CYP2C9: gliclazide 1884 to 1890

*1 = no CYP2C9 gene variant, normal activity, *2 = CYP2C9 gene variant with decreased activity, *3 = CYP2C9 gene variant with strongly decreased activity, Cl_{or} = oral clearance, HbA_{1c} = glycated haemoglobin, IM = IM OTHER = intermediate metaboliser, other genotype (decreased CYP2C9 enzyme activity due to a gene variant with decreased activity other than *2 or *3), NM = normal metaboliser (*1/*1) (normal CYP2C9 enzyme activity), NS = not significant, OR = odds ratio, PM = PM OTHER = poor metaboliser, other genotype (strongly decreased CYP2C9 enzyme activity due to the presence of two gene variants with decreased activity, of which at least one other than *2 or *3), S = significant.

Brief summary and justification of choices:
Gliclazide is almost entirely converted in the liver to inactive metabolites. It is metabolised by CYP2C9 and CYP2C19. In two large studies, the observed clinical effect for patients heterozygous or homozygous for a gene variant leading to a decreased CYP2C9 activity (*2 and/or *3) was positive (Zeng 2016 (72 *1/*3 and 2 *3/*3) and Zhou 2010 (174 *1/*2, 99 *1/*3, 17 *2/*2, 17 *2/*3, and 4 *3/*3)). In both studies the efficacy of treatment was increased, resulting in an increase in the percentage of patients who achieved the treatment goal of HbA_{1c} < 53 mmol/ml in Zhou 2010 and the treatment goal of fasting plasma glucose concentrations below 7.8 and 7.0 mmol/ml in Zeng 2016. Three studies did not find a significant increase in hypoglycaemia (Zeng 2016 (72 *1/*3 and 2 *3/*3), Gökalp 2011 (17 *1/*2+*1/*3 and 4 *2/*2+*2/*3+*3/*3), and Ragia 2009 (12 patients with and 10 without gliclazide-induced hypoglycaemia). Two small studies in healthy volunteers did not find a significant effect of gene variants leading to a decreased CYP2C9 activity on gliclazide pharmacokinetics (Xu 2008 (6 *1/*2, 1 *2/*2, and 3 *1/*3) and Zhang 2007 (8 *1/*3 and 3 *1/*13)).
Because of the clinical effect being positive, the KNMP Pharmacogenetics Working Group decided that no action is needed for these gene-drug interactions (yes/no-interactions).
You can find a detailed overview of the observed kinetic and clinical effects in the background information text of the gene-drug interactions in the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

<table>
<tr><th>Source</th><th>Code</th><th>Effect</th><th>Comments</th></tr>
<tr>
<td>ref. 1
Zeng W et al.
CYP2C93 variant is associated with antidiabetes efficacy of gliclazide in Chinese type 2 diabetes patients.
J Diabetes Investig 2016;7:764-8.
PubMed PMID: 27181593.</td>
<td>3

*1/*3 + *3/*3: AA#</td>
<td>746 patients were treated with gliclazide monotherapy for 4 weeks, The initial dose of gliclazide was 40 mg twice daily. The dose was increased with 40 mg on day 15 for patients with a fasting plasma glucose concentration ≥ 7.0 mmol/L. The fasting plasma glucose concentration after 4 weeks of treatment were determined to establish treatment success. Hypoglycaemia was established by self-report and was defined as the occurrence of any of the following symptoms: palpitations, tremor, sweating, hunger, anxiety, behavioural changes, difficulty in concentrating and thinking, confusion, cognitive impairment, convulsions, and coma. Corticosteroids were excluded, but other relevant co-medication was not.

Genotyping:
- 672x *1/*1
- 72x *1/*3
- 2x *3/*3

Results:
<table>
<tr><td colspan="3">Treatment results compared to *1/*1:</td></tr>
<tr><td></td><td>*1/*3 + *3/*3</td><td>value for *1/*1</td></tr>
<tr><td>% of patients with fasting plasma glucose < 7.8 mmol/L</td><td>x 1.5 (S)</td><td>37.5%</td></tr>
<tr><td>% of patients with fasting plasma glucose < 7.0 mmol/L</td><td>x 1.6 (S)</td><td>32.3%</td></tr>
<tr><td>% of patients with fasting plasma</td><td>x 1.5 (S)</td><td>48.3%</td></tr>
</table>
</td>
<td>Authors' conclusion: 'The present study showed that the polymorphism at rs1057910 significantly affected the therapeutic response of gliclazide in type 2 diabetes mellitus patients. The risk allele is associated with a greater decrease of fasting blood glucose and a higher rate of treatment success with gliclazide monotherapy.'</td>
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</table>

