

## Increase in blood glucose concentration during antihypertensive treatment as a predictor of myocardial infarction: population based cohort study

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### Abstract

**Objective** To investigate the impact of an increase in blood glucose on the risk of developing myocardial infarction, with particular emphasis on people taking antihypertensive drugs.

**Design** Prospective population based cohort study.

**Setting** Uppsala, Sweden.

**Participants** 1860 men who had participated in 1970-3 at age 50 in a health survey aimed at identifying risk factors for cardiovascular disease and were re-examined at age 60 and then followed for 17.4 years.

**Main outcome measure** Myocardial infarction after age 60.

**Results** The incidence of myocardial infarction was significantly higher in men treated for hypertension than in those without such treatment (23% *v* 13.5%,  $P < 0.0001$ ). Participants who developed myocardial infarction after the age of 60 ( $n=253$ ) showed a significantly larger increase in blood glucose between age 50 and 60 than did those without myocardial infarction. In multivariate Cox proportional hazard models increase in blood glucose was an independent risk factor for myocardial infarction ( $P=0.0001$ ) in men receiving antihypertensive treatment at age 60 ( $n=291$ , mainly  $\beta$  blockers and thiazide diuretics) but not in those without such treatment. The impact of increase in blood glucose declined after inclusion of serum proinsulin concentrations at baseline but was still significant. A significant interaction existed between proinsulin concentration (a marker of insulin resistance) at baseline and antihypertensive treatment on increase in blood glucose.

**Conclusions** Increase in blood glucose between the ages of 50 and 60 and baseline proinsulin concentration were important risk factors for myocardial infarction in men receiving antihypertensive treatment, indicating that both an insulin resistant state and the metabolic impact of  $\beta$  blockers and diuretics increase the risk of myocardial infarction.

### Introduction

During the past decade several studies have shown that a large proportion of patients with hypertension are

resistant to insulin stimulated glucose uptake and are hyperinsulinaemic compared with normotensive controls.<sup>1-4</sup> Treatment with  $\beta$  blockers or thiazide diuretics further increases insulin resistance,<sup>5, 6</sup> thereby increasing the risk of developing type 2 diabetes mellitus or impaired glucose tolerance.<sup>7-11</sup> Diabetes mellitus and impaired glucose tolerance are both associated with an increased risk of coronary heart disease,<sup>12, 13</sup> but whether these conditions when induced by  $\beta$  blockers or thiazides are associated with increased risk of coronary heart disease is unknown.

We investigated the impact of variations in fasting blood glucose, blood pressure, and body mass index between the ages of 50 and 60 on the risk of developing a myocardial infarction after this 10 year period (mean follow up 17.4 years) in a population based sample of men. We paid special attention to the men receiving antihypertensive treatment, with the hypothesis that a drug induced increase in fasting blood glucose would increase the risk of myocardial infarction.

### Methods

The Uppsala longitudinal study of men has been extensively described.<sup>14</sup> Between 1970 and 1974, 2322 men aged 50 underwent a physical examination, including measurement of height, weight, pulse rate, blood pressure, fasting blood glucose, and serum insulin. In 1980 total cholesterol, high density lipoprotein cholesterol, triglycerides, and low density lipoprotein cholesterol were analysed in serum that had been frozen since the baseline examinations. In 1995-8 the concentrations of intact and 32-33 split proinsulin were analysed in all available serum samples ( $n=1335$ ).

Between 1980 and 1984 the investigators re-examined 1860 eligible men (at age 60) who had participated in the first survey. This examination included anthropometric data, blood pressure, and blood samples. The investigators collected data on admissions to hospital or death from myocardial infarction (ICD-9 code 410) or angina pectoris (ICD 413) from the official cause of death and hospital registers.

We based our study on the 1860 men who participated in both the baseline investigations at age 50 and the re-examination at age 60. We excluded participants who had been admitted to hospital for myocardial

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infarction before the examination at age 60, as well as those with angina pectoris during the follow up period.

We grouped the population into participants receiving and not receiving antihypertensive treatment at age 60. Of the 316 men who had received antihypertensive treatment, 82 had a non-selective  $\beta$  blocker, 65 had a selective  $\beta$  blocker, 66 had a thiazide diuretic, and 103 received a combination of  $\beta$  blocker and thiazide diuretic. Forty one participants had hydralazine added to the treatment. After exclusion of participants with myocardial infarction or angina pectoris before the age of 60, 291 men in the group with antihypertensive treatment and 1358 men in the group without such treatment remained at age 60.

