Phase II study of tight glycaemic control in COPD patients with exacerbations admitted to the acute medical unit

John R H Archer,1 Shivani Misra,1 Marcus Simmgen,2 Paul W Jones,3 Emma H Baker1

ABSTRACT
Background: Hyperglycaemia is associated with poor outcomes from exacerbations of chronic obstructive pulmonary disease (COPD). Glycaemic control could improve outcomes by reducing infection, inflammation and myopathy. Most patients with COPD are managed on the acute medical unit (AMU) outside intensive care (ICU).

Objective: To determine the feasibility, safety and efficacy of tight glycaemic control in patients on an AMU.

Design: Prospective, non-randomised, phase II, single-arm study of tight glycaemic control in COPD patients with acute exacerbations and hyperglycaemia admitted to the AMU. Participants received intravenous, then subcutaneous, insulin to control blood glucose to 4.4–6.5 mmol/l. Tight glycaemic control was evaluated: feasibility, protocol adherence; acceptability, patient questionnaire; safety, frequency of hypoglycaemia (capillary blood glucose (CBG) <2.2 mmol/l and 2.2–3.3 mmol/l); efficacy, median CBG, fasting CBG, proportion of measurements/time in target range, glycaemic variability. Results were compared with 25 published ICU studies.

Results: 20 patients (10 females, age 71±9 years; forced expiratory volume in 1 s: 41±16% predicted) were recruited. Tight glycaemic control was feasible (78% CBG measurements and 89% of insulin-dose adjustments were adherent to protocol) and acceptable to patients. 0.2% CBG measurements were <2.2 mmol/l and 4.1% measurements 2.2–3.3 mmol/l. The study CBG and proportion of measurements/time in target range were similar to that of ICU studies, whereas the fasting CBG was lower, and the glycaemic variability was greater.

Conclusions: Tight glycaemic control is feasible and has similar safety and efficacy on AMU to ICU. However, as more recent ICU studies have shown no benefit and possible harm from tight glycaemic control, alternative strategies for blood glucose control in COPD exacerbations should now be explored.

Strengths and limitations of this study
This study was conducted when tight glycaemic control with insulin was feasible and acceptable to patients in a general ward setting. The efficacy and safety of tight glycaemic control with insulin in COPD patients with exacerbations on acute medical wards, towards testing this intervention in a randomised controlled trial.

INTRODUCTION
Half of all COPD patients admitted to hospital with exacerbations have elevated random blood glucose ≥7 mmol/l.1 2 This hyperglycaemia is caused not only by underlying glucose intolerance (5–18% have an established diagnosis of diabetes mellitus) or steroid use prior to hospital admission (18% patients) but also by the physiological stress of acute illness. Underlying mechanisms
include induction of peripheral insulin resistance by hypoxia, acidosis and systemic inflammation.

Acute hyperglycaemia during COPD exacerbations is associated with poor exacerbation outcomes. In a retrospective study, the risk of death or prolonged hospital stay during COPD exacerbations was increased by 15% for each 1 mmol/l increase in plasma glucose. In a prospective study of COPD patients with type II respiratory failure requiring non-invasive ventilation (NIV), acute hyperglycaemia, but not diabetes mellitus, was associated with NIV failure. In COPD patients on respiratory intensive care units (ICUs), hyperglycaemia was associated with ‘late failure’ (>48 h) of NIV after initial success.

A causative link between hyperglycaemia and poor outcomes from COPD exacerbations has not been proven. However, hyperglycaemia could be detrimental for COPD patients by driving infection, inflammation and myopathy. In COPD patients with exacerbations, acute hyperglycaemia is associated with increased likelihood of positive sputum cultures and increased risk of hospital-acquired pulmonary infection. Experimental hyperglycaemia raises plasma levels of pro-inflammatory cytokines, including IL-6, TNF-α and IL-18. In mouse models of hyperglycaemia, high glucose concentrations stimulate muscle-protein degradation and inhibit protein synthesis, which could contribute to muscle wasting.

