Influence of captopril on symptomatic and hormonal responses to hypoglycaemia in humans

Kerstin M. Oltmanns, Eva Deininger, Peter Wellhoener, Bernd Schultes, Werner Kern, Esther Marx, Peter Dominiak,¹ Jan Born,² Horst L. Fehm & Achim Peters

Department of Internal Medicine I, ¹Institute of Pharmacology and ²Clinical Neuroendocrinology, Medical University of Luebeck, Germany, Ratzeburger Allee 160, 23538 Luebeck, Germany

Aims Hypoglycaemic symptoms and hormonal counter-regulation are of high importance to avoid the risk of severe hypoglycaemia in patients with diabetes mellitus. Various antihypertensive drugs, such as angiotensin-converting enzyme (ACE) inhibitors, have been suspected for a long time to reduce this response to hypoglycaemia in diabetic subjects. Although ACE inhibitors are approved for controlling diabetic complications, previous investigations regarding this putative side-effect are controversial.

Methods We performed clamp experiments in 16 healthy men lasting for 6 h each. The subjects were pretreated for 7 days with captopril $3 \times 25 \text{ mg day}^{-1}$ *vs* placebo in a randomized, double-blind, crossover study. Plasma glucose was decreased in a stepwise manner during a hypoglycaemic clamp session and counter-regulatory hormones [epinephrine (adrenaline), norepinephrine (adrenaline), ACTH, cortisol, glucagon], symptoms, and haemodynamic parameters (blood pressure, heart rate) were measured.

Results Counter-regulatory hormone concentrations significantly increased in both sessions (ACE inhibitor *vs* placebo) during hypoglycaemia. The rise of counter-regulatory hormones as well as symptom scores were equal under both ACE inhibitor and placebo treatment. Systolic blood pressure and heart rate increased (from 110 ± 3 *vs* 115 ± 3 mmHg to 132 ± 4 *vs* 133 ± 4 mmHg) whereas diastolic blood pressure slightly decreased (from 63 ± 2 *vs* 70 ± 3 mmHg to 61 ± 2 *vs* 64 ± 2 mmHg) independent of pretreatment. Systolic and diastolic blood pressure were significantly lower in the captopril session *vs* placebo ($P < 0.05$).

Conclusions Our results demonstrate that subchronic treatment with captopril does not attenuate symptomatic and hormonal response to hypoglycaemia. Thus, to patients at risk of hypoglycaemia who require antihypertensive or nephroprotective treatment, we would continue giving an ACE inhibitor.

Keywords: awareness, blood pressure, diabetes mellitus, heart rate, hormones, human, hypoglycaemic response, symptoms

Introduction

Failure of the symptomatic and hormonal response to hypoglycaemia is a serious problem in modern diabetes management. The inability to recognize warning symptoms, such as tremor, sweating, or palpitations before the

onset of neuroglycopenia is commonly termed hypoglycaemia unawareness [1]. In the past 20 years, several studies aimed to investigate the frequency of hypoglycaemia unawareness among insulin-treated patients. The most extensive evaluation of this issue is that of Hepburn *et al.* who administered a questionnaire to 628 patients participating in a follow-up study of diabetic complications [2]. They found that approximately 20% of patients claimed to have reduced awareness of hypoglycaemia. Physiological counter-regulation against hypoglycaemia includes a decline of insulin secretion and a rise in glucagon concentrations. The latter responses are frequently absent in patients with long lasting type 1 diabetes. Severe

Correspondence: Kerstin M. Oltmanns, MD, Medical Clinic I, Medical University of Luebeck, Germany, Ratzeburger Allee 160, 23538 Luebeck, Germany. Tel: +49 451 5003642; Fax: +49 451 5003640; E-mail: Oltmanns@medinf.mu-luebeck.de

Received 3 April 2002, accepted 11 October 2002.

hypoglycaemia usually results from the interplay of absolute or relative insulin excess and compromised glucose counter-regulation, and patients at high risk of severe hypoglycaemia have type 1 rather than type 2 diabetes [3, 4]. Additional risk factors are a long disease duration, low levels of glycosylated haemoglobin, autonomic neuropathy, or previous episodes of hypoglycaemia [4, 5].

