Effect of CYP2C9 polymorphisms on prescribed dose and time-to-stable dose of sulfonylureas in primary care patients with Type 2 diabetes mellitus

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Effect of *CYP2C9* polymorphisms on prescribed dose and time-to-stable dose of sulfonylureas in primary care patients with Type 2 diabetes mellitus

Aims: Sulfonylureas are mainly metabolized by the enzyme CYP2C9. Two allelic variants, *CYP2C9*2* and *CYP2C9*3*, result in decreased metabolic capacity and have been associated with elevated sulfonylurea serum levels. However, most of the available data originates from pharmacokinetic analyses performed in healthy individuals. In this study, the effect of *CYP2C9*2* and *CYP2C9*3* alleles on prescribed dose and time-to-stable dose of sulfonylureas was investigated. **Materials & methods:** A group of 207 incident sulfonylurea users treated in four university affiliated primary care centers were identified. The effect of the *CYP2C9*2* and *CYP2C9*3* alleles on prescribed dose and time-to-stable dose was then assessed. **Results:** No significant effects of the *CYP2C9*2* and *CYP2C9*3* alleles were found. However, a trend towards a lower stable glimepiride dose for carriers of the *CYP2C9*3* allele was observed. **Conclusion:** Genotyping for the *CYP2C9*2* and *CYP2C9*3* alleles currently appears to have no clinical implications for dosing of sulfonylureas in primary care patients with Type 2 diabetes mellitus.

KEYWORDS: ***CYP2C9*** ■ **glibenclamide** ■ **gliclazide** ■ **glimepiride** ■ **pharmacogenetics** ■ **sulfonylureas** ■ **tolbutamide** ■ **Type 2 diabetes mellitus**

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Sulfonylureas (SUs) are part of the mainstay of treatment of Type 2 diabetes mellitus (T2DM) with oral antidiabetic drugs. They act by closing the pancreatic β-cell potassium channels, stimulating insulin secretion [1]. SUs are initiated at a low dose and titrated up to the optimal dose with intervals of 2–4 weeks until the glycemic target is achieved. Undertreatment will increase the risk of long-term microvascular and macrovascular complications, whereas overtreatment will lead to hypoglycemia, a well recognized adverse event that limits rapid dose escalation and is reported to be fatal in 1.4–10% of cases [2].

The enzyme CYP2C9 plays an important role in the pharmacokinetics of SUs. Two allelic variants, *CYP2C9*2* and *CYP2C9*3*, result in decreased metabolic capacity. Both alleles are relatively common in Caucasians [101]. Most of the available data regarding the effect of *CYP2C9* polymorphisms on SU treatment originate from pharmacokinetic analyses performed in healthy individuals [3–9]. Only four studies have assessed the effect of *CYP2C9* polymorphisms in T2DM patients. Presence of the *CYP2C9*3* allele was associated with hypoglycemia [10,11]. Furthermore, the *CYP2C9*3* allele is associated with the absence of tolbutamide dose escalation and carriers of the *CYP2C9*2* or *CYP2C9*3* allele are less likely to fail on SU monotherapy [12,13]. However, none of these studies have assessed the effect of the *CYP2C9* genotype on the time required for SU dose titration. Therefore, the aim of this study was to investigate the effect of *CYP2C9*2* and *CYP2C9*3* alleles on prescribed dose and time-to-stable dose of SUs in T2DM patients in a primary care setting.

Materials & methods

Study setting

In The Netherlands patients are listed with one family physician (FP) who is consulted for all healthcare problems and indicates whether referral to secondary care is appropriate. The FP keeps an electronic patient record (EPR) that covers all medical information, including prescription data concerning the patient. T2DM patients are treated according to the T2DM guideline of the Dutch College of General Practitioners [14].

Study population

Patients were recruited from four university affiliated primary care centers located in the vicinity of Leiden, The Netherlands. Approximately 37,000 patients were enlisted. Retrospective clinical and prescription data were retrieved from the EPR. Patients were eligible for the study if they had received at least one prescription of tolbutamide, glibenclamide, glimepiride or gliclazide after 1992, were at least 18 years of age and were without insulin use at the time of first SU prescription and had at least 270 days of follow-up registered in the EPR. To

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ascertain that a SU prescription was the first, a period of at least 6 months without SU prescriptions prior to that prescription recorded in the EPR was required.