If hyperglycaemia is truly detrimental during COPD exacerbations, then control of blood glucose could improve exacerbation outcomes. However, there is currently no evidence to inform practice in this patient group. Intensive insulin therapy to control blood glucose to physiological concentrations has been tested on ICUs in critically ill patients with acute hyperglycaemia. In mechanistic studies, tight glycaemic control with insulin reduced sepsis and the need for prolonged antibiotic therapy, prevented nosocomial infection, accelerated resolution of inflammation and reduced muscle catabolism. Despite these physiological benefits, a meta-analysis of 26 studies found no difference in mortality between patients undergoing tight glycaemic control and those receiving usual care. This may be explained by a sixfold increase in the rate of hypoglycaemia in patients undergoing intensive insulin therapy, which may have negated the beneficial effects of blood glucose control.

COPD patients requiring hospital admission for exacerbations are usually managed on general wards outside ICU. In this environment, blood glucose control is poor even in patients with an established diagnosis of diabetes mellitus. There are no randomised controlled trials to inform management of acute hyperglycaemia in patients without prior diabetes mellitus in this setting, and current best practice is based on clinical experience and judgement. Barriers to effective glycaemic control include fear of hypoglycaemia, inappropriate use of medication and lack of knowledge and training. The aim of our study was to develop a protocol for control of acute hyperglycaemia in COPD patients with exacerbations managed on acute medical wards and to determine the feasibility, safety and efficacy of this protocol.

METHODS

Study design

A prospective, non-randomised, phase II, single-arm study of tight glycaemic control was conducted in patients with acute exacerbations of COPD admitted to the acute medical unit (AMU) of St George’s Hospital. The AMU consists of 60 beds on two sites and has a nurse:patient care ratio of 1:6. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Medicines and Healthcare Regulatory Authority (UK) and National Research Ethics Committee. All participants gave written, informed consent for inclusion in the study.

Participants

Patients admitted to AMU with an acute exacerbation of COPD within the previous 48 h who gave written informed consent were entered into the study. COPD exacerbations were defined as acute deterioration in symptoms from baseline including one or more of: increased cough, wheeze, dyspnoea or sputum volume; change in sputum colour; or chest tightness. Exclusion criteria were: predicted short admission (<48 h); ICU admission; moribund or not for active treatment; type 1 diabetes mellitus; increased risk of hypoglycaemia (eg, renal or hepatic failure); reduced awareness of potential hypoglycaemia (low Glasgow coma score or treatment with β-blockers).

Assessment at study entry

Demographic information collected on all participants included age and gender.

Chronic obstructive pulmonary disease

Smoking history, prior diagnosis of COPD by respiratory specialist or spirometry, exacerbation symptoms, admission chest x-ray results, arterial blood gases, inflammatory markers (C reactive protein (CRP) and white cell count (WCC)) and discharge spirometry were recorded. Use of oral corticosteroids before or during hospital admission was noted.

Glucose tolerance

Body mass index, prior diagnosis of type 2 diabetes, HbA1C and capillary blood glucose (CBG) were recorded at study entry.

Clinical care during COPD exacerbations

Participants received care for their COPD exacerbations at the discretion of the treating clinician according to local guidelines. In patients with type 2 diabetes mellitus,
oral hypoglycaemic treatment was discontinued at study entry and recommenced prior to hospital discharge.

Protocol for glycaemic control
The aim of the protocol was to control CBG to 4.4–6.5 mmol/l using insulin as required.

Choice of blood glucose target
The majority of ICU studies of intensive insulin therapy have aimed to control blood glucose to physiological concentrations (>6.1 mmol/l). We selected a slightly higher blood glucose target of 4.4–6.5 mmol/l because of the unknown risk of hypoglycaemia in non-diabetic COPD patients with acute, but not critical, illness on general medical wards.

CBG measurements
Blood was obtained by fingerprick and analysed using a bedside glucometer (OneTouch Ultra2, LifeScan, High Wycombe, UK). The same device was used for all measurements in the study and was calibrated weekly.