Some antihypertensive drugs, such as angiotensin-converting enzyme (ACE) inhibitors, have been suspected to reduce hypoglycaemic symptoms and subsequently hormonal counter-regulation [6–9] which was demonstrated with the angiotensin I antagonist losartan [10]. These effects of subchronic ACE inhibitor treatment on symptomatic and hormonal responses to hypoglycaemia have not been investigated yet.

Methods

Subjects

Sixteen healthy Caucasian men participated in the study (age 26 ± 1 years; BMI 23.0 ± 0.4 kg m⁻²). Exclusion criteria were chronic or acute illness, current medication of any kind, smoking, alcohol or drug abuse, and diabetes or hypertension in first-degree relatives. Studies were approved by the local ethics committee, and each volunteer gave written informed consent.

Experimental design

The subjects were randomized to receive either captopril 25 mg three times daily or matching placebo for 7 days, according to a double-blind crossover study design. On day 8, after an additional morning dose of the respective agent, they participated in a stepwise hypoglycaemic clamp session. Following a recovery period of at least 4 weeks, the subjects were crossed to the alternative regimen for another 7 days, and on day 8 underwent a second clamp session identical to the first. To assess whether active treatment effectively blocked the renin-angiotensin-aldosterone system (RAAS), plasma renin concentrations were measured both before initiating treatment (day 1) and before administering the last dose (baseline period of day 8). In addition, on the same occasions, resting blood pressure and heart rate were recorded.

All subjects were requested to abstain from alcohol, not to perform any kind of exhausting physical activity, and to go to bed no later than 22.00 h on the day preceding the study. On the days of the study, subjects came to the medical research unit at 08.00 h after an overnight fast of at least 10 h. The experiments took place in a sound-attenuated room with the subjects lying on a bed with their trunk in an almost upright position

(about 60°). A cannula was inserted into a vein on the back of the hand, which was placed in a heated box (50–55 °C) to obtain arterialized venous blood. A second cannula was inserted into an antecubital vein of the contralateral arm. Both cannulas were connected to long thin tubes, which enabled blood sampling and adjustment of the rate of dextrose infusion from an adjacent room without the subject being aware. After a 1-h baseline period, insulin (H-insulin; Hoechst, Frankfurt, Germany) was infused at a continuous rate of $1.5 \text{ mU min}^{-1} \text{ kg}^{-1}$. A 20% dextrose solution was simultaneously infused at a variable rate to control plasma glucose concentrations. Arterialized blood was drawn at 5-min intervals to measure plasma glucose concentration (Glucose Analyser; Beckman Coulter Inc., Munich, Germany). Subsequently, plasma glucose concentrations were reduced in a stepwise manner to achieve four respective plateaus of 4.5, 3.8, 3.1 and 2.4 mmol l⁻¹. Each plateau was maintained for a 45-min period and the next lower plateau was induced gradually within the next 45 min. Blood samples for determination of insulin and counter-regulatory hormones were collected every 30 min. A semiquantitative symptom questionnaire was presented every 15 min. Subjects scored from 1 (none) to 5 (very severe) for each of the following symptoms: hunger, tremor, nervousness, palpitations, sweating, drowsiness, blurred vision, headache, weakness, and inability to concentrate. The total symptom score was calculated as the sum of values measured at each time point. Finally, at baseline and at the end of each glycaemic plateau, blood pressure and heart rate were measured automatically by machine (BC 40; Bos-Prestige 'Automatic'; Bosch und Sohn, Jungingen, Germany) simulating the Riva-Rocci procedure.