Sample collection

Eligible patients received a written invitation by mail from their FP. After consent, a saliva collection kit (DNA Genotek, ON, Canada) was mailed. The ethics committee of the Leiden University Medical Center approved the study and informed consent was obtained from all participants.

Genotyping

Genotyping of *CYP2C9*2* (rs1799853) and *CYP2C9*3* (rs1057910) was performed by a TaqMan® allelic discrimination assay (Applied Biosystems, CA, USA), independently and without knowledge of the patient data. Assays were used according to the manufacturer's instructions and performed on 10 ng genomic DNA. Fluorescence detection and genotype calling were performed using an ABI Prism® 7750 Sequence Detection System (Applied Biosystems).

Definition of effect of *CYP2C9*2* & *CYP2C9*3* alleles on SU dose & time-to-stable dose

The primary end point of our study was the effect of the *CYP2C9*2* and *CYP2C9*3* alleles on the stable SU dose. This was defined as the first period of 270 consecutive days or more without SU dose adjustment, or initiation or adjustment of therapy with another SUs, insulin or metformin. Dose was normalized to allow for the pooling of different SUs by dividing the prescribed daily dose with the standard daily dose used by the Dutch Healthcare Insurance Board (10 mg glibenclamide; 1000 mg tolbutamide; 160 mg gliclazide; 2 mg glimepiride) [15]. The period of 270 days or more was chosen because prescriptions in The Netherlands are limited to a maximum of 90 days, and 270 days or more equals three consecutive prescriptions.

The secondary end points of our study were the effect of *CYP2C9*2* and *CYP2C9*3* alleles on the time to the first stable SU dose, and the effect of the *CYP2C9*2* and *CYP2C9*3* alleles on the number of dose adjustments during the first year of SU treatment. Finally, the effect of the *CYP2C9*2* and *CYP2C9*3* alleles on the change in fasting glucose levels was analyzed in a subset of the cohort with measurements available 90 days before and during stable dose.

Statistical analysis

A difference in stable dose of 0.33 was considered to be clinically relevant. According to the T2DM guidelines of the Dutch College of General Practitioners this equals a difference in titration time of approximately 4 weeks. In the power analysis, we calculated that 120 patients were to be included in order to test for statistical difference at a two-sided 5% significance level with at least 80% power.

The data were analyzed using the SPSS statistical package (version 16.0, SPSS, IL, USA). Possible deviation from Hardy–Weinberg equilibrium was tested by the χ^2 test. Differences in stable SU dose, number of dose adjustments, and fasting glucose levels were analyzed with Kruskal–Wallis nonparametric tests and multivariate linear regression analysis. All demographic and clinical variables were tested univariately against stable SU dose. The variables with a p-value of less than 0.1 were selected for multivariate analysis. In addition, age, gender and genotype were included in the multivariate analysis regardless of their univariate p-value.

Associations between the *CYP2C9*2* and *CYP2C9*3* alleles and time-to-stable dose were evaluated using Kaplan–Meier survival analysis techniques.

Results

Figure 1 depicts the study population. In total, 207 T2DM patients were available for data analysis. Table 1 presents the patient characteristics. The mean age at the time of first SU prescription was 61.5 years and 52.2% of the study population were men. Mean follow-up was 6.0 years, reflecting that most patients (74.4%) were included after 1st January 2000. The majority of patients started with tolbutamide (42.5%) or glimepiride (39.6%). Patients received an average of 26 SU prescriptions with a median duration of 90 days per prescription. In total, 30.4% of the patients used metformin when they started SU treatment. The population was in Hardy–Weinberg equilibrium ($\chi^2 = 5.50$; $p = 0.14$), indicating a low likelihood of selection bias or errors in genotyping.

