Hypoglycaemia
Islet cell tumors

Pánczél Pál
Hypoglycaemia

- Hypoglycaemia is a patophysiologic state and not a disease. It warrants diagnosis of the underlying illness causing the low plasma glucose level (2.5-3.9 mmol/l)
- The plasma glucose level is maintained within narrow bound in spite of intermittent food ingestion and period of fasting, as the net balance between the rates of the glucose production and utilization.
- Food ingestion → elevation of plasma glucose → elevation of plasma insulin → decrease of hepatic glucose production + increase of peripheral glucose disposal (muscle, adipose tissue, liver) → decrease of plasma glucose → decrease of plasma insulin → increase of hepatic glucose production (glycogenolysis, followed by gluconeogenesis).
• In the post absorptive phase the glucose production and utilization is about 2 mg/kg/min.

• The maintained blood glucose level in the post absorptive (i.e. in the fasting) state is 3,9 – 6,1 mmol/l.

• In the post absorptive phase the glucose production is primarily from hepatic glycogenolysis (75%). Only 25% is from gluconeogenesis. Hepatic glycogen stores exhausted after 24-36 hours of fasting. Glycogenolysis is stimulated by glucagon, epinephrine and inhibited by insulin. Several enzymes are involved in this process, abnormalities of these enzymes cause hypoglycaemia (von Gierke’s disease).

• The generation of glucose from non-carbohydrate sources is called gluconeogenesis. Lactate and pyruvate (58%), glycerol (13%), amino acids /alanine, glutamine/ (29%) are the main sources for gluconeogenesis.

• Defects in gluconeogenesis can induce hypoglycaemia (the most important cause of this is the alcohol intake, which inhibits several important gluconeogenic enzymes).
From a practical point of view …

- **Hypoglycaemia in diabetes**: all episodes of an abnormally low plasma glucose concentration that expose the individual to potential harm.

- It is not possible to state a single plasma glucose concentration that defines hypoglycaemia because the glycaemic thresholds for responses to falling glucose levels, including those for symptoms, are dynamic.

- It is recommended that people with diabetes should become concerned about the possibility of developing hypoglycaemia at a self monitored plasma glucose concentration of <, or = 3,9 mmol/l.

- **So**: self monitored 3,9 mmol/l is the glucose alert value for preventing hypoglycaemia in diabetic patients treated with insulin or insulin secretagogues: the patient has to consider actions ranging from repeating the measurement in the short term, through avoiding exercise or driving, to carbohydrate ingestion and adjustments of the treatment regimen.
• Normal limits of plasma glucose levels in the fasting phase:
  **3,9-6,1 mmol/l** (in non-diabetic individuals)

• **3,9 mmol/l** is
  • (1) the glycaemic threshold for activation of the glucose counter-regulatory systems, and
  • (2) low enough to cause reduced glucose counter-regulatory responses to subsequent hypoglycaemia in non-diabetics and
  • (3) higher than the glucose levels required to produce symptoms in non-diabetic individuals (2,8 – 3,1 mmol/l) and
  • (4) substantially higher than those that do so in people with well-controlled diabetes, although
  • (5) individuals with poorly controlled diabetes sometimes have symptoms at higher glucose levels.
Langerhans’ islet

~ 3,000 cells
75% beta-cells (insulin)
25% other (A,D,PP) cells

Micrograph: Lelio Orci, Geneva
## Hormonal control of glucose homeostasis

<table>
<thead>
<tr>
<th>hormone</th>
<th>hepatic glucose production</th>
<th>extra hepatic glucose utilization</th>
<th>basal glucose production</th>
<th>relative importance to recovery from IIH</th>
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<tbody>
<tr>
<td>Insulin</td>
<td>neg</td>
<td>pos</td>
<td>neg</td>
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<tr>
<td>Glucagon</td>
<td>pos</td>
<td>0</td>
<td>pos</td>
<td>+++</td>
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<td>Epinephrine</td>
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<td>neg</td>
<td>0</td>
<td>+</td>
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<td>Cortisol</td>
<td>pos</td>
<td>neg</td>
<td>pos</td>
<td>0</td>
</tr>
<tr>
<td>GH</td>
<td>pos</td>
<td>neg</td>
<td>0</td>
<td>0</td>
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</table>
Clinical evaluation of hypoglycaemia