Assays

Plasma glucose was measured in duplicate using the glucose oxidase method [intra-assay coefficient of variation (CV) < 1.8%; interassay CV < 2.6%] on a glucose analyser (Beckmann Coulter Inc.). Blood samples for measurement of renin, insulin, and counter-regulatory hormones were immediately centrifuged and the supernatants stored at -24 °C until assay. RIAs were used to measure active plasma renin (intra-assay CV < 2.8%; inter-assay CV < 6.8%; Sanofi Diagnostics Pasteur, Marnes-la-Coquette, France), serum insulin (intra-assay CV < 5.8%; inter-assay CV < 7.5%; Kabi Pharmacia Diagnostics, Uppsala, Sweden) and glucagon (intra-assay CV < 4.9%; inter-assay CV < 6.1%; Serono Diagnostics, Freiburg, Germany). High pressure liquid chromatography was applied to measure plasma epinephrine (adrenaline; intra-assay CV < 2.9%; inter-assay CV < 4.2%) and norepinephrine (noradrenaline; intra-assay CV < 2.6%; inter-

assay CV < 3.9%; Chromosystems, Munich, Germany). Intact ACTH was measured using the immunoluminometric assay (intra-assay CV < 3.2% inter-assay CV < 5.1%; Henning, Berlin, Germany). Cortisol was determined by ELISA (intra-assay CV < 2.0%; inter-assay CV < 3.9%; Boehringer Mannheim Diagnostica, Mannheim, Germany).

Statistical analysis

Data are reported as mean $\pm$ SEM. We calculated the statistical power for epinephrine as the main outcome variable. A sample size of 16 subjects provided a statistical power of 0.89 to detect differences of epinephrine concentrations between active treatment and placebo smaller than 2000 pmol l⁻¹ (given an SD of 2500 pmol l⁻¹). The intra-subject effects of active treatment *vs* placebo on plasma glucose, dextrose infusion rate, hormones, symptoms, and haemodynamic parameters, were assessed by analyses of variance (ANOVA) for repeated measures. Analyses of covariance (ANCOVA) were performed to assess RAAS blockade, with values measured on day 1 serving as covariates. A *P* value < 0.05 was considered significant. All calculations were performed using the SPSS statistical programme (version 6.1; SPSS Inc, Chicago, IL, USA).

Results

Renin and blood pressure within the period of day 1 to day 8

In the captopril treatment sequence, plasma renin concentrations increased four-fold within the period of day 1 to day 8 (16 ± 1 pg ml⁻¹ to 60 ± 8 pg ml⁻¹) whereas no substantial alteration was found after placebo application (15 ± 2 pg ml⁻¹ to 13 ± 3 pg ml⁻¹; captopril *vs* placebo *P* < 0.001). This finding indicates that ACE inhibition suppresses the feedback inhibition of renin release by angiotensin II. Systolic blood pressure remained essentially unchanged during captopril treatment (118 ± 3 mmHg to 110 ± 3 mmHg) and was stable after placebo application (119 ± 3 mmHg to 115 ± 3 mmHg; captopril *vs* placebo, not significant). Diastolic blood pressure and heart rate were unaffected during both conditions.

Glucose and insulin on day 8

Baseline plasma glucose and serum insulin concentrations were nearly identical in both sessions (Table 1). After onset of the insulin infusion, plasma glucose decreased and serum insulin increased in the same manner in both protocols (Table 1). The dextrose infusion rate required to achieve target plasma glucose concentrations was

significantly lower after captopril treatment *vs* placebo (*P* < 0.05, Table 1).

Symptomatic and hormonal response to hypoglycaemia

Counter-regulatory hormone concentrations (epinephrine, norepinephrine, ACTH, cortisol, glucagon) significantly increased in both sessions during stepwise hypoglycaemia (*P* < 0.001, Table 1). The rise after captopril treatment was identical to the increase after placebo application. Symptom scores during hypoglycaemia rose significantly under both conditions and showed no difference between captopril or placebo treatment (Table 1).

Systolic blood pressure and heart rate increased during hypoglycaemia whereas diastolic blood pressure slightly decreased in both protocols (Table 1). Systolic and diastolic blood pressure were significantly lower after captopril treatment *vs* placebo (*P* < 0.05, Table 1).