Table 2 summarizes the effect of the *CYP2C9*2* and *CYP2C9*3* alleles on the SU dose. The mean starting dose was 0.62. As expected, no differences in mean starting dose were observed between the genotype groups. Of the 207 T2DM patients, 152 (73.4%) achieved stable dose. There were no statistically significant differences in the percentage of patients that achieved stable dose between carriers of the *CYP2C9*2* (70.7%) and/or *CYP2C9*3* (77.5%) allele compared with homozygous carriers

of the *CYP2C9*1* (79.4%) allele (p = 0.48). For mean stable glimepiride dose, a trend towards a lower dose for carriers of a *CYP2C9*3* allele in comparison to homozygous carriers of the *CYP2C9*1* allele was observed (1.01 vs 0.61; p = 0.07).

To identify possible associations between demographic and clinical variables and stable SU dose, univariate regression analysis was performed. The SU starting dose and the use of metformin were associated with the mean stable SU dose (Table 3). To adjust for the effects of metformin and initial SU dose, a multivariate regression analysis with *CYP2C9* genotype, age and sex was performed. In summary, the results remained similar to the data as presented in Table 2.

Since SUs are titrated to the optimal dose, an analysis of the time-to-stable SU dose and *CYP2C9* genotype was performed. Median time-to-stable dose was 56, 50 and 48 days for homozygous carriers of the *CYP2C9*1* allele, carriers of the *CYP2C9*2* allele or the *CYP2C9*3* allele, respectively. The Kaplan–Meier curves for time-to-stable dose demonstrated no significant differences between carriers of the *CYP2C9*1*, *CYP2C9*2* or *CYP2C9*3* alleles (p = 0.58) (Figure 2). For all *CYP2C9* genotypes, approximately 35% of the patients achieved stability without any dose adjustment from the first prescription. The mean number of dose adjustments in the first year of SU therapy was 1.02 (range: 0–6) for all patients, and did not differ between the genotype groups with 0.95 dose adjustments for homozygous carriers of the *CYP2C9*1* allele, 1.22 dose adjustments for carriers of the *CYP2C9*2* allele and 1.06 dose adjustments for carriers of the *CYP2C9*3* allele (p = 0.24).

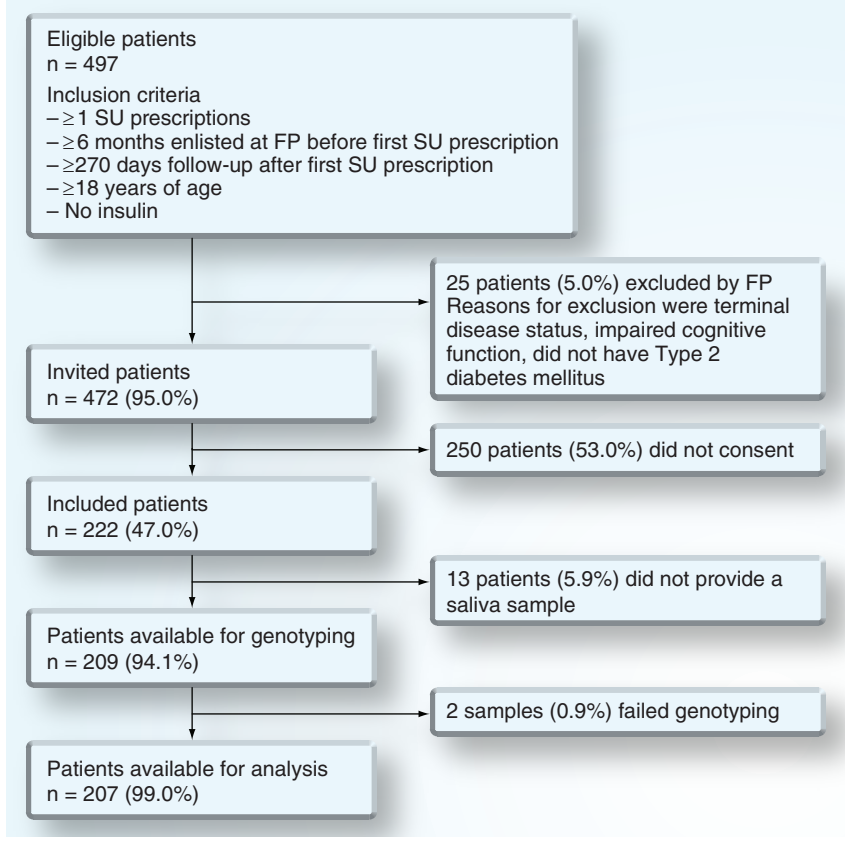

Figure 1. Study population.
FP: Family physician; SU: Sulfonylurea.