CBG monitoring and insulin administration
Participants commenced three-hourly monitoring of CBG. When CBG was >6.5 mmol/l, an intravenous insulin infusion was started (50 IU soluble insulin in 50 ml NaCl 0.9%) at a predefined rate according to protocol. The insulin infusion rate was adjusted in response to hourly CBG measurements.

After at least 24 h of intravenous insulin, daytime (07:00–23:00) and night-time (23:00–07:00) insulin requirements were calculated and converted to a subcutaneous basal-bolus insulin regime. Basal insulin was given as once-daily insulin glargine or twice-daily insulin detemir. Insulin aspart was given three times daily with meals. CBG was monitored every 3 h, and insulin dose was adjusted daily to maintain blood glucose at 4.4–6.5 mmol/l. Subcutaneous insulin was continued until discharge or until respiratory function had returned to premorbid levels.

Hypoglycaemia
Hypoglycaemia was defined as CBG ≤3.3 mmol/l or as symptoms consistent with hypoglycaemia with CBG 3.4–6.6 mmol/l. On detection of hypoglycaemia, participants were immediately given oral or intravenous glucose. CBG was remeasured and glucose administered every 20 min until CBG >3.3 mmol/l and/or until symptoms had resolved. Intravenous insulin infusions were stopped immediately on detection of hypoglycaemia and restarted at half the previous infusion rate once the CBG was >6.5 mmol/l. During subcutaneous insulin treatment, CBG monitoring was continued hourly after hypoglycaemia until the next meal when insulin doses were reviewed.

Serum potassium
If serum potassium (K+) concentrations were <3.5 mmol/l at study entry, participants received oral or intravenous replacement to ensure a K+ concentration of ≥3.5 mmol/l prior to insulin administration. When insulin treatment was started, K+ was checked at 2, 4 and 6 h, then six-hourly during intravenous insulin and 24-hourly during subcutaneous insulin treatment. A K+ of <3.5 mmol/l during insulin treatment was treated with potassium replacement.

Outcome measures and analysis
Safety
The primary outcome measure for the study was the frequency of severe hypoglycaemia, defined as neuroglycopaenic symptoms (agitation (other than mild), drowsiness, confusion, ataxia) responsive to administration of carbohydrate. Secondary safety outcome measures were: frequency of symptomatic hypoglycaemia (CBG ≤3.3 mmol/l OR <2.2 mmol/l with autonomic symptoms (sweating, tremor, palpitations, tachycardia)); frequency of asymptomatic hypoglycaemia (CBG ≤3.3 mmol/l OR <2.2 mmol/l without symptoms); and frequency of hypokalaemia (serum potassium <3.5 mmol/l).

Efficacy
Efficacy of glycaemic control was assessed by: fasting morning CBG (median of all 06:00 CBG values); study CBG concentration (median of all CBG values); proportion of all CBG measurements/time spent in target range (4.4–6.5 mmol/l); hyperglycaemic index (median area under the curve of blood glucose over time above the hyperglycaemic threshold (6.5 mmol/l) calculated by the trapezoidal rule); and blood glucose variability (±SD from mean blood glucose).

Protocol adherence
CBG measurements were defined as adherent to protocol if taken within ±10 min of the time stated by the protocol. Treatment decisions were defined as adherent to protocol if an appropriate adjustment or non-adjustment of insulin treatment was made in response to CBG level. This was only assessed during intravenous insulin administration.

Patient acceptability
Patient acceptance of insulin treatment and CBG monitoring was assessed using a Likert Scale questionnaire.

Comparison to outcomes of ICU studies
Studies were identified from a systematic review of tight glycaemic control in critically ill patients on ICU. Original papers were obtained and searched to identify the target blood-glucose range and indicators of safety, efficacy and protocol adherence. For each indicator, mean or median values from individual studies were included in the analysis, and median, minimum and maximum values for all studies were calculated.

Statistics
Values with normal distribution are presented as mean±SD and compared using unpaired or paired t tests. Values that are not normally distributed are...
presented as median (IQR) and compared using Mann–Whitney U or Wilcoxon signed rank tests. Categorical variables are expressed as percentages and compared using χ² tests. A statistical analysis was carried out using SPSS for Windows, V.16.0. A p value of <0.05 was considered significant.

