced GLP-1RA response suggests that this is a robust finding.

Limitations of this study include that our major assessment of \( \beta \)-cell function is fasting blood or post–home meal urine C-peptide. These are affected by concurrent glucose, insulin sensitivity, and C-peptide clearance and therefore represent relatively crude indicators of underlying \( \beta \)-cell function (15). Physiological assessment of \( \beta \)-cell function would ideally involve measures after a standardized stimulus alongside correction for insulin sensitivity (35); however, these measures would not be feasible for clinical practice. \( \beta \)-Cell function and insulin sensitivity are inversely related (36,37). A role for \( \beta \)-cell failure (rather than insulin sensitivity) in reduced GLP-1RA glycemic response is supported by the direction of association (better insulin sensitivity being an unlikely cause of reduced treatment response) and finding associations for factors predominately associated with \( \beta \)-cell failure (autoantibodies [13], absolute insulin deficiency, insulin cotreatment and diabetes duration [14]). In addition, characteristics associated with insulin resistance (BMI, triglycerides, HDL, sex hormone–binding globulin, and HOMA2%S [38,39]) were not associated with glycemic response in this cohort \((P > 0.6 \text{ for all}) (\text{Supplementary Table 5}).

An additional potential limitation of fasting C-peptide measurement in a cohort including insulin-treated patients is the potential suppression of fasting C-peptide if concurrent insulin results in low fasting glucose (40). However, study participants had high fasting glucose at the time of C-peptide assessment, and the difference between those treated with and without insulin was small (mean fasting glucose 11.2 and 12.4 mmol/L, respectively).

**Clinical Implications**

The main clinical implications of this study are for use of GLP-1RA therapy in insulin-treated patients. Our study confirms that overall less glycemic response should be expected in those who are insulin treated. Where insulin-treated patients are known to be antibody positive or have low C-peptide, our results suggest that these patients are

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**Figure 2**—HbA1c change post–GLP-1RA therapy in those with and without severe insulin deficiency (C-peptide \( \leq 0.25 \text{ nmol/L}; n = 13 \text{ of 516}) (A) and positive GAD and/or IA2 antibodies \((n = 19 \text{ of 501}) (B). \text{Bar represents mean change, and error bars represent SE.}
unlikely to receive glycemic benefit from GLP-1RA therapy. This would be consistent with existing guidelines, which do not recommend GLP-1RA therapy for type 1 diabetes. When the antibody and C-peptide status is not known, the cost of testing needs to be balanced against an empirical trial of therapy, further larger studies to confirm the effect size and prevalence of these features would be needed to determine whether a testing for this reason would be cost-effective.

Our results show that a significant proportion of insulin-treated patients receiving these treatments in the U.K. have islet autoantibodies and/or low C-peptide, despite having a clinical diagnosis of type 2 diabetes. These patients could not be identified by their clinical features. This may relate to the obese (and relatively young) nature of our cohort, as U.K. guidelines restrict these treatments to the obese (1). Differentiating type 1 and type 2 diabetes is particularly difficult in younger obese individuals. Both the clinical presentation and course of autoimmune diabetes can be very different from classical type 1 diabetes in the obese (41).

Our study does not support the measurement of antibodies and C-peptide in non-insulin-treated patients, as prevalence of low C-peptide and positive autoantibodies was very low in this group and an association with response was not seen.

**Unanswered Questions and Future Research**

Our findings of reduced response in those with positive autoantibodies and severe insulin deficiency need replication, as they are driven by a marked difference in response in a relatively small number of participants. This would ideally be in the setting of a randomized trial targeting insulin-treated patients who are more likely to have these characteristics. Further research is also needed to assess whether insulin-treated patients with high antibody titres and/or absolute insulin deficiency have reduced response to all noninsulin glucose-lowering cotherapies. This is an important question given the increasing difficulties distinguishing type 1 and 2 diabetes as obesity becomes more prevalent and the lack of glycemic effect of noninsulin treatments in type 1 diabetes.

![Figure 3](image-url)
randomized controlled trials to date (33,34,42–44), which may relate to loss of endogenous insulin secretion even where a treatment’s mechanism of action appears unrelated (45).

Summary
In summary, markers of reduced insulin secretion are associated with less glycemic response to GLP-1RA therapy. C-peptide and autoantibodies represent potential biomarkers for the stratification of glucose-lowering treatment in insulin-treated diabetes.

Acknowledgments. The authors thank staff of the National Institute for Health Research Exeter Clinical Research Facility and National Institute for Health Research Diabetes Research Network for assistance with conducting the study. The authors thank Mandy Perry and technicians of the Blood Sciences Department, Royal Devon, and Exeter Hospital for assistance with laboratory analysis. The authors thank the members of the Predicting Response to Incretin Based Agents (PRIBA) study group (Supplementary Data) and all study participants.

Funding. The PRIBA study was funded by the National Institute for Health Research (U.K.) (DFR-2010-03-72) and supported by the National Institute for Health Research Clinical Research Network. A.G.J. was funded by a National Institute for Health Research Doctoral Research Fellowship and is a National Institute for Health Research Clinical Lecturer. T.J.M. is a National Institute for Health Research-CSO Clinical Scientist Fellow. B.M.S., A.V.H., B.A.K., and A.T.H. are core staff members of the National Institute for Health Research Exeter Clinical Research Facility. A.T.H. is a National Institute for Health Research Senior Investigator and a Wellcome Trust Senior Investigator.

The views given in this paper do not necessarily represent those of the National Institute for Health Research, the National Health Service, or the Department of Health.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. A.G.J., T.J.M., A.V.H., B.A.K., and A.T.H. researched data. A.G.J. and B.M.S. analyzed data. A.G.J. wrote the manuscript. T.J.M., B.M.S., A.V.H., C.J.H., B.A.K., and A.T.H. provided helpful discussion and reviewed and edited the manuscript. A.G.J. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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