Table 1. Characteristics of the Type 2 diabetes mellitus patient population in primary care.

Variable, n (%)[†]	All patients	*CYP2C9*1/*1*	*CYP2C9*1/*2* or *CYP2C9*2/*2*[‡]	*CYP2C9*1/*3* or *CYP2C9*2/*3*[§]	p-value
Subjects	207	133 (64.3)	40 (19.3)	34 (16.4)	NA
Men	108 (52.2)	73 (54.9)	18 (45.0)	17 (50.0)	0.53
Women	99 (47.8)	60 (45.1)	22 (55.0)	17 (50.0)	
Age, mean (SD), years	61.5 (10.7)	61.2 (11.1)	61.8 (10.7)	62.3 (8.8)	0.85
Follow-up, mean (SD), years	6.0 (3.0)	5.8 (3.0)	6.3 (3.1)	6.1 (2.9)	0.68
Visits year 1 (SD)	9.6 (4.67)	9.9 (5.03)	9.5 (3.73)	8.8 (4.23)	0.20
Metformin	63 (30.4)	45 (33.8)	7 (17.5)	11 (32.4)	0.14
Primary sulfonylureas					
Glibenclamide	12 (5.8)	8 (6.0)	3 (7.5)	1 (2.9)	0.03[¶]
Tolbutamide	88 (42.5)	45 (33.8)	24 (60.0)	19 (55.9)	
Gliclazide	25 (12.1)	29 (15.8)	2 (5.0)	2 (5.9)	
Glimepiride	82 (39.6)	59 (44.4)	11 (27.5)	12 (35.3)	

[†]*Unless stated otherwise.*
[‡]*4 patients were carriers of the* CYP2C9*2/*2 *genotype.*
[§]*1 patient was a carrier of the* CYP2C9*2/*3 *genotype.*
[¶]χ^2 *for primary sulfonylureas vs genotype group.*
NA: Not applicable; SD: Standard deviation.

Table 2. Prescribed dose of sulfonylurea at first and stable prescription stratified by *CYP2C9* genotype group in Type 2 diabetes mellitus patients in primary care[†].

Dose, mean (SD)	*CYP2C9*1/*1*	n	*CYP2C9*1/*2* or *CYP2C9*2/*2*	n	p-value	*CYP2C9*1/*3* or *CYP2C9*2/*3*	n	p-value
All patients								
First	0.61 (0.25)	133	0.66 (0.31)	40	0.55	0.61 (0.26)	34	0.91
Stable	0.92 (0.59)	94	0.94 (0.45)	31	0.49	0.80 (0.37)	27	0.48
Glibenclamide								
First	0.63 (0.23)	8	0.58 (0.38)	3	0.63	0.25 (NA)	1	0.06
Stable	0.75 (0.42)	6	1.00 (0.41)	4	0.30	1.50 (NA)	1	0.16
Tolbutamide								
First	0.58 (0.20)	45	0.65 (0.23)	24	0.23	0.63 (0.28)	19	0.59
Stable	0.90 (0.47)	35	0.78 (0.31)	15	0.56	0.86 (0.41)	14	0.86
Gliclazide								
First	0.64 (0.35)	21	0.88 (0.88)	2	0.95	0.75 (0.35)	2	0.48
Stable	0.78 (0.45)	13	0.88 (0.88)	2	0.86	0.83 (0.29)	3	0.78
Glimepiride								
First	0.63 (0.26)	59	0.66 (0.36)	11	0.96	0.58 (0.19)	12	0.65
Stable	1.01 (0.74)	40	1.15 (0.53)	10	0.21	0.61 (0.22)	9	0.07

Patients were allowed to switch from SU in the period between the first prescribed SU and stable dose. As a consequence the number of patients may differ within SU.
[†]To allow pooling of different SUs, dose was normalized by dividing the prescribed daily dose with the standard daily dose used by the Dutch Healthcare Insurance Board (10 mg glibenclamide, 1000 mg tolbutamide, 160 mg gliclazide and 2 mg glimepiride).
NA: Not applicable; SD: Standard deviation; SU: Sulfonylurea.

