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Glitazones in the treatment of diabetes mellitus type 2¹

Executive Summary

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Executive summary

Background

In its letter of 22 February 2005, the Federal Joint Committee commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of various oral antidiabetics approved in Germany in the treatment of patients with diabetes mellitus type 2. This also included the benefit assessment of glitazones.

Research questions

The aims of this research were the comparative benefit assessments of long-term treatment with

- pioglitazone or rosiglitazone vs. placebo,
- pioglitazone or rosiglitazone vs. another glucose-lowering drug or non-drug intervention,
- pioglitazone vs. rosiglitazone,

in each case

- as monotherapy or in combination with another glucose-lowering therapy,
- in patients with diabetes mellitus type 2 treated within the framework of the valid drug approval criteria.

The focus of the assessment was on patient-relevant therapy goals.

The benefit assessment was based on the comparison of desired and undesired effects of the individual drugs.

Methods

The assessment was performed on the basis of randomized controlled trials (RCTs) investigating the research questions outlined above. For this purpose, a systematic literature search was performed in the following databases: BIOSIS Previews; CCMed; EMBASE; MEDLINE (additional comparison with PubMed); Cochrane Central Register of Controlled Trials (Clinical Trials); and the publisher databases of Hogrefe, Karger, Kluwer, Krause & Pachernegg, Springer, and Thieme. The period up to September 2008 was covered. In addition, reference lists were screened of relevant secondary publications (systematic reviews, HTA reports); trial registries; “Rote-Hand-Briefe” (Urgent Safety Information) by the manufacturers of glitazones (retrieved from the database of the Drug Commission of the German Medical Association); and publicly accessible drug approval documents. Moreover, the manufacturers of rosiglitazone (GlaxoSmithKline) and pioglitazone (Takeda) were asked

to provide relevant information on published and unpublished studies. RCTs with a duration of at least 24 weeks were included in which 1 of the 2 glitazones named above was investigated within the framework of the valid European drug approval (status: March 2008). The literature screening was performed by 2 reviewers independently of one another. After an assessment of study quality, the results of the individual trials were organized according to therapy regimens and collated according to therapy goals and outcomes. IQWiG's preliminary benefit assessment, the preliminary report, was published on the Internet (www.iqwig.de) and interested parties were invited to submit comments (hearing).

Unclear aspects of these written comments were discussed in a scientific debate on 19 August 2008. The final report was subsequently produced, taking the comments submitted into consideration.

In a separate part of the final report, results of studies are presented in which the glitazones were not used within the framework of the European drug approval (off-label use), and where it remained unclear whether the results were applicable to patients treated within the framework of the approval.

Results

A total of 7 studies for the assessment of pioglitazone and 16 studies for the assessment of rosiglitazone were identified. The following therapy options for pioglitazone and rosiglitazone were investigated in the studies included.

Pioglitazone	Rosiglitazone
2-drug therapy including metformin	2-drug therapy including sulfonylurea
- vs. metformin and sulfonylurea	- vs. placebo and sulfonylurea
- vs. metformin and vildagliptin	2-drug therapy including metformin
3-drug therapy including metformin and sulfonylurea	- vs. placebo and metformin
- vs. placebo, metformin and sulfonylurea	- vs. sulfonylurea and metformin
Combination with human insulin	3-drug therapy including metformin and sulfonylurea
- vs. human insulin as monotherapy	- vs. metformin and sulfonylurea (with/without placebo)
Administration within the framework of different therapeutic regimens	- vs. insulin glargine, metformin and sulfonylurea
- vs. placebo with different therapy regimens (e.g., metformin, sulfonylurea, insulin, diet)	- vs. NPH insulin, metformin and sulfonylurea
- vs. glimepiride with different therapy regimens (metformin and/or insulin)	

No relevant data in the included studies were available on the outcomes “dialysis required”, “hyperosmolar coma”, “ketoacidotic coma”, and “symptoms related to chronic hyperglycaemia”.

Macro- and microvascular late complications and mortality

The PROactive study compared therapy optimization with and without pioglitazone (pioglitazone vs. placebo, with optimization of the glucose-lowering therapy in both groups). In this study, no advantage of pioglitazone vs. placebo could be identified in patients with evidence of macrovascular disease with regard to the composite outcome of all-cause mortality; non-fatal myocardial infarction (MI) (incl. silent MI); stroke; acute coronary syndrome; cardiac interventions (incl. coronary bypass surgery or percutaneous coronary intervention [PCI]); and amputation above the ankle or bypass surgery/revascularization of the leg arteries (hazard ratio 0.90 [95% CI 0.80; 1.02]). There were also no statistically significant differences between treatment groups regarding the individual components of the composite outcome.