Discussion

The present data demonstrate that captopril does not affect symptomatic or hormonal responses to hypoglycaemia in humans. ACE inhibitors have been found to be associated with severe hypoglycaemia in some case reports and in proximate cross-sectional studies [6–9]. These studies were criticized as not being representative because of their limited number of cases or because of their case-control study design [11–14]. By contrast, the EUCLID study, a placebo-controlled, randomized clinical trial in 530 patients with type 1 diabetes, did not find a treatment difference between lisinopril and placebo in hypoglycaemic events as assessed by glycosylated haemoglobin [15]. The authors stated no treatment difference in hypoglycaemic episodes. Despite the large number of patients examined in the EUCLID study, the number of actually reported hypoglycaemic events was 12 in all lisinopril-treated subjects whereas the placebo group complained of 10 episodes. Due to the small number of cases, these data do not represent sufficient evidence that ACE inhibitor treatment is precluded as a cause of hypoglycaemic events in diabetic patients. In a further study, the authors investigated the stress hormone responses to insulin-induced hypoglycaemia in eight healthy subjects who were treated with a single dose of enalapril or placebo [16]. They found no significant differences with respect to ACTH and cortisol concentrations. Unfortunately, the authors did not determine epinephrine or norepinephrine. Nevertheless, our results support the finding of the last named two studies that ACE inhibitors appear to be safe with respect to hypoglycaemia.

Supplementary evidence for a modulating role of ACE on hypoglycaemic events was recently published.

Table 1 Plasma glucose, serum insulin, dextrose infusion rate, counter-regulatory hormones, symptoms, and haemodynamic parameters during a stepwise hypoglycaemic clamp session on day 8 after onset of captopril or placebo application. Values taken at baseline (0 min) and at the end of each glycaemic plateau (90, 180, 270, 360 min).

	0	90	180	270	360	P value*	
						drug	time
Plasma glucose, serum insulin, and dextrose infusion rate							
Plasma glucose (nmol l ⁻¹)							
Captopril	5.3 ± 0.1 (5.1, 5.5)	4.5 ± 0.1 (4.3, 4.7)	3.9 ± 0.1 (3.7, 4.1)	3.0 ± 0.1 (2.8, 3.2)	2.4 ± 0.1 (2.2, 2.6)	0.23	< 0.001
Placebo	5.2 ± 0.1 (5.0, 5.4)	4.6 ± 0.1 (4.4, 4.8)	3.8 ± 0.1 (3.6, 4.0)	3.0 ± 0.1 (2.8, 3.2)	2.3 ± 0.1 (2.1, 2.5)		0.59
Insulin (pmol l ⁻¹)							
Captopril	39 ± 3 (32, 45)	602 ± 18 (564, 640)	605 ± 19 (565, 645)	557 ± 23 (508, 606)	597 ± 27 (539, 655)	0.56	0.12
Placebo	42 ± 7 (27, 57)	602 ± 18 (564, 640)	594 ± 16 (560, 628)	574 ± 19 (534, 614)	557 ± 27 (499, 615)		0.40
Dextrose infusion rate (mmol kg ⁻¹ min ⁻¹)							
Captopril	0.25 ± 0.01 (0.23, 0.27)	0.40 ± 0.02 (0.36, 0.44)	0.38 ± 0.03 (0.32, 0.44)	0.22 ± 0.03 (0.16, 0.28)	0.05 ± 0.02 (0.01, 0.09)	< 0.05	< 0.001
Placebo	0.24 ± 0.00 (0.24, 0.24)	0.44 ± 0.02 (0.40, 0.48)	0.43 ± 0.02 (0.39, 0.47)	0.28 ± 0.03 (0.22, 0.34)	0.09 ± 0.02 (0.05, 0.13)		0.12
Hormonal and symptomatic responses							
Epinephrine (pmol l ⁻¹)							
Captopril	220 ± 30 (156, 284)	410 ± 120 (154, 666)	1250 ± 310 (589, 1911)	2970 ± 460 (1990, 3950)	5970 ± 630 (4627, 7313)	0.83	< 0.001
Placebo	220 ± 20 (157, 283)	350 ± 90 (158, 542)	860 ± 120 (604, 1116)	3200 ± 460 (2220, 4120)	6510 ± 670 (5082, 7938)		0.42
Norepinephrine (nmol l ⁻¹)							
Captopril	1.3 ± 0.2 (0.9, 1.7)	1.6 ± 0.1 (1.4, 1.8)	1.8 ± 0.2 (1.4, 2.2)	2.1 ± 0.2 (1.7, 2.5)	2.7 ± 0.2 (2.3, 3.1)	0.18	< 0.001
Placebo	1.2 ± 0.2 (0.8, 1.6)	1.5 ± 0.2 (1.1, 1.9)	1.4 ± 0.1 (1.2, 1.6)	1.9 ± 0.2 (1.5, 2.3)	2.5 ± 0.2 (2.1, 2.9)		0.50
ACTH (pmol l ⁻¹)							
Captopril	4 ± 1 (2, 6)	4 ± 1 (2, 6)	6 ± 2 (2, 10)	12 ± 3 (6, 18)	21 ± 2 (17, 25)	0.89	< 0.001
Placebo	4 ± 1 (2, 6)	4 ± 0 (4, 4)	5 ± 1 (3, 7)	12 ± 2 (8, 16)	21 ± 1 (19, 23)		0.97