In addition, differences in fasting glucose levels were assessed for the *CYP2C9* genotypes. For 75 patients (49.3%), fasting glucose level measurements were available in the period 90 days prior to the first SU prescription and during stable SU dose. Fasting glucose levels decreased with 2.8, 2.6 and 2.4 mmol/l for homozygous carriers of the *CYP2C9*1* allele, carriers of the *CYP2C9*2* allele, and carriers of the *CYP2C9*3* allele, respectively (p = 0.89).

Discussion

In this retrospective study of 207 primary care patients with T2DM, no statistically significant effect of the *CYP2C9*2* and *CYP2C9*3* alleles on the prescribed stable dose or time-to-stable dose of SUs was found. However, a trend towards a lower stable dose for carriers of the *CYP2C9*3* allele was observed, in the subgroup of patients treated with glimepiride.

Table 3. Analysis of multiple factors relevant for stable sulfonylurea dose in Type 2 diabetes mellitus patients in primary care.

Factor	Multivariate			Univariate		
	Difference in change[†]	95% CI	p-value	Difference in change[†]	95% CI	p-value
Constant	0.912	0.307–1.516	0.003			
Male vs female gender	-0.190	-0.355 to -0.025	0.024	-0.15	-0.32–0.02	0.083
The effect of age (per year increase)	-0.005	-0.013–0.004	0.280	-0.005	-0.014–0.003	0.218
Metformin use vs no metformin use at stable sulfonylurea dose	0.142	-0.038–0.321	0.120	0.177	-0.01–0.361	0.060
Carrier of *CYP2C9*2* allele vs wild-type	0.001	-0.209–0.211	0.992	0.041	-0.171–0.254	0.701
Carrier of *CYP2C9*3* allele vs wild-type	-0.088	-0.307–0.130	0.425	-0.129	-0.352–0.094	0.254
First sulfonylurea dose	0.583	0.266–0.899	0.000	0.569	0.253–0.885	0.000

[†]This considers the change in stable sulfonylurea dose (expressed as the prescribed daily dose divided by the standard daily dose used by the Dutch Healthcare Insurance Board).