### Statistical analysis

We evaluated differences in metabolic characteristics between groups by factorial analysis of variance, and we used stepwise multiple Cox proportional hazard analysis to evaluate the independent power of the risk factors (see [bmj.com](http://bmj.com) for more details).

### Results

Table 1 presents metabolic characteristics at age 50, changes in selected variables between age 50 and 60, and the effect of these variables on the risk of having a myocardial infarction after age 60. Participants being treated for hypertension at age 60 showed higher concentrations of indices of the metabolic syndrome, such as serum proinsulin, fasting blood glucose, and serum triglycerides, as well as a larger increase in fasting blood glucose between the ages of 50 and 60 compared with those without such treatment.

Participants who developed myocardial infarction after the age of 60 ( $n=253$  over the 17.4 year follow up) showed a significantly larger increase in fasting blood glucose than those who did not develop myocardial infarction (0.28 (SD 1.61) mmol/l *v* -0.04 (0.94) mmol/l,  $P=0.001$ ). The incidence of myocardial infarction was significantly higher in men treated for hypertension than in those without treatment (67/291

(23.0%) *v* 183/1358 (13.5%),  $P<0.0001$ ). Further analysis of the changes between age 50 and age 60 showed that after adjustment for baseline values an increase in fasting blood glucose predicted myocardial infarction in the group receiving antihypertensive treatment but not in the group without such treatment (see [bmj.com](http://bmj.com)).

We included all variables that were significant predictors of subsequent myocardial infarction in stepwise multivariate Cox proportional hazard models (table 2). In the group being treated with antihypertensive drugs at age 60 the ratio of low density lipoprotein to high density lipoprotein cholesterol at age 50 and increase in fasting blood glucose were significant risk factors in the multivariate model. The impact of increase in blood glucose declined after addition of proinsulin to the models, but it was still a significant predictor of future myocardial infarction. In the group not receiving antihypertensive drugs the ratio of low density lipoprotein to high density lipoprotein cholesterol, serum proinsulin at age 50, and increase in systolic blood pressure were independent predictors of subsequent myocardial infarction, but increase in fasting blood glucose was not a risk factor in this group.

We also performed the analysis in only the 977 participants for whom proinsulin concentrations were available. This reduction in sample size did not substantially change the results.

Serum proinsulin at age 50 was significantly correlated with increase in fasting blood glucose in the group with antihypertensive treatment ( $r=0.32$ ,  $P<0.0001$ ). A significant interaction also existed between proinsulin and antihypertensive treatment regarding increase in fasting blood glucose ( $P=0.0004$ ). The men with the highest proinsulin concentrations at baseline showed the greatest increases in fasting blood glucose concentrations between the ages of 50 and 60, especially in the group receiving antihypertensive treatment during this period (figure). A significant relation ( $r=0.47$ ,  $P<0.0001$ ) existed between the change in fasting blood glucose and the average of

**Table 1** Metabolic characteristics at age 50, changes between age 50 and 60, and effect of these variables on risk of having a myocardial infarction after age 60