Cortisol (nmol l ⁻¹)									
Captopril	640 ± 80 (469, 810)	490 ± 40 (405, 575)	610 ± 60 (482, 738)	950 ± 70 (801, 1099)	1320 ± 50 (1213, 1427)	0.17	< 0.001	0.47	
Placebo	510 ± 50 (403, 617)	500 ± 40 (415, 585)	580 ± 50 (473, 687)	940 ± 70 (791, 1089)	1310 ± 80 (1140, 1480)				
Glucagon (ng l ⁻¹)									
Captopril	120 ± 10 (99, 141)	100 ± 10 (79, 121)	120 ± 10 (99, 141)	130 ± 10 (109, 151)	130 ± 10 (109, 151)	0.12	< 0.001	0.34	
Placebo	140 ± 10 (119, 161)	110 ± 10 (89, 131)	120 ± 10 (99, 141)	140 ± 10 (119, 161)	150 ± 10 (129, 171)				
Total symptom score									
Captopril	16.4 ± 1 (14.3, 18.5)	17.2 ± 1 (15.1, 19.3)	20.8 ± 2 (16.5, 25.1)	26.8 ± 2 (22.5, 31.1)	30.0 ± 2 (25.7, 34.2)	0.47	< 0.001	0.95	
Placebo	16.5 ± 1 (14.3, 18.6)	17.6 ± 1 (15.5, 19.7)	20.6 ± 2 (16.3, 24.9)	26.4 ± 2 (22.1, 30.7)	29.4 ± 2 (25.1, 33.7)				
<i>Haemodynamic parameters</i>									
Systolic blood pressure (mm Hg)									
Captopril	110 ± 3 (104, 116)	114 ± 2 (110, 118)	115 ± 3 (109, 121)	122 ± 3 (116, 128)	132 ± 4 (123, 141)	< 0.05	< 0.001	0.62	
Placebo	115 ± 3 (109, 121)	120 ± 2 (116, 124)	123 ± 2 (119, 127)	125 ± 2 (121, 129)	133 ± 4 (124, 142)				
Diastolic blood pressure (mm Hg)									
Captopril	63 ± 2 (59, 67)	66 ± 2 (62, 70)	64 ± 1 (62, 66)	60 ± 2 (56, 64)	61 ± 2 (57, 65)	< 0.05	< 0.001	0.30	
Placebo	70 ± 3 (64, 76)	72 ± 2 (68, 76)	70 ± 3 (64, 76)	62 ± 2 (58, 66)	64 ± 2 (60, 68)				
Heart rate (beats min ⁻¹)									
Captopril	61 ± 3 (55, 67)	61 ± 2 (57, 65)	67 ± 3 (61, 73)	68 ± 3 (62, 74)	70 ± 3 (64, 76)	0.69	< 0.001	0.25	
Placebo	58 ± 1 (56, 60)	64 ± 2 (60, 68)	71 ± 3 (65, 77)	73 ± 4 (64, 82)	67 ± 2 (63, 71)				

*ANOVA for repeated measures (except serum insulin: only glycaemic plateaus were included in ANOVA). Confidence intervals (95% level of confidence) are indicated in parentheses.