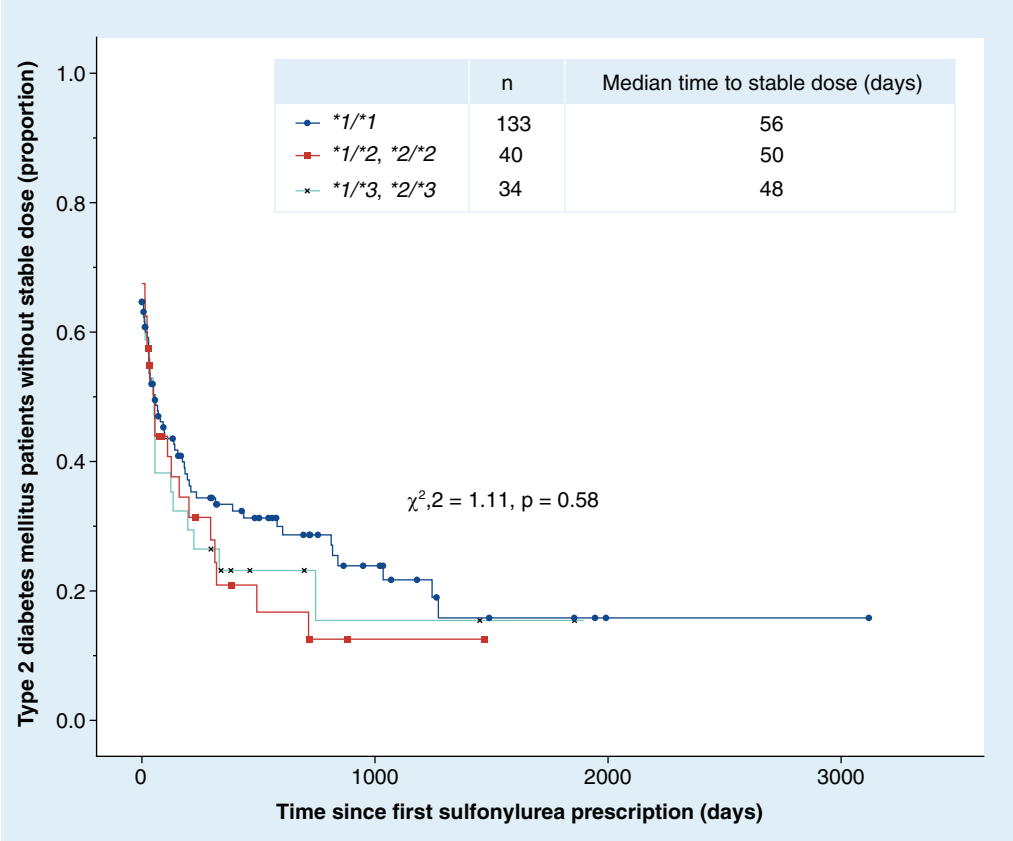

Figure 2. Kaplan–Meier survival plots of time to the first stable dose of sulfonylurea in Type 2 diabetes mellitus patients in primary care stratified by *CYP2C9* genotype.

Since no difference in stable dose or time-to-stable dose between the different genotypes was observed, we hypothesized that carriers of the *CYP2C9*2* and *CYP2C9*3* alleles might have a larger decrease in fasting glucose levels. There was however, no significant difference in decrease in fasting glucose levels during stable dose between carriers of the *CYP2C9*2* or *CYP2C9*3* alleles and homozygous carriers of the *CYP2C9*1* allele in the relatively small subgroup of patients with fasting glucose level measurements available.

Our study has some limitations. In general, observational studies may potentially be affected by bias. The FPs were unaware of the genotype, thereby excluding this information bias. In our study, no data was available for patients who had switched to another family practice or who died in the period after 1992. As a consequence, we cannot completely rule out the possibility of selection bias. However, our population was in Hardy–Weinberg equilibrium, suggesting that no selection bias on genotype occurred. Moreover, a nonresponse analysis on age, gender, type of first prescribed SU, metformin use and FP revealed no differences between participants and patients who did not consent to our study, indicating that no selection bias on any of these parameters occurred.

The analysis of time-to-stable dose assumes that FPs adhere to the T2DM guideline of the Dutch College of General Practitioners. In general, adherence to guidelines by Dutch FPs is good [16]. If FPs do not adhere to the guideline, they can initiate treatment with a different dose or follow different titration intervals. In both situations this could introduce an error to our analyses of time-to-stable dose. However, there is no reason to assume that this error is not divided randomly over the different genotype groups. Therefore it does not affect the comparison of time-to-stable dose between the genotype groups but can only affect the absolute results of the time-to-stable dose analyses.

The *CYP2C9* genotype is known to have a significant effect on the pharmacokinetics of SUs in healthy volunteers [3–7,9]. Less information is available regarding the effect of the *CYP2C9* genotype in T2DM patients. Two retrospective studies assessed the effect of the *CYP2C9*2* and *CYP2C9*3* alleles on treatment outcomes with SUs. Becker *et al.* found

that carriers of the *CYP2C9*3* allele treated with tolbutamide received significantly lower doses on the arbitrarily chosen 10th prescription compared with patients with the wild-type genotype, No such effect was found for any of the other assessed SUs [12]. In addition, Zhou *et al.* observed a trend towards a 5% dose increase for patients with none or one copy versus no dose increase in carriers of two copies of the *CYP2C9*2* or *CYP2C9*3* alleles in patients who were mainly treated with gliclazide monotherapy [13]. We report similar findings towards a lower stable SU dose for patients with a *CYP2C9*3* allele for a population of whom approximately 40% of the patients is treated with glimepiride. These findings indicate that the *CYP2C9*3* allele influences the treatment of T2DM patients with SUs. However, although inconclusive, our study suggests that the effect is probably small and we therefore feel that there is currently insufficient evidence to support the genotyping of *CYP2C9* prior to prescribing SUs to an individual.