Characteristic	Antihypertensive treatment (n=291)		No antihypertensive treatment (n=1358)		P value†
	Mean (SD)	Hazard ratio* (95% CI)	Mean (SD)	Hazard ratio* (95% CI)	
<b>Age 50 (baseline)</b>					
Blood glucose (mmol/l)	5.09 (0.72)	1.06 (0.83 to 1.30)	4.96 (0.63)	1.12 (0.98 to 1.26)	0.008
Body mass index (kg/m <sup>2</sup> )	26.0 (3.41)	1.16 (0.93 to 1.44)	24.6 (2.99)	1.20 (1.03 to 1.38)	<0.0001
Immunoreactive insulin ( $\mu$ U/ml)	14.4 (7.71)	1.05 (0.80 to 1.38)	12.4 (7.30)	1.07 (0.91 to 1.26)	<0.0001
Intact proinsulin (pmol/l)	3.69 (3.92)	1.59 (1.20 to 2.10)	2.78 (2.69)	1.54 (1.28 to 1.84)	0.0004
Split proinsulin (pmol/l)	8.98 (9.08)	1.48 (1.12 to 1.94)	6.59 (5.84)	1.26 (1.04 to 1.52)	<0.0001
LDL cholesterol (mmol/l)	5.39 (1.29)	1.36 (1.08 to 1.66)	5.23 (1.24)	1.35 (1.18 to 1.53)	0.08
HDL cholesterol (mmol/l)	1.32 (0.37)	0.77 (0.55 to 1.06)	1.38 (0.38)	0.76 (0.63 to 0.91)	0.04
LDL:HDL cholesterol ratio	4.44 (1.96)	1.29 (1.09 to 1.48)	4.12 (1.59)	1.44 (1.25 to 1.65)	0.008
Serum triglycerides (mmol/l)	2.10 (1.15)	1.16 (0.88 to 1.35)	1.84 (1.12)	1.29 (1.12 to 1.48)	<0.0001
Systolic blood pressure (mm Hg)	153 (20.9)	1.02 (0.83 to 1.25)	128 (13.6)	1.22 (1.02 to 1.45)	<0.0001
Diastolic blood pressure (mm Hg)	96 (11.7)	1.07 (0.85 to 1.33)	80 (8.50)	1.26 (1.04 to 1.51)	<0.0001
<b>Change from age 50 to 60</b>					
Glucose	0.38 (1.51)	1.38 (1.16 to 1.60)	-0.06 (0.94)	1.08 (0.92 to 1.26)	<0.0001
Body mass index	0.66 (1.96)	0.85 (0.68 to 1.08)	0.46 (1.71)	0.94 (0.81 to 1.10)	0.07
Systolic blood pressure	0.5 (24.2)	0.96 (0.80 to 1.16)	12 (15.5)	1.22 (1.04 to 1.43)	<0.0001
Diastolic blood pressure	-3 (12.4)	0.90 (0.74 to 1.10)	6 (8.70)	0.92 (0.78 to 1.09)	<0.0001

LDL=low density lipoprotein; HDL=high density lipoprotein.

\*For risk of having myocardial infarction after age 60. Hazard ratios for a one standard deviation variation in the variables.

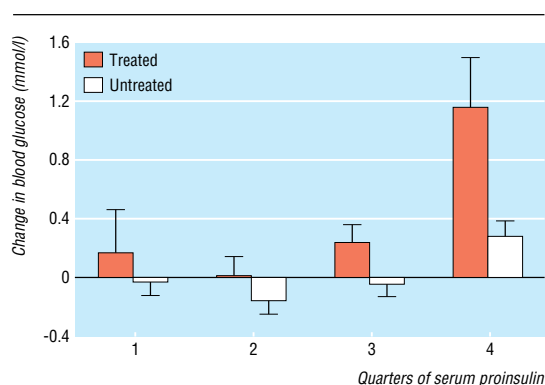
†P value for differences between means.

**Table 2** Stepwise multivariate Cox proportional hazard analysis of variables identified in univariate analysis as risk factors for myocardial infarction after age 60

Risk factor	Excluding serum proinsulin		Including serum proinsulin	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
<b>Antihypertensive treatment (n=291)</b>				
Change in glucose	1.50 (1.25 to 1.78)	0.0001	1.29 (1.06 to 1.55)	0.01
LDL:HDL cholesterol ratio	1.32 (1.10 to 1.51)	0.004	1.28 (1.05 to 1.49)	0.02
Intact proinsulin	NA	NA	1.33 (1.01 to 1.78)	0.05
<b>No antihypertensive treatment (n=1358)</b>				
Change in glucose	1.04 (0.86 to 1.24)	0.72	0.99 (0.81 to 1.21)	0.98
LDL:HDL cholesterol ratio	1.42 (1.22 to 1.67)	<0.0001	1.39 (1.18 to 1.61)	0.0001
Change in systolic blood pressure	1.24 (1.03 to 1.48)	0.02	1.26 (1.01 to 1.55)	0.04
Intact proinsulin	NA	NA	1.38 (1.13 to 1.67)	0.0016

LDL=low density lipoprotein; HDL=high density lipoprotein; NA=not applicable.

\*Hazard ratios for a one standard deviation (given in table 1) variation in the variables.



Mean (plus standard error of the mean) change in blood glucose between age 50 and 60 according to serum proinsulin levels at age 50 in the groups with and without antihypertensive treatment at age 60

fasting blood glucose at age 50 and 60, indicating that no regression towards the mean occurred.