Common causes of hypoglycaemia

- Medications (insulin, sulphonylureas)
- Ethanol
- Factitious
- Insulinoma
- Non-islet-cell tumor (insulin like growth factor)
- Multifactorial in sick patient
- Islet dysplasia in infancy
- Nesidioblastosis
What is to be done with a patient with suspected hypoglycaemia

• 20 ml of blood should be withdrawn → glucose should be administered (40% glucose solution, intravenously) → the patient must be observed + the blood should be analyzed (glucose, insulin, C-peptide, insulin antibodies, cortisol)

• Whipple’s triad: symptoms of hypoglycaemia + low blood sugar level + relief of symptoms by correction of hypoglycaemia
Symptoms of hypoglycaemia

• „A” Secondary to catecholamine release: sweating, shakiness, anxiety, palpitation, weakness, tremor, hunger, faintness, tachycardia

• „B” Secondary to CNS dysfunction (neuroglycopenia): confusion, irritability, headache, abnormal behavior, weakness, diplopia, inappropriate affect, motor incoordination, convulsion, coma.

• „C” Nocturnal hypoglycaemia (due to insulin therapy): morning headache, lassitude, night sweats, nightmares, difficulty in waking, psychological changes, restlessness during sleep, loud respiration. In these cases the blood sugar level can be high in the morning = Somogyi’s phenomenon (posthypoglycaemial hyperglycaemia).
Postprandial hypoglycaemia  
( hypoglycaemia in 3-6 hours after a meal)

Causes

- Alimentary hypoglycaemia (after gastric surgery)
- Idiopathic reactive hypoglycaemia (psychological problems)
- Genetic disorders (galactosaemia, fructose intolerance)
- Gin and tonic (ethanol + carbohydrate) consuming
Fasting hypoglycaemia

- Symptoms of hypoglycaemia developed in the fasting state, 12-14 hours after the last meal.
- Drug induced hypoglycaemia (insulin, sulphonylureas, salicylates, propranolol, alcohol and so on).

Insulinoma. 1.

- 60% of such patients are women
- The median age at diagnosis is 50 years
- 80% have single benign tumor, 15% have single malignant tumor, the remainder have multiple insulinoma or hyperplasia of the beta-cells.
- Symptoms of hypoglycaemia may be present for many years before the diagnosis.
Insulinoma. 2.

Diagnosis:
• Prolonged supervised fasting (blood sample should be taken from time-to-time, and during symptoms of hypoglycaemia → blood sugar level, insulin, C-peptide).
• The test lasts till symptoms develop, or 72 hours.
• Localization of the tumor (pancreatic angiography, CT, intraoperative ultrasonography) is frequently unsuccessful.

Treatment:
• Surgical removal of the tumor, or partial, or total pancreatectomy.
• Chemotherapy with diazoxide or streptozotocine
Factitial hypoglycaemia

- Diagnosis:
- Parallel determination of insulin and C-peptide in the case of insulin administration (insulin level high, but C-peptide level is low), supplemental determination of sulphonylureas (levels of insulin and C-peptide are high, but sulphonylurea positive) if sulphonylurea administration is suspected.