For the composite outcome of all-cause mortality, non-fatal MI (excl. silent MI), and stroke, a statistically significant advantage of therapy optimization with pioglitazone was shown vs. therapy without pioglitazone (hazard ratio 0.84 [95 % CI 0.72; 0.98]). The effects in favour of pioglitazone were also shown for 3 of 4 further outcomes that represented some components of the combined outcome of all-cause mortality, non-fatal MI (excluding silent MI), and stroke.² For 2 of these outcomes, the group difference achieved statistical significance. For a further component (cardiovascular mortality) the effect was smaller and not statistically significant (hazard ratio: 0.94 [95% CI 0.74; 1.20]).

No statistically significant difference between treatment groups was found for transient ischaemic attacks and causes of death such as MI, other cardiac (e.g., arrhythmia), cardiovascular (e.g., pulmonary embolism), cerebrovascular and non-cardiovascular fatal events.

A statistically significant interaction test suggested different effects of pioglitazone in the subgroups of patients who had or had not experienced a stroke. In one subgroup analysis, a statistically significant advantage for pioglitazone vs. placebo was shown for the outcome “frequency of stroke” in patients who had already experienced a stroke before baseline (hazard ratio 0.53 [95% CI 0.33; 0.85]). This advantage for pioglitazone was not demonstrated separately in this subgroup for the composite outcomes of cardiovascular mortality, non-fatal MI, and stroke or cardiovascular mortality and stroke. In patients who had already experienced an MI, an interaction test did not suggest that the effects of pioglitazone in this subgroup differed from those in the subgroup of patients who had not experienced an MI.

No statistically significant difference between the pioglitazone and the placebo group was shown for photocoagulation therapy in the prevention of late microvascular complications

² A.) Cardiovascular mortality + non-fatal MI (excl. silent MI) + stroke: statistically significant group difference
B.) Cardiovascular mortality + non-fatal MI (excl. silent MI)
C.) Fatal or non-fatal MI (excl. silent MI): statistically significant group difference

(blindness) caused by diabetic retinopathy/diabetic macula oedema (hazard ratio 1.01 [95% CI 0.82; 1.25]).

In the PERISCOPE study, no statistically significant difference between treatment groups was shown for pioglitazone vs. glimepiride in a therapy optimization regimen with/without metformin and/or insulin with regard to any composite outcome on cardiovascular events or any individual component of the combined outcomes. However, except for coronary revascularization, event rates were relatively low. No statistically significant difference between pioglitazone vs. glimepiride was shown for coronary revascularization events (10.7% vs. 11.0% of patients with at least one event).

On the basis of the studies included, no statements can be made on the effects of glitazones on mortality and micro- and macrovascular late complications (except for the PROactive study and, with restrictions, for cardiac interventions in the PERISCOPE study).

Hospital stays

No statistically significant difference between therapy options were identified in any of the included studies on pioglitazone and rosiglitazone with regard to the patient-relevant outcome “hospital stays” (insofar as the corresponding information could be obtained from study reports and publications).

In summary, for this outcome no indication can be inferred from the available information of an advantage or disadvantage of glitazone therapy vs. other treatment options.

Conjoint assessment of long-term glucose lowering and hypoglycaemia

Pioglitazone

The comparison of pioglitazone and placebo in the 3-drug therapy with metformin and sulfonylurea showed an increased hypoglycaemia rate in the pioglitazone group (24.1% vs. 7.1% of patients with at least one event), with simultaneous greater glucose lowering (MD: -1.18 [95% CI -1.39; -0.97]). Severe/serious hypoglycaemic events did not occur. Therefore no advantage for either therapy option was shown.

In 2 studies, fewer hypoglycaemic events occurred with pioglitazone than with sulfonylurea (in the 2-drug therapy with metformin): 2.2% vs. 11.5% and 0.9% vs. 33% of patients with at least one event. The degree of glucose lowering did not differ between the 2 treatment options. These data showed an advantage for pioglitazone. No statement can be made on severe/serious hypoglycaemic events.

In the comparison of pioglitazone/metformin vs. vildagliptin/metformin, no difference in the degree of glucose lowering was shown between the 2 treatment options. Hypoglycaemic events with vildagliptin therapy only occurred in a single case. No advantage for one of the treatment options can be inferred from these data.