<table>
<tr>
<td>ref. 1, continuation</td>
<td></td>
<td>
<table>
<tr><td>glucose < 7.2 mmol/L and ≥ 3.9 mmol/L</td><td></td><td></td></tr>
<tr><td>number of hypoglaecemic events</td><td>NS</td><td>1.0</td></tr>
<tr><td>fasting plasma glucose after treatment</td><td>x 0.88 (S)</td><td>8.3 mmol/L</td></tr>
<tr><td>absolute decrease in fasting plasma glucose during treatment</td><td>x 1.2 (S)</td><td>3.0 mmol/L</td></tr>
<tr><td>percentage of decrease in fasting plasma glucose during treatment</td><td>x 1.3 (S)</td><td>24,5%</td></tr>
<tr><td>total dose (in pills of 40 mg)</td><td>NS</td><td>39 pills</td></tr>
</table>

NOTE: Genotyping was for *2 and *3. Data for *2 were not analysed because of the low frequency in this Chinese patient group (3x *1/*2 and 743x *1/*1).
</td>
<td></td>
</tr>
<tr>
<td>ref. 2
Gökalp O et al.
Mild hypoglycaemic attacks induced by sulphonylureas related to CYP2C9, CYP2C19 and CYP2C8 polymorphisms in routine clinical setting.
Eur J Clin Pharmacol
2011;67:1223-9.
PubMed PMID:
21691805.</td>
<td>3

*1/*2 +
*1/*3: AA

*2/*2 +
*2/*3 +
*3/*3: AA</td>
<td>46 patients were treated with gliclazide for 3 months or longer, 76% of patients was also treated with other antidiabetics. 5 patients (11%) reported hypoglycaemia. None of these patients needed hospitalisation.
Hypoglycaemia was defined by symptoms of sweating, tremor, anxiety and/or palpitations and confirmed by home capillary blood glucose determinations showing values < 3.9 mmol/L and response to sugar intake. Occurrence was assessed during a 3-month period.
Co-medication with CYP2C9 substrates, inhibitors or indu--cers was not excluded.

Genotyping:
- 25x *1/*1
- 17x *1/*2+*1/*3
- 4x *2/*2+*2/*3+*3/*3

Results:
<table>
<tr><td colspan="3">Percentage of patients with hypoglycaemia:</td></tr>
<tr><td>*1/*1</td><td>0%</td><td rowspan="3">S for *2/*2+*2/*3+*3/*3 versus *1/*2+*1/*3 versus *1/*1</td></tr>
<tr><td>*1/*2+*1/*3</td><td>24%</td></tr>
<tr><td>*2/*2+*2/*3+*3/*3</td><td>25%</td></tr>
<tr><td colspan="3">Logistic regression analysis did not show a significant effect of CYP2C9 genotypes on the occurrence of hypoglycaemia (NS).</td></tr>
</table>
NOTE: Genotyping was for *2 and *3. These are the most important gene variant in this Turkish patient group.
</td>
<td>Authors' conclusion: 'CYP2C9 polymorphisms leading to decreased enzyme activity show a modest impact on the risk of mild hypoglycaemia attacks during oral antidiabetic treatment, with a significant association in patients treated with gliclazide.'</td>
</tr>
<tr>
<td>ref. 3
Zhou K et al.
Loss-of-function CYP2C9 variants improve therapeutic response to sulfonylureas in type 2 diabetes: a Go-DARTS study.
Clin Pharmacol Ther
2010;87:52-6.</td>
<td>3

*1/*2 +
*1/*3 +
*2/*2 +
*2/*3 +
*3/*3:
AA#</td>
<td>A total of 845 diabetes patients, ≥ 6 months of stable gliclazide therapy (monotherapy or in addition to metformin), approx. 534x *1/*1, 174x *1/*2, 99x *1/*3, 17x *2/*2, 17x *2/*3, 4x *3/*3, relevant co-medication not excluded.