RESULTS

Study entry

Twenty participants (10 females, age 71±9 years) were enrolled in the study.

Lung function

Participants had a 65±43 pack-year smoking history. All had a formal diagnosis of COPD and discharge spirometry was forced expiratory volume in 1 s (FEV₁) 41±16% predicted, FEV₁/forced vital capacity% 55±18% (n=18). Exacerbations were characterised by increased dyspnoea (100%), wheeze (85%), chest tightness (70%) and cough (65%). Chest x-ray showed consolidation in 15% (100%), wheeze (85%), chest tightness (70%) and cough (65%). Chest x-ray showed consolidation in 15% patients, and 20% patients had type II respiratory failure (pH 7.23±0.15, Paco₂ 10.8±5.1 kPa). CRP was 21 (7–70) mg/l, and WCC was 12.7±7.3×10⁹/l. Fifty percent of participants were taking oral corticosteroids prior to hospital admission, and all patients received prednisolone 30 mg daily during the inpatient stay.

Glucose tolerance

Men weighed 89±24 kg, with a body mass index (BMI) of 31.5±9.1 kg/m², and women weighed 55±13 kg, with a BMI of 22.4±5.9 kg/m². Hba₁c was 6.2±0.5% in participants without prior diabetes (n=16) and 7.9±1.6% in participants with diabetes (n=4). Diabetes was treated with diet (n=6) or oral hypoglycaemics (n=4).

Insulin treatment

Twenty participants received insulin for a total of 90 days. Insulin was commenced when CBG was >6.5 mmol/l, either at (n=17) or within 3 h (n=3) of study entry. Participants received intravenous insulin for 28 (26–41) h at 55 (33–101) IU/24 h, and then subcutaneous insulin for 88 (48–123) h at 46 (20–74) IU/24 h. Insulin requirements by gender and for patients with and without diabetes mellitus are shown in Table 1. Male patients with and without diabetes received similar amounts of insulin, although blood glucose was less well controlled in the patients with diabetes. Outcome measures during intravenous and subcutaneous insulin treatment are compared in Table 2.

Insulin requirements in the first 24 h were significantly correlated with WCC (R=0.692, p=0.001), Hba₁c (R=0.593, p=0.006) and body weight (R=0.820, p=0.000), but not with age, lung function, CRP, arterial pH or Paco₂. Insulin requirements were not affected by oral corticosteroid use prior to hospital admission. On univariate analysis, weight was the only independent predictor of insulin requirement in the first 24 h.

Outcomes

Outcome measures for the whole group are summarised and compared with outcomes of ICU studies in Table 3. Twenty-five ICU studies with a blood glucose target range of 4.5±0.6 to 6.8±0.8 mmol/l were included in the analysis.

Safety

Participants had 1111 CBG measurements in total. There was a single episode of severe hypoglycaemia with confusion and CBG 2.3 mmol/l. This was caused by