Insulin auto antibodies caused hypoglycaemia

- Extremely rare

Artifactual hypoglycaemia

- Leukemia (excessive glycolysis by leukocytes
- Polycythaemia rubra vera (excessive glycolysis by erythrocytes, or unequivocal distribution of glucose between erythrocytes and plasma)
- Mesenchymal tumors and hepatoma also can cause hypoglycaemia
Hypoglycaemia associated with Whipple’s triad

Fasting:
- Suppressed plasma insulin
- Alcohol and other drugs
- Addison’s disease
- Hypopituitarism
- Extra pancreatic tu.
- Liver disease
- Sepsis
- Renal failure
- Starvation

Following food intake:
- Alimentary hypoglycaemia
- Idiopathic reactive hypoglaemia
- Genetic disorders
- Suppressed Cp.
- Elevated Cp.
- Factitious insulin adm.
- Insulin auto antibodies
- Insulinoma
- Sulphonylurea
Case report

- 39 years old male patient
- Duodenal ulcer, many relapses.
- Surgical intervention: proximal selective vagotony.
- 3 months after surgery: attacks with tremor, sweating, hunger, visual disturbances.
- Relief of these symptoms with meal, rich in carbohydrates.
- Blood sugar level was low (2.3 and 3.8 mmol/l) during attacks.
- Hypoglycaemia occurred in the fasting state.
- Prolonged supervised fasting: Whipple’s triad + high plasma insulin and C-peptide levels.
- Diagnosis: fasting hypoglycaemia. Insulinoma?
- Localization of the suspected tumor was not successful.
- Surgical intervention: proximal subtotal pancreatectomy.
- The patient died two days after surgery (pulmonary embolism).
- Histological diagnosis: nesidioblastosis
- Discussion: the role of elevated gastrin level after vagotony?
Microphoto: Illyés György dr.
Beta cells are originating from ductal cells.

HE staining.

Microphoto: Illyés György dr.
Reaction for glucagon containing cells.
Microphoto: Illyés György dr.
Reaction for glucagon containing cells
Microphoto: Illyés György dr.
Reaction with glucagon antibodies

Microphoto: Pánczél Pál dr. és Illyés György dr.
Reaction with insulin antibodies
Microphoto: Illyés György, Pánczél Pál
Reaction with insulin antibodies.
Microphoto: Illyés György, Pánczél Pál
Reaction with insulin antibodies.
Mickrophoto: Illyés György, Pánczél Pál
A case of factitious hypoglycaemia

- Type 1 diabetes at 25 years of age.
- At 30 repetitive hypoglycaemia: step by step the insulin doses were decreased and insulin administration was stopped at last (by the doctor).
- Fasting hypoglycaemia in spite of insulin withdrawal.
- Total pancreatectomy in 2001.
- No hypoglycaemia after surgical intervention. Insulin dose 30 U/day.
• Serum samples before surgical intervention:
• ICA: 20 JDFU (positive), GADA and anti-IA2 negative
• Serum C-peptide: from the fasting and postprandial samples 0 ng/ml
• Histological evaluation of the removed pancreas: no beta cells. Glucagon producing cells only.
• Definitive diagnosis: factitious hypoglycaemia. Type 1 diabetes mellitus.
Microphoto: Pánczél Pál, Illés György
NSE  (Neuron Specific Enolase)

Microphoto: Illyés György
Glucagon

Microphoto: Illyés György
Islet cell tumors
Langerhans’ islet

~ 3,000 cells
75% beta-cells (insulin)
25% other (A,D,PP) cells

200 µm

Micrograph: Lelio Orci, Geneva
Nomenclature of islet cell tumors
name of the hormonoma

- Gastrinoma
- Glucagonoma
- VIPoma (vasoactive intestinal polypeptide)
- Somatostatinoma
- PPoma (pancreas polypeptide)
- Hormonally inactive (no specific clinical syndrome). Symptoms are caused by the tumor mass. Hormone can be found immunohistochemically.
Gastrinoma
Zollinger-Ellison’ syndrome

- Tumor of the gastrin producing cells. These cells are located in the pancreatic islets and in the duodenum.
- 0.1-1% of all the duodenal ulcers
- Part of MEN-1
- Size: 0.1-20 centimeters. Mainly in the head of the pancreas. Frequently malignant with metastases in the liver.
- Epigastric pain caused by multiple duodenal/ventricular ulcers which are resistant to standard therapy. Diarrhea (in 7 % as a sole symptom). Steatorrhea (the acid inactivates the pancreatic lipase).
- Diagnosis: endoscopy, increased gastrin level > 1000 pg/ml, CT, MRI
- Therapy: surgical intervention, PPI
Glucagonoma