Pedersen-Bjergaard *et al.* found a significant relationship between serum ACE activity and the rate of severe hypoglycaemia, corresponding to a 3.5-times higher risk for patients in the highest quartile than those in the lowest quartile [17]. These data pertain to the group of diabetic patients who did not receive an ACE inhibitor. As ACE inhibitors suppress serum activity of ACE effectively, treated patients would be expected to have lower rates of severe hypoglycaemia. Pedersen-Bjergaard *et al.* failed to show a significant correlation at this point. However, this study investigated the incidence of severe hypoglycaemia in diabetic patients but did not explore counter-regulation after onset of hypoglycaemia.

An additional finding in our study was that the subjects under captopril treatment required lower dextrose infusion rates for achieving target plasma glucose concentrations. This indicates that they were more insulin-resistant during hypoglycaemia compared with the placebo-treated subjects. Although the drug has previously been suspected to improve insulin sensitivity, this hypothesis has been as controversial as the association between hypoglycaemia and ACE inhibitor treatment itself [18–21]. However, the influence of subchronic ACE inhibitor treatment on insulin action in the hypoglycaemic state has not been examined yet. Our data indicate that captopril reduces insulin sensitivity at least under hypoglycaemic conditions.

A limitation of our study might be that it was performed with healthy volunteers and not with diabetic patients. However, two issues have to be considered. Firstly, several authors reported interactions between treatment with ACE inhibitors and antidiabetic therapy, i.e. insulin or sulphonylureas [6, 7, 18, 19]. This putative connection would help to explain the contradictory findings of previous investigators who determined effects of ACE inhibitors in diabetic patients because the studied patients were not subclassified according to their antidiabetic treatment. Secondly, responses to hypoglycaemia are modified by several factors such as antecedent hypoglycaemic episodes, glycaemic control, hyperinsulinaemia, and autonomic neuropathy. Examining healthy volunteers allowed us to assess the drug effects on hypoglycaemic responses independent of potential confounding factors. However, this study certainly cannot provide sufficient evidence to stipulate drug choice in the treatment of patients with diabetes.

Our results show that captopril does not attenuate symptomatic and hormonal response to hypoglycaemia. As it has been demonstrated that the angiotensin I antagonist losartan has such side-effects [10], captopril might represent an important alternative drug for patients with hypoglycaemia unawareness. In the light of our results, we would furthermore recommend that an ACE inhibitor is given to prevent diabetic nephropathy

and to treat hypertension in diabetic patients at risk of hypoglycaemia.

We thank Dr Brian Frier (The Royal Infirmary of Edinburgh, Department of Diabetes) for revising the manuscript and providing invaluable advice and criticism. We also thank Dr Vincent McAulay (The Royal Infirmary of Edinburgh) for his invaluable suggestions. We gratefully thank Christiane Zinke and Steffi Baxmann for their expert laboratory assistance and Anja Otterbein for her organizational work.