### Table 1: Comparison of treatment and outcomes in participants with and without type 2 diabetes mellitus

<table>
<thead>
<tr>
<th></th>
<th>No diabetes (n=16)</th>
<th>Type 2 diabetes (n=4)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study entry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entry CBG (mmol/l)</td>
<td>8.7 (6.5–12.1)</td>
<td>11.9 (8.7–17.7)</td>
<td>0.211</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>6 male: 86±25</td>
<td>4 male: 93±26</td>
<td>0.762</td>
</tr>
<tr>
<td></td>
<td>10 female: 55±13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>6 male: 31.1±10</td>
<td>4 male: 32.0±9.3</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>10 female: 22.4±5.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous insulin (IU/24 h)</td>
<td>6 male: 74 (43–93)</td>
<td>4 male: 116 (57–146)</td>
<td>0.257</td>
</tr>
<tr>
<td></td>
<td>10 female: 36 (20–66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcutaneous insulin (IU/24 h)</td>
<td>5 male: 67 (34–81)</td>
<td>4 male: 90 (26–118)</td>
<td>0.571</td>
</tr>
<tr>
<td></td>
<td>7 female: 20 (16–53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBG &lt;2.2 mmol/l (%) measurements</td>
<td>0.2%</td>
<td>0%</td>
<td>0.674</td>
</tr>
<tr>
<td>CBG ≥3.3 mmol/l (%)</td>
<td>4.5%</td>
<td>2.0%</td>
<td>0.071</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study CBG (mmol/l)</td>
<td>5.8 (5.3–6.3)</td>
<td>6.9 (6.2–8.0)</td>
<td>0.022</td>
</tr>
<tr>
<td>06:00 CBG (mmol/l)</td>
<td>4.7 (4.2–5.2)</td>
<td>6.1 (5.8–6.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>Percentage of CBG measurements in target range</td>
<td>43</td>
<td>27</td>
<td>0.000</td>
</tr>
<tr>
<td>Percentage of time CBG in target range</td>
<td>44±12</td>
<td>28±9</td>
<td>0.024</td>
</tr>
<tr>
<td>Hyperglycaemic index</td>
<td>1.0 (0.6–1.2)</td>
<td>1.7 (1.6–2.2)</td>
<td>0.005</td>
</tr>
<tr>
<td>Glycaemic variability (mmol/l)</td>
<td>2.7±0.7</td>
<td>3.1±0.7</td>
<td>0.395</td>
</tr>
</tbody>
</table>

CBG: capillary blood glucose.
a protocol violation, where short-acting subcutaneous insulin was administered 2.5 h after eating rather than before the meal.

There were three episodes of symptomatic hypoglycaemia with blurred vision and sweating, CBG 2.8 (2.6–2.9) mmol/l. There were 41 episodes of asymptomatic hypoglycaemia, 39 with CBG 2.2–3.3 mmol/l (2.9 (2.6–3.2) mmol/l) and two with CBG <2.2 mmol/l (1.1 and 1.9 mmol/l). The percentage of CBG measurements <2.2 mmol/l was within the range seen in ICU studies, although CBG<3.3 mmol/l occurred more frequently in AMU (table 3).

Two (10%) patients each had one episode where CBG was <2.2 mM. In single-centre20 and multicentre21 intensive insulin trials, 18.7% and 6.8% patients respectively on intensive insulin therapy experienced severe hypoglycaemia.

All hypoglycaemic events were treated promptly with oral glucose, and the time from detection of hypoglycaemia to CBG >3.3 mmol/l was 35 (25–60) min. There was no evidence of clinical complications following hypoglycaemia.

Serum potassium was 4.2 (60.4) mmol/l at study entry and fell by 0.6 (60.3) mmol/l (p=0.000) during insulin treatment. Serum potassium fell below 3.5 mmol/l (3.0–3.4 mmol/l) in five patients and was corrected promptly to >3.5 mmol/l with oral or intravenous supplementation without clinical sequelae.

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Intravenous insulin</th>
<th>Subcutaneous insulin</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose in first 24 h of insulin treatment (IU)</td>
<td>54 (36–81)</td>
<td>34 (17–70)</td>
<td>0.001</td>
</tr>
<tr>
<td>Median dose of insulin (IU/24 h)</td>
<td>55 (33–101)</td>
<td>46 (20–74)</td>
<td>0.017</td>
</tr>
<tr>
<td>Safety</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no of CBG measurements</td>
<td>617</td>
<td>494</td>
<td></td>
</tr>
<tr>
<td>CBG &lt;2.2 mmol/l (percentage of measurements)</td>
<td>0.2</td>
<td>0.2</td>
<td>0.844</td>
</tr>
<tr>
<td>CBG ≤3.3 mmol/l (percentage of measurements)</td>
<td>5</td>
<td>3</td>
<td>0.001</td>
</tr>
<tr>
<td>Efficacy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study CBG (mmol/l)</td>
<td>6.0 (5.2–6.3)</td>
<td>6.4 (5.7–6.9)</td>
<td>0.044</td>
</tr>
<tr>
<td>06:00 CBG (mmol/l)</td>
<td>4.8 (4.3–5.8)</td>
<td>5.2 (4.5–6.2)</td>
<td>0.127</td>
</tr>
<tr>
<td>Percentage of CBG measurements in target range</td>
<td>41</td>
<td>39</td>
<td>0.480</td>
</tr>
<tr>
<td>Percentage of time CBG in target range</td>
<td>40±14</td>
<td>39±14</td>
<td>0.511</td>
</tr>
<tr>
<td>Hyperglycaemic index</td>
<td>0.9 (0.6–1.6)</td>
<td>1.0 (0.7–1.7)</td>
<td>0.836</td>
</tr>
<tr>
<td>Glycaemic variability (mmol/l)</td>
<td>2.4 (2.0–3.4)</td>
<td>2.8 (2.5–3.4)</td>
<td>0.301</td>
</tr>
</tbody>
</table>