## Discussion

Our study shows that an increase in fasting blood glucose between the ages of 50 and 60 and high concentrations of circulating proinsulin are important risk factors for development of acute myocardial infarction after age 60 in men receiving antihypertensive treatment with  $\beta$  blockers, thiazide diuretics, or both. The relation of insulin resistance to coronary heart disease has been well established,<sup>15</sup> but the influence of the metabolic changes induced by antihypertensive treatment on the risk of myocardial infarction has been questioned. In contrast to our data, Samuelsson et al found that development of diabetes mellitus related to antihypertensive treatment did not increase the risk of coronary events.<sup>16</sup>

In our study the incidence of myocardial infarction was significantly higher in the group with antihypertensive treatment than in participants without such treatment at age 60. A Swedish study presented similar findings.<sup>17</sup> We also found that an increase in fasting blood glucose, a high ratio of low density lipoprotein to high density lipoprotein cholesterol, and high serum proinsulin at baseline were significant risk factors for myocardial infarction after age 60 in the group with antihypertensive treatment. In spite of the treatment, the blood pressure at age 60 was not normalised, but neither baseline blood pressure nor achieved blood

pressure at age 60 was related to the incidence of myocardial infarction.

In the multivariate analysis the impact of increase in fasting blood glucose on the risk of myocardial infarction declined when proinsulin was added to the models, indicating that insulin resistance at baseline, for which proinsulin may be a marker,<sup>18, 19</sup> partly explains the predictive power of the induced increase in fasting blood glucose in hypertensive patients. However, when the impact of insulin resistance (proinsulin concentration) was taken into account the deleterious effect of the increase in fasting glucose was still significant, indicating that both insulin resistance and the metabolic consequences of the antihypertensive treatment could be deleterious. Blood glucose may also directly affect the development of arteriosclerosis by impairing endothelial function.

A limitation of our study is that we analysed proinsulin in only 55% of the sample. However, when we restricted the Cox proportional hazard analysis to participants with proinsulin determinations we obtained essentially the same, still significant, results, implying that no bias was introduced by the limited number of observations with proinsulin determinations. Another limitation of this study is that the results are not generalisable as the sample was restricted to 50 to 60 year old white men.

### What is already known on this topic

Patients with hypertension are resistant to insulin stimulated glucose uptake and are hyperinsulinaemic compared with normotensive controls

Treatment with  $\beta$  blockers and thiazide diuretics further increases insulin resistance, thereby increasing the risk of developing type 2 diabetes mellitus or impaired glucose tolerance

The influence of metabolic changes induced by antihypertensive treatment on the risk of myocardial infarction has been questioned

### What this study adds

Men who received antihypertensive treatment showed a larger increase in blood glucose during a 10 year period than those without such treatment

Increase in blood glucose during antihypertensive treatment was a significant, independent risk factor for myocardial infarction in men with an insulin resistant state at baseline

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Ethical approval: Local ethics committee of the medical faculty at Uppsala University, Uppsala, Sweden.

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## Ethnographic study of incidence and severity of intravenous drug errors

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### Abstract

**Objectives** To determine the incidence and clinical importance of errors in the preparation and administration of intravenous drugs and the stages of the process in which errors occur.

**Design** Prospective ethnographic study using disguised observation.

**Participants** Nurses who prepared and administered intravenous drugs.

**Setting** 10 wards in a teaching and non-teaching hospital in the United Kingdom.

**Main outcome measures** Number, type, and clinical importance of errors.

**Results** 249 errors were identified. At least one error occurred in 212 out of 430 intravenous drug doses (49%, 95% confidence interval 45% to 54%). Three doses (1%) had potentially severe errors, 126 (29%) potentially moderate errors, and 83 (19%) potentially minor errors. Most errors occurred when giving bolus doses or making up drugs that required multiple step preparation.

**Conclusions** The rate of intravenous drug errors was high. Although most errors would cause only short term adverse effects, a few could have been serious. A combination of reducing the amount of preparation on the ward, training, and technology to administer

slow bolus doses would probably have the greatest effect on error rates.

### Introduction

In most European countries, nurses generally prepare and administer intravenous drugs prescribed by doctors. Administration of intravenous therapy is associated with considerable risk, and the UK Department of Health has targeted this to increase patient safety.<sup>1</sup> Similar initiatives have been proposed in the United States.<sup>2</sup>

Little prospective research has been done into the incidence, causes, and severity of intravenous drug errors. Single site studies carried out on one or two wards have reported errors in preparing and administering intravenous drugs of 13%-84%,<sup>3-6</sup> but the studies used different definitions and did not assess the severity of errors. Epidemiological studies using retrospective record review have shown that adverse drug events are common but have not provided details of the type of errors.<sup>7-10</sup>

### Participants and methods

We used a purposive sampling strategy to select study hospitals and study wards, with the aim of exploring the preparation and administration of intravenous



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