- Tumor of the A-cells of the pancreatic islets
- Clinical presentation: waxing and waning skin rush (necrolytic migratory erythema) 67% (erythema → induration → superficial central blistering → erosion and crusting over → healing with hyperpigmentation), diabetes mellitus (60%), IGT (30%), weight loss, anaemia, diarrhea, abdominal pain
- Diagnosis: serum glucagon > 500 pg/ml
- Therapy: surgical intervention
VIPoma
Vasoactive Intestinal Polypeptide, WDHA syndrome, Verner-Morrison’s syndrome, pancreatic cholera

- Watery diarrhea, hypokalaemia, achlorhydria
- Clinical presentation: profound but intermittent secretory diarrhea (>3 liters/day). Fecal potassium loss can reach 300 mEq/day (contrary to diarrhea caused by laxative abuse). Serum potassium < 3 mmol/l (muscle weakness, flaccid paralysis). Diabetes (50%). Dilatation of the gallbladder and small intestines. Hypochlorhydria/achlorhydria.
- Islet cell tumor producing VIP. Half of the cases are malignant.
- Therapy: surgical intervention (enucleation, subtotal/total pancreatectomy)
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Main Symptoms</th>
<th>Other Hormones</th>
<th>Malignancy</th>
<th>Hyperplasia</th>
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<tbody>
<tr>
<td>Insulinoma</td>
<td>Hypoglyc.</td>
<td>Gastrin, glucagon</td>
<td>10%</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PP</td>
<td></td>
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</tr>
<tr>
<td>Gastrinoma</td>
<td>Peptic ulcer, hyperacidity</td>
<td>Insulin, glucagon</td>
<td>40%</td>
<td>+/-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VIP, somatostatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIP-oma</td>
<td>Watery diarrhea, hypokalaemia, achlorhydria (WDHA, Verner-Morrison sy.)</td>
<td>Parathormon, PP</td>
<td>40%</td>
<td>20%</td>
</tr>
<tr>
<td>Glukagonoma</td>
<td>Rush, diabetes, weight loss, anemia</td>
<td>PP, VIP, gastrin</td>
<td>60%</td>
<td>+/-</td>
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<tr>
<td>Somatostatinoma</td>
<td>Diabetes, cholelith., steatorrhea, malabs., weight loss</td>
<td>ACTH, gastrin, calcitonin, glucagon</td>
<td>66%</td>
<td>-</td>
</tr>
<tr>
<td>PP-oma</td>
<td>WDHA +/-</td>
<td>Glucagon, ins., VIP</td>
<td>40%</td>
<td>+/-</td>
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</table>
Multiplex endocrine neoplasia (MEN) type 1 (Wermer’ syndrome)

- Autosomal-dominant inheritance
- Familial clustering of the following endocrine tumors (benign or malignant): at least two of the three main components.

- **Parathyroid adenoma** (>90%) + **hypophysis tumors** (40-50%): prolactinoma, ACTH producing, GH producing, hormonal inactive + **entero-pancreatic tumors** (60-70%): gastrinoma, insulinoma, hormonal inactive, VIP-oma, glucagonoma, PP-oma, somatostatinoma

- Prevalence: 1/30 000
- Genetic background: MEN 1 gene on the chromosome 11q13
MEN-1 (cont. 1)

- Gene product: menin, polypeptide (610 amino acids)
- Menin regulates a lot of nuclear genes, which have roles in the regulation of cell cycle, cell growth, stability of the genome. Menin is a tumor suppressor protein.
- Mutations of the gene cause decrease of the function of gene product menin.
- Two possibilities: both alleles were mutated (already in the parents of the given person), or only one allele is congenitally mutated and the other allele becomes mutated during the life of the person inside the tumor tissue.
MEN-1 (cont. 2.)