CBG, capillary blood glucose.

### Table 3

Glycaemic indicators in studies of tight glycaemic control comparing outcomes on general medical wards (this study) with published studies performed in intensive care units19

<table>
<thead>
<tr>
<th></th>
<th>Chronic obstructive pulmonary disease patients on general medical wards</th>
<th>Published intensive care unit studies</th>
<th>No of intensive care unit studies using indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capillary glucose &lt;2.2 mmol/l (percentage of measurements)</td>
<td>0.2</td>
<td>0.1 (range 0–0.2)</td>
<td>12</td>
</tr>
<tr>
<td>Capillary glucose ≤3.3 mmol/l (percentage of measurements)</td>
<td>4.1</td>
<td>0.3 (range 0.1–2.1)</td>
<td>7</td>
</tr>
<tr>
<td>Efficacy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study CBG (mmol/l)</td>
<td>5.9 (IQR 5.4–6.5)</td>
<td>6.8 (range 5.7–8.5)</td>
<td>10</td>
</tr>
<tr>
<td>06:00 CBG (mmol/l)</td>
<td>4.8 (IQR 4.4–5.8)</td>
<td>6.5 (range 5.7–8.1)</td>
<td>5</td>
</tr>
<tr>
<td>Percentage of CBG measurements in target range</td>
<td>40</td>
<td>51 (range 29–69)</td>
<td>11</td>
</tr>
<tr>
<td>Percentage of time CBG in target range</td>
<td>41</td>
<td>53 (range 34–96)</td>
<td>9</td>
</tr>
<tr>
<td>Hyperglycaemic index</td>
<td>1.1 (IQR 0.7–1.6) (threshold 6.5 mmol/l)</td>
<td>1.0 (IQR 0.9–1.8) (threshold 6.0 mmol/l)</td>
<td>2</td>
</tr>
<tr>
<td>Glycaemic variability (mmol/l)</td>
<td>2.9 (IQR 2.2–3.3)</td>
<td>1.7 (IQR 1.3–2.3)</td>
<td>4</td>
</tr>
<tr>
<td>Protocol adherence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adherent CBG measurements (%)</td>
<td>82</td>
<td>53 (range 29–98)</td>
<td>4</td>
</tr>
<tr>
<td>Adherent insulin (intravenous) dose adjustments (%)</td>
<td>89</td>
<td>72 (range 56–100)</td>
<td>4</td>
</tr>
</tbody>
</table>

Values are median values for participants (this study) or for studies (ICU).19 The range is minimum—maximum. CBG, capillary blood glucose.
Glycaemic control in COPD

Efficacy
CBG was 9.7 (7.6–12.2) mmol/l at study entry, and all participants required insulin during the study. Study CBG concentrations, proportion of all CBG measurements/time spent in target range and hyperglycaemic index were within the ranges achieved by ICU studies (table 3). Fasting morning CBG values appeared lower than those seen in ICU studies, and CBG was more likely to be in the target range during the night (23:00–07:00, 58%) than during the day (7:00–23:00, 32%, p=0.001). Glycaemic variability was greater in COPD patients than on ICU. Glycaemic control was worse in participants with type 2 diabetes compared with non-diabetic patients (table 1).