The pathogenesis of T2DM is not yet fully understood. Current theories include defects in insulin-mediated glucose uptake in muscle, dysregulation of the adipocyte as a secretory organ, dysfunction of the pancreatic β-cell and impaired insulin action in the liver [17]. Several studies including linkage analysis, candidate gene approaches and genome-wide association studies have identified 20 common genetic variants associated with T2DM reflecting the disease's multifaceted genetic background [18]. Probably as a consequence of this heterogeneity, interpatient variability of drug response remains largely unexplained. It is possible that the multifaceted genetic background of T2DM surpasses the effect of the *CYP2C9* genotype on SU response. Therefore, there may be subpopulations of T2DM patients in which the effect of the *CYP2C9*2* and *CYP2C9*3* alleles may be of clinical relevance.

Conclusion

In conclusion, no association between the *CYP2C9*2* or *CYP2C9*3* alleles and time-to-stable dose was found in T2DM patients in primary care, whereas carriers of a *CYP2C9*3* allele showed a trend towards a lower stable glimepiride dose. However, there are many other factors influencing SU treatment outcome. Therefore, the effect of the *CYP2C9*2* and *CYP2C9*3* alleles currently has no clinical implications to dosing of SUs in T2DM patients.

Executive summary

- The enzyme CYP2C9 plays an important role in the pharmacokinetics of sulfonylureas (SUs), but only four studies have assessed the effect of *CYP2C9* polymorphisms in Type 2 diabetes mellitus (T2DM) patients.
- *CYP2C9*2* and *CYP2C9*3* alleles have been associated with hypoglycemia, absence of tolbutamide dose escalation and carriers have been proven to be less likely to fail on SU treatment.
- The aim of this study was to investigate the effect of *CYP2C9*2* and *CYP2C9*3* alleles on prescribed dose and time-to-stable dose of SUs in T2DM in a primary care setting.

Materials & methods

- T2DM mellitus patients with a SU prescription were recruited from four university affiliated primary care centers.
- The primary end point was the effect of the *CYP2C9*2* and *CYP2C9*3* alleles on the stable SU dose.
- Secondary end points were the effect on the time to the first stable SU dose and the effect on the number of dose adjustments during the first year of SU treatment.
- In an additional analysis, the effect of the *CYP2C9*2* and *CYP2C9*3* alleles on fasting glucose levels was assessed in patients for whom a fasting glucose level measurement was available in the period 90 days prior to the first SU prescription and during stable SU dose.

Results

- In this study of 207 incident SU users with T2DM, no statistically significant effect of the *CYP2C9*2* and *CYP2C9*3* alleles on the stable dose was found.
- However, a trend towards a lower stable dose for carriers of the *CYP2C9*3* allele, compared with homozygous carriers of the *CYP2C9*1* allele, was observed in the subgroup of patients treated with glimepiride (0.61 vs 1.01, $p = 0.07$).
- Of the patients, 152 (73.4%) achieved stable dose with a median time-to-stable dose of 56, 50 and 48 days for homozygous carriers of the *CYP2C9*1* allele, carriers of the *CYP2C9*2* and *CYP2C9*3* alleles, respectively ($p = 0.58$).

Discussion

- No significant effects of the *CYP2C9*2* and *CYP2C9*3* alleles were found on time-to-stable dose in T2DM patients in primary care, whereas carriers of the *CYP2C9*3* allele show a trend towards a lower stable glimepiride dose.
- Besides *CYP2C9* genotype, there are many other factors influencing SU treatment outcome.

Conclusion

- Genotyping for the *CYP2C9*2* and *CYP2C9*3* alleles currently appears to have no clinical implications for dosing of SUs in primary care patients with T2DM.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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