- manifestation of MEN-1 (more than 90% over 40 years of age).
  **Hyperparathyroidism:** most frequent
- All four parathyroid glands are involved and transformed.
- Hypercalcaemia, renal stones, cysts inside the bones, increased PTH
MEN-1 (cont. 3.)

- **Enteropancreatic neuroendocrine tumors**
  - Gastrinoma (30%). Multiple gastric and duodenal ulcers, diarrhea. Frequently malignant.
  - Insulinoma (10%). Malignant in 25%. Fasting hypoglycemia, weight gain.
  - Glucagonoma, VIPoma
  - 30-40% of these tumors do not cause clinically endocrine syndrome, in spite of the elevated hormone levels.
MEN-1 (cont. 4.)

- **Tumor of the hypophysis** (10-60%)
- Prolactinoma is the most frequent manifestation.
- Acromegalia (GH, GHRH), Cushing (ACTH)
- **Carcinoid tumors** (5-15%). Originated mainly from the thymus, bronchus, stomach
MEN-1 (cont. 5.)

- **Tumors of the adrenal cortex** (20-40%)
  - Mainly hormonally inactive, rarely Cushing, primary hyperaldosteronism.
- **Skin** (angiofibroma of the face, collagenomas)

- **Diagnosis**: increased serum calcium and PTH (1-3% of all primary hyperparathyroidism), hypoglycemia + increased insulin/C-peptide, increased 5-HIAA, MRI/CT scan (hypophysis, adrenal cortex), mutation of the MEN-1 gene

- **Therapy**: surgical intervention, diazoxide, octreotid (somatostatin analog)
Hypoglycemia and the treatment of type 2 diabetes mellitus

Association of hypoglycaemia with cardiovascular and all cause mortality
**NNT** = number of patients needed to treat aiming to prevent the given complication

<table>
<thead>
<tr>
<th></th>
<th>CHD (fatal and nonfatal AMI+ sudden death)</th>
<th>Stroke</th>
<th>CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NNT for 5 years</strong></td>
<td></td>
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<tr>
<td>Cholesterol 1 mmol/l</td>
<td>59,2</td>
<td>177,7</td>
<td>44,4</td>
</tr>
<tr>
<td>Blood pressure 10/5 Hgmm</td>
<td>61,8</td>
<td>73,7</td>
<td>33,6</td>
</tr>
<tr>
<td>hbA1c 0,9%</td>
<td>140,3</td>
<td>767,7</td>
<td>118,5</td>
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</table>
The most dangerous risk of the intensified glucose control is the hypoglycaemia, especially in the case of CHD.
The VADT study: glucose lowering therapy at baseline and at the end of the study. Dark columns=conventional therapy, light columns=intensified treatment.


Higher rate of therapies causing hypoglycaemia
The effect of intensified glucose control on the base of >140 000 person years

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of cases/1000/5 years</th>
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<tr>
<td>CHD</td>
<td>-7 ( p&lt;0.03 )</td>
</tr>
<tr>
<td>Stroke</td>
<td>-1</td>
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<tr>
<td>Blindness in one eye</td>
<td>-4</td>
</tr>
<tr>
<td>End stage renal insuff.</td>
<td>-2</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>+3</td>
</tr>
<tr>
<td>Cardiovasc. mortality</td>
<td>+4</td>
</tr>
<tr>
<td>Severe hypoglycaemia</td>
<td>+47 ( p&lt;0.00001 )</td>
</tr>
</tbody>
</table>
Treatment would have been started in the early stage of T2DM, with appropriate method (lifestyle intervention + metformin + ?)