Protocol adherence
Overall protocol adherence was at least as good as that seen in ICU studies (table 3). Of 1111 CBG measurements, 82% were adherent to protocol, 8% were early, and 10% were late. Of the late measurements, four (0.3% of all measurements) were ≤3.4 mmol/l and may have delayed identification of hypoglycaemia.

During intravenous insulin administration, 89% of treatment decisions were adherent to protocol. The non-adherent decisions resulted in: inappropriate cessation of insulin treatment (34%), inadequate insulin (7%), failure to change insulin appropriately (35%) and too much insulin (24%). One decision to give too much insulin was followed by asymptomatic hypoglycaemia.

Patient acceptability
Fourteen participants completed the questionnaire. In general, the study was well tolerated with 12 patients being willing to go through the same procedures again. Seven participants expressed concerns about risk of hypoglycaemia, two were unhappy with the number of fingerpricks required to measure CBG, and seven found that the study interrupted their sleep.

DISCUSSION
We used an intensive insulin protocol to control acute hyperglycaemia in patients admitted to an acute medical unit with exacerbations of COPD. Tight glycaemic control was acceptable to patients in this healthcare setting and was feasible, with 82% of CBG (CBG) measurements and 89% of insulin dose adjustment decisions being adherent to protocol. From a safety perspective, severe hypoglycaemia (CBG <2.2 mmol/l) was rare, but moderate hypoglycaemia (CBG 2.2–3.3 mmol/l) was more common. Median study and fasting morning CBG values and 40% of all measurements were in the target range of 4.4–6.5 mmol/l. Tight glycaemic control was therefore feasible in the acute medical unit and could be performed with similar safety and efficacy to tight glycaemic control in ICU (table 3).

Intensive insulin treatment to control acute hyperglycaemia has been extensively evaluated for patients with critical illness on ICU. Even in this setting, with a high nursing:patient ratio, intensive monitoring, controlled nutrition and lack of patient activity, blood glucose control is imperfect, achieving 29–69% blood glucose measurements within the target range (table 3). Prior to this study, we did not know whether control of acute hyperglycaemia to a target blood glucose range could be achieved in the acute medical unit (AMU), where lower nurse:patient ratios, less intensive monitoring and erratic nutrition and activity present barriers to glycaemic control. Despite these impediments, we found that tight glycaemic control with insulin was feasible in the AMU. Part of this success was directly attributable to care provided by a dedicated study physician. However, the majority of CBG measurements and insulin adjustments were made by clinical nurses supported by a written protocol and telephone advice. Other studies have found that computerised decision support further improved glycaemic control.22

A key aim of our study was to determine the safety of tight glycaemic control on the acute medical unit. Hypoglycaemia is the most important adverse reaction in patients treated with insulin. In critically ill patients undergoing tight glycaemic control on ICU, hypoglycaemia was independently associated with mortality,23 and the adverse effects of hypoglycaemia potentially offset the beneficial effects of insulin. Hypoglycaemia with CBG <2.2 mmol/l occurred with a similar frequency in our study to that seen in ICU studies (table 3). CBG measurements have been shown to be inaccurate in detecting hypoglycaemia in critically ill patients.24 It is therefore possible that our study underestimated the frequency of hypoglycaemia. There were no obvious immediate detrimental consequences of hypoglycaemia in participants in our study, but it was not designed to detect these. Patients on general wards may be less susceptible to immediate adverse effects of severe hypoglycaemia than ICU patients owing to less serious illness or more effective counter-regulatory responses. They should also potentially be able to report symptoms of low blood glucose early to prevent severe hypoglycaemia. However, in our study, the majority of hypoglycaemic episodes were asymptomatic, probably because hypoglycaemia was detected biochemically at concentrations above those at which autonomic activation and neuroglycopenic symptoms occur.25 Hypoglycaemia could also have long-term detrimental effects on cognitive function, although detection of this was beyond the scope of our study. In older patients with type 2 diabetes (mean 65 years), the risk of dementia was increased by 2.4% per year by occurrence of severe hypoglycaemia.26