- increase in the percentage of patients who achieved the treatment goal (HbA_{1c} < 53 mmol/mL) with an increase in the number of *2 and *3 alleles (OR = 1.33) (S)
- non-significant increase in the drop in HbA_{1c} concentration with an increase in the number of *2 and *3 alleles (ß = 0.12) (NS)

For the entire study group (845x gliclazide, 136x glipizide, 57x multiple sulfonylurea, 20x glimepiride, 15x glibenclamide), there was a significant association with both the above-mentioned measures of outcome. The effect was strongest for *2/*3 (OR = 7.54; ß = 0.83) followed by *2/*2+*2/*3+*3/*3 (OR = 3.44; ß = 0.50). The effect was not significant for the other genotypes and for *1/*2+*1/*3.</td>
<td>Authors' conclusion: "CYP2C9 loss-of-function alleles are associated with greater response to sulfonylureas and decreased failure of therapy consistent with the pharmacokinetic role of CYP2C9."</td>
</tr>
</table>

ref. 4 Ragia G et al. Presence of CYP-2C9*3 allele increases risk for hypoglycemia in Type 2 diabetic patients treated with sulfonylureas. Pharmacogenomics 2009;10:1781-7.	3 *1/*2: AA *1/*3: AA	Case-control study involving 12 diabetes patients with gliclazide-induced hypoglycaemia, 9x *1/*1, 2x *1/*2, 1x *1/*3, and 10 patients without gliclazide-induced hypoglycaemia, 8x *1/*1, 2x *1/*2, no CYP2C9 inhibitors, anti-hypertensive medication that can mask symptoms of hypoglycaemia was not excluded. Cases versus controls: - no significant difference in frequency *1/*2 (NS) - no significant increase in the frequency of *1/*3 (NS) - no significant difference in average dose of gliclazide (109 versus 106 mg/day) Dose versus *1/*1 for both groups combined: - no significant difference in dose for *1/*2 and for *1/*3 (NS) The total study group (cases: 80x glimepiride, 12x gliclazide) exhibited a significant increase in the frequency of *1/*3, but not of *1/*2, in the case group versus the control group.	Authors' conclusion: "In Type 2 diabetic patients, CYP2C9*3 increases the risk of hypoglycaemia when they are treated with sulfonylureas, possibly due to impaired metabolism of these drugs. CYP2C9 genotyping might thus be a useful tool for predicting adverse effects caused by sulfonylureas and help clinicians in safer prescribing of oral hypoglycaemic agents."
ref. 5 Xu H et al. Effects of St John's wort and CYP2C9 genotype on the pharmacokinetics and pharmacodynamics of gliclazide. Br J Pharmacol 2008;153:1579-86. **ref. 3, continuation**	3 *1/*2 + *2/*2: AA *1/*3: AA	A total of 21 healthy volunteers (11x *1/*1, 6x *1/*2, 1x *2/*2, 3x *1/*3) received a single dose of 80 mg gliclazide followed after 0.5 hours by 75 g glucose. *1/*2 + *2/*2 versus *1/*1: - decrease in Cl_{or} from 24.0 to 18.5 mL/hour per kg (NS, by 23%) *1/*3 versus *1/*1: - increase in Cl_{or} from 24.0 to 25.4 mL/hour per kg (NS, by 6%)	
ref. 6 Zhang Y et al. Influence of CYP2C9 and CYP2C19 genetic polymorphisms on pharmacokinetics of gliclazide MR in Chinese subjects. Br J Clin Pharmacol 2007;64:67-74.	3 *1/*3: AA *1/*13: AA	A total of 24 Chinese healthy volunteers (13x *1/*1, 8x *1/*3, 3x *1/*13, with CYP2C19 polymorphisms also present) received a single dose of 30 mg gliclazide modified release: - no significant differences in pharmacokinetic parameters between *1/*1, *1/*3 and *1/*13. N.B.: Also a study arm with only CYP2C9 *1/*1 and CYP2C19 polymorphisms. No significant difference was found between CYP2C19 NM and IM.	Authors' conclusion: "The pharmacokinetics of gliclazide MR are affected mainly by CYP2C19 genetic polymorphism instead of CYP2C9 genetic polymorphism."

Risk group	--

Comments:

- For the period after 2010 only studies with clinical outcomes in patients were included. Other studies did not add enough to the evidence.

Date of literature search: 23 January 2023.

	Genotype	Code	Gene-drug interaction	Action	Date
KNMP Pharmacogenetics Working Group decision	*1/*2	3 AA[#]	Yes	No	16 May 2023
	*1/*3	3 AA[#]	Yes	No	
	*2/*2	3 AA[#]	Yes	No	
	*2/*3	3 AA[#]	Yes	No	
	*3/*3	3 AA[#]	Yes	No	
	IM	3 AA	Yes	No	
	PM	-	Yes	No	

Mechanism:
Gliclazide is almost entirely converted in the liver to inactive metabolites. It is metabolised by CYP2C9 and CYP2C19.