Preserve the beta cells, avoid increase of body weight!
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<tbody>
<tr>
<td>glucose mmol/l</td>
<td>7,4</td>
<td>7,65</td>
<td>6</td>
<td>4,84</td>
<td>4,37</td>
<td>5,24</td>
<td>4,97</td>
<td>5,55</td>
<td>4,57</td>
<td>4,21</td>
<td>5,27</td>
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<tr>
<td>hbA1c %</td>
<td>6,8</td>
<td>9,37</td>
<td>7,43</td>
<td>6,12</td>
<td>6,13</td>
<td>6,05</td>
<td>5,76</td>
<td>6,25</td>
<td>7,49</td>
<td>6,5</td>
<td>6,1</td>
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<td>Total cholest. mmol/l</td>
<td>4,32</td>
<td>4,64</td>
<td>5,23</td>
<td>4,55</td>
<td>3,69</td>
<td>5,19</td>
<td>5,19</td>
<td>3,47</td>
<td>4,59</td>
<td>4,76</td>
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<tr>
<td>triglycerid mmol/l</td>
<td>0,95</td>
<td>1,12</td>
<td>0,91</td>
<td>0,53</td>
<td>0,93</td>
<td>2,22</td>
<td>1,47</td>
<td>0,8</td>
<td>1,1</td>
<td>1,07</td>
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<tr>
<td>HDL-cholest. mmol/l</td>
<td>1</td>
<td>1,17</td>
<td>1,33</td>
<td>1,41</td>
<td>0,92</td>
<td>1,15</td>
<td>3,37</td>
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<td>height cm.</td>
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<td>weight kg</td>
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<td>81,2</td>
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<td>85,1</td>
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<td>83,7</td>
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</tbody>
</table>

Dec. 2009.: sudden death after swimming

Male, 1937 (72 years old)

T2DM from 1991
Female, 61 years old, T2DM discovered 9 years ago with screening (13 mmol/l blood sugar level). Immediately metformin (2000 and 3000 mg/die) + gliklazid (30 and 60 mg)
Caused of referral: 14 mmol/l fasting blood glucose

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Blood gl. mmol/l</td>
<td>9,16</td>
<td>10,29</td>
</tr>
<tr>
<td>hbA1c %</td>
<td>7,42</td>
<td>6,37</td>
</tr>
<tr>
<td>C-peptide ng/ml</td>
<td>2,5</td>
<td>2,36</td>
</tr>
<tr>
<td>Weight kg</td>
<td>75</td>
<td>73,7</td>
</tr>
<tr>
<td>Height cm</td>
<td>170</td>
<td>170</td>
</tr>
<tr>
<td>Therapy</td>
<td>3000 mg metformin + 60 mg gliclasid</td>
<td>2000 mg metformin + 30 mg gliclasid</td>
</tr>
</tbody>
</table>

Nocturnal hypoglycaemia
The hypoglycaemic events lead to hypoglycaemic events.

Frequent occurrence of hypoglycaemia < 3,3 mmol/l.

The symptoms of hypoglycemia will be less severe.

Hypoglycaemic unawareness develops.

Adapted from Hermanns et al. Diabetologie 2009; 4: R 93-R112
The complications of severe hypoglycaemia

Plasma glucose level

Arrhythmia risk increases

- Abnormally increased repolarization:
  - ↑ QTc and QTd
  - Ventricular arrhythmias
  - Sudden death

Progressive neuroglycopenia

- cognitive disturbances
- Unusual behavior
- spasms
- coma
- death

Severe hypoglycemia causes QTc prolongation

$P=NS$

Studies with sulphonylurea treatment

All cause mortality

Cardiovascular mortality

Cardiovascular hospitalization + death

Gallwitz B et al Diab Obes Metab 2009
Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database

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## Results:

Risk of all cause mortality:

<table>
<thead>
<tr>
<th>Models and treatments</th>
<th>No of events</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 3 (928 702 intervals):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First generation sulphonylureas</td>
<td>101</td>
<td>1.37 (1.11 to 1.71)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Second generation sulphonylureas</td>
<td>1379</td>
<td>1.24 (1.14 to 1.35)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>