An increase in glycaemic variability (excursions of blood glucose around the mean) may also be an adverse effect of tight glycaemic control with detrimental consequences. In ICU patients, increased glycaemic variability was associated with increased risk of death.27 Glycaemic variability activates oxidative stress,28 impairs endothelial-mediated vascular relaxation29 and
enhances hyperglycaemia-mediated release of pro-inflammatory cytokines. Patients in our study had considerable glycaemic variability, which was greater than that seen in ICU studies. Glycaemic variability was probably increased by insulin treatment, although we did not have an untreated comparator group to confirm this.

Blood-glucose control in COPD patients with exacerbations may provide some insights into mechanisms underlying acute hyperglycaemia. Weight was the only independent predictor of insulin requirements, indicating increased insulin resistance in heavier patients consistent with other patient groups. However, as most patients had a normal HbA1c, indicating normal glucose tolerance prior to hospital admission, and all patients required insulin even if underweight, chronic insulin resistance is not the only responsible mechanism. In COPD patients, blood-glucose control was better at night than in the morning, and fasting morning blood glucose was well below the range seen in ICU patients (table 3). This could be explained by nutritional intake during the day, but also could be an effect of oral corticosteroids. After a dose of oral prednisolone 30 mg, blood-glucose concentrations rise to a maximum concentration at around 9 h postdose. Study participants were prescribed prednisolone at 08:00 with a predicted maximal glycaemic effect at 17:00. In this small study in patients with a similar severity of acute illness, all of whom were taking a large dose of oral corticosteroids, it was not possible to detect an effect of illness severity on insulin resistance. In an ICU study, development of pneumonia in patients with severe injury was associated with increased insulin requirements.

We have shown that tight glycaemic control can be achieved on the acute medical unit with a similar safety and efficacy to that accomplished in intensive care. However, the major limitation of our study is that it is still not known whether and to what levels blood glucose should be controlled in this acute situation. In the absence of prospective, randomised controlled trials, current recommendations for management of acute hyperglycaemia outside the ICU setting are based on clinical experience and judgement. A consensus statement on inpatient glycaemic control from the American Association of Clinical Endocrinologists and American Diabetes Association identified ‘investigation of optimal and safe glycaemic targets in non-critically ill patients on medical and surgical wards’ as an important area for future research.

In summary, hyperglycaemia is associated with adverse outcomes from COPD exacerbations, and control of blood glucose could potentially improve management of infection, inflammation and myopathy that underlie exacerbations. Blood glucose can be controlled with insulin to a predefined target in patients on an acute medical unit with similar safety and efficacy to that achieved in ICU. However, this study was conducted when tight glycaemic control was standard practice in intensive care units (ICU), following the publication of two single-centre studies demonstrating reduced morbidity and mortality compared with conventional glycaemic control. More recent ICU studies have shown no benefit and possible harm from tight glycaemic control. In this context, our finding that tight glycaemic control in the acute medical unit has a similar safety and efficacy to ICU protocols indicates that we should explore alternative strategies for blood-glucose control in COPD exacerbations.

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Contributors JRHA: protocol design, regulatory approval, patient recruitment and assessment, data entry and analysis, drafting paper for publication, trial governance. SM: protocol design, regulatory approval, patient recruitment and assessment, data entry and analysis, reviewing drafts of paper. MS: protocol design, supervised patient recruitment and assessment, data analysis, reviewing drafts of paper. PWJ: study design, data analysis, contribution to writing paper. EHB: chief investigator with overall responsibility for the study; study and protocol design, regulatory approval, supervision of patient recruitment and assessment, data analysis, writing paper for publication. All authors approved the final submitted version of the manuscript.

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Glycaemic control in COPD


Phase II study of tight glycaemic control in COPD patients with exacerbations admitted to the acute medical unit

John R H Archer, Shivani Misra, Marcus Simmgen, Paul W Jones and Emma H Baker

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