The PROactive study, which compared therapy optimization with pioglitazone with therapy optimization without pioglitazone, showed an increased rate of hypoglycaemic events in the pioglitazone group with greater glucose lowering (28.3% vs. 20.2% of patients with at least one hypoglycaemic event; glucose lowering: MD -0.53 [95% CI -0.61; -0.45]). There was no statistically significant difference in the rate of severe/serious hypoglycaemic events between treatment groups. Therefore no advantage for any of the treatments investigated was shown.

In the PERISCOPE study, fewer severe hypoglycaemic events occurred with pioglitazone vs. glimepiride (in a therapy optimization regimen with metformin and/or insulin in both groups) and the overall hypoglycaemia rate was lower (with simultaneous greater glucose lowering):

- patients with at least one severe hypoglycaemic event: 0.4% vs. 2.9%;
- patients with at least one hypoglycaemic event: 15.2% vs. 37%;
- difference in glucose lowering: MD -0.41 [95% CI -0.61; -0.22].

The results showed an advantage for pioglitazone.

Rosiglitazone

The comparison of rosiglitazone and placebo in the 2-drug therapy with sulfonylurea or metformin showed greater glucose lowering with rosiglitazone, with comparable low rates of hypoglycaemic events:

- vs. sulfonylurea: MD -0.74 [95% CI -1.15; -0.33];
- vs. metformin: WMD -1.01 [95% CI -1.28; -0.73] (rosiglitazone 4 mg); WMD -1.07 [95% CI -1.40; -0.75] (rosiglitazone 8 mg).

Severe/serious hypoglycaemic events did not occur. With restrictions, an advantage for rosiglitazone can be inferred from these data.

In 2 studies, the hypoglycaemic rates were increased with the 3-drug therapy including rosiglitazone/metformin/sulfonylurea compared with placebo/metformin/sulfonylurea. At the same time, glucose lowering was greater with the 3-drug therapy including rosiglitazone. Severe/serious hypoglycaemic events did not occur or differences were not statistically significantly different. No advantage for one of the treatment options was therefore shown.

In the comparison of rosiglitazone/metformin vs. sulfonylurea/metformin, in one study there was a statistically significant difference in the rate of severe hypoglycaemic events (0.3% vs. 3.3% of patients with at least one event); in 3 studies, the overall rate of hypoglycaemic events was lower with rosiglitazone/metformin, whilst glucose lowering was comparable. The results showed an advantage for rosiglitazone.

Regarding a difference in hypoglycaemia rates between rosiglitazone and insulin glargine, no evidence of sufficient certainty could be inferred from the studies investigating the 3-drug

therapy with rosiglitazone/metformin/sulfonylurea vs. insulin glargine/metformin/sulfonylurea. This was due to the open study design and the associated high uncertainty of results in the recording of hypoglycaemic events. Likewise, no difference in the hypoglycaemia rate was shown compared with NPH insulin/metformin/sulfonylurea. Due to low event rates, no statement on severe/serious hypoglycaemic events can be made. Therefore no advantage of any therapy option was shown for the overall rate of hypoglycaemic events and for severe/serious hypoglycaemic events.

In the comparison between the 3-drug therapy of rosiglitazone/metformin/sulfonylurea vs. insulin glargine/metformin/sulfonylurea, a lower rate was shown for nocturnal hypoglycaemic events with a glucose level of < 70 mg/dL (10.7% vs. 27.6% of patients with at least one event). An advantage for rosiglitazone can be inferred from this result.

Adverse events

In patients treated with pioglitazone no statistically significant difference between treatment groups was determined for any of the options investigated regarding the occurrence of adverse events and study discontinuations due to adverse events. Serious adverse events occurred statistically significantly more often with pioglitazone/metformin than with vildagliptin/metformin (8.9% vs. 4.1% of patients with at least one serious adverse event).

In patients treated with rosiglitazone, no statistically significant difference between treatment options was shown for the overall rate of adverse events and serious adverse events.

In the placebo-controlled studies on rosiglitazone in 2-drug or 3-drug therapy, no differences between treatment groups were shown regarding study discontinuations due to adverse events.

In the active-controlled studies investigating a 2-drug therapy with rosiglitazone/metformin vs. sulfonylurea/metformin, in one study a statistically significantly higher rate of study discontinuations due to adverse events was shown in the rosiglitazone/metformin group (1.3% vs. 5.7%). However, in 2 longer-term studies including more patients, no difference was shown for study discontinuations due to adverse events, so that overall one can assume comparable event rates in patients treated with rosiglitazone and sulfonylurea (in each case in combination with metformin).