References

- Gerich JE, Mookan M, Veneman T, Korytkowski M, Mitrakou A. Hypoglycemia unawareness. *Endocrinol Rev* 1991; **12**: 356–371.
- Hepburn DA, Patrick AW, Eadington DW, Ewing DJ, Frier BM. Unawareness of hypoglycaemia in insulin-treated diabetic patients: prevalence and relationship to autonomic neuropathy. *Diabet Med* 1990; **7**: 711–717.
- Cryer PE. Banting Lecture. Hypoglycemia: the limiting factor in the management of IDDM. *Diabetes* 1994; **43**: 1378–1389.
- The Diabetes Control and Complications Trial Research Group. Hypoglycemia in the Diabetes Control and Complications Trial. *Diabetes* 1997; **46**: 271–286.
- Gold AE, Frier BM, MacLeod KM, Deary IJ. A structural equation model for predictors of severe hypoglycaemia in patients with insulin-dependent diabetes mellitus. *Diabet Med* 1997; **14**: 309–315.
- Arauz-Pacheco C, Ramirez LC, Rios JM, Raskin P. Hypoglycemia induced by angiotensin-converting enzyme inhibitors in patients with non-insulin-dependent diabetes receiving sulphonylurea therapy. *Am J Med* 1990; **89**: 811–813.
- Rett K, Wicklmayr M, Dietze GJ. Hypoglycemia in hypertensive diabetic patients treated with sulphonylureas, biguanides, and captopril. *N Engl J Med* 1988; **319**: 1609.
- Herings RM, de Boer A, Stricker BH, Leufkens HG, Porsius A. Hypoglycaemia associated with use of inhibitors of angiotensin converting enzyme. *Lancet* 1995; **345**: 1195–1198.
- Morris AD, Boyle DI, McMahon AD, *et al.* ACE inhibitor use is associated with hospitalization for severe hypoglycemia in patients with diabetes. DARTS/MEMO Collaboration. Diabetes Audit and Research in Tayside, Scotland. Medicines Monitoring Unit. *Diabetes Care* 1997; **20**: 1363–1367.
- Deininger E, Oltmanns KM, Wellhoener P, *et al.* Losartan attenuates symptomatic and hormonal responses to hypoglycemia in humans. *Clin Pharmacol Ther* 2001; **70**: 362–369.
- Feher MD, Amiel SACE inhibitors and hypoglycaemia. *Lancet* 1995; **346**: 125–126.
- Kong N, Bates A, Ryder REACE inhibitors and hypoglycaemia. *Lancet* 1995; **346**: 125–127.
- Strachan MW, Frier BM. Risk of severe hypoglycemia in diabetes patients taking ACE inhibitors. *Diabetes Care* 1998; **21**: 470–472.
- Chaturvedi N, Fuller JH. ACE inhibitors and risk of hypoglycemia in people with diabetes. *Diabetes Care* 1998; **21**: 470–472.
- The EUCLID Study Group. Randomised placebo-controlled trial of lisinopril in normotensive patients with insulin-

- dependent diabetes and normoalbuminuria or microalbuminuria. *Lancet* 1997; **349**: 1787–1792.
- 16 Winer LM, Molteni A, Molitch ME. Effect of angiotensin-converting enzyme inhibition on pituitary hormone responses to insulin-induced hypoglycemia in humans. *J Clin Endocrinol Metab* 1990; **71**: 256–259.
 - 17 Pedersen-Bjergaard U, Agerholm-Larsen B, Pramming S, Hougaard P, Thorsteinsson B. Activity of angiotensin-converting enzyme and risk of severe hypoglycaemia in type 1 diabetes mellitus. *Lancet* 2001; **357**: 1248–1253.
 - 18 McMurray J, Fraser DM. Captopril enalapril, and blood glucose. *Lancet* 1986; **i**: 1035.
 - 19 Thamer M, Ray NF, Taylor T. Association between antihypertensive drug use and hypoglycemia: a case-control study of diabetic users of insulin or sulfonylureas. *Clin Ther* 1999; **21**: 1387–1400.
 - 20 Wiggam MI, Hunter SJ, Atkinson AB, *et al.* Captopril does not improve insulin action in essential hypertension: a double-blind placebo-controlled study. *J Hypertens* 1998; **16**: 1651–1657.
 - 21 Tillmann HC, Walker RJ, Lewis-Barned NJ, Edwards EA, Robertson MC. A long-term comparison between enalapril and captopril on insulin sensitivity in normotensive non-insulin dependent diabetic volunteers. *J Clin Pharm Ther* 1997; **22**: 273–278.