In the meta-analysis of 2 studies comparing a 3-drug therapy with rosiglitazone/metformin/sulfonylurea vs. a 3-drug therapy with insulin glargine/metformin/sulfonylurea, a statistically significantly higher risk was shown for study discontinuations due to an adverse event in the rosiglitazone group (relative risk 4.7; [95% CI 1.23; 17.92]). Likewise, compared with NPH insulin, the discontinuation rate over a year was higher in patients receiving rosiglitazone; however, this difference did not reach statistical significance (4 patients [7%] vs. 0 patients). The evidential value of these data is limited due to the open study design.

Oedema

The adverse event “oedema” occurred statistically significantly more often with pioglitazone than in the control groups in the 2-drug therapy including metformin vs. metformin/sulfonylurea (7.6% vs. 3.5% of patients with at least one event). The same applied to the PROactive study investigating an optimized antidiabetic therapy with pioglitazone vs. therapy optimization without pioglitazone (27.3% vs. 15.9% of patients with at least one event). In the PERISCOPE study, peripheral oedema occurred statistically significantly more often with pioglitazone vs. the comparator treatment with glimepiride (17.8% vs. 11.0% of patients with at least one event). In contrast, the overall oedema rate in the PERISCOPE study was not statistically significantly different between treatment groups, while the numerical event rate was higher in patients treated with pioglitazone (18.9% vs. 13.6% of patients with at least one event).

Peripheral oedema occurred statistically significantly more often in the combination therapy with pioglitazone and human insulin 70/30 vs. monotherapy with human insulin 70/30 (19 [63.3%] vs. 0 [0%] patients with at least one event). In the comparison of pioglitazone/metformin/sulfonylurea vs. placebo/metformin/sulfonylurea, the same number of oedema was reported in both groups; however the overall number was very small. Likewise, no statistically significant difference in the peripheral oedema rate was shown in the comparison between pioglitazone/metformin vs. vildagliptin/metformin.

In addition, in the PROactive study, study discontinuations due to oedema were statistically significantly more common in the group with therapy optimization including pioglitazone than in the group with therapy optimization without pioglitazone (2.7% vs. 0.8% of patients). Only isolated study discontinuations due to oedema were reported in the other studies. Furthermore, in the studies included, the rate of serious oedema was relatively low (or no such events occurred) and statistically significant differences between treatment arms were not reported in any of the studies.

In the studies on rosiglitazone, in all placebo-controlled studies the oedema rate was higher in the rosiglitazone group than in the placebo group in the 2-drug combination with metformin or sulfonylurea and in the 3-drug combination with metformin and sulfonylurea. The number of oedema rose with the increase in rosiglitazone dose. The difference between groups reached statistical significance in 1 of the 4 studies on 2-drug therapy, as well as in a meta-analysis of the studies on rosiglitazone/metformin (8 mg) vs. placebo/metformin (RR 2.97 [95% CI 1.13; 7.83]), and in both studies on 3-drug therapy. The oedema rate was also higher in the active-controlled studies in the rosiglitazone group in the 2-drug combination with metformin vs. sulfonylurea and metformin, as well as in the 3-drug combination with sulfonylurea and metformin vs. insulin glargine or NPH insulin (in combination with sulfonylurea and metformin). The group differences were statistically significant for the 2-drug therapy (5.9% vs. 2.2% of patients with at least one event) and for the 3-drug therapy (12.5% vs. 0% of patients with at least one event) in each case in 1 of 2 studies for which data on oedema were available. With the exception of study 49653/137, in which a serious oedema

occurred in a patient treated with rosiglitazone, no such event occurred in other patients receiving rosiglitazone (or no data on oedema were reported).

Study discontinuations due to oedema were reported for the 2-drug therapy with metformin and the 3-drug therapy with sulfonylurea and metformin; however, no statistically significant differences were shown between the groups compared.

Body weight and BMI

Pioglitazone

Treatment with pioglitazone/metformin/sulfonylurea was associated with a statistically significant increase in body weight/BMI compared with placebo/metformin/sulfonylurea. The mean group difference was 4.1 kg (1.5 kg/m²). No difference in the increase in body weight/BMI was determined for the combination of pioglitazone and human insulin 70/30 compared with insulin monotherapy. In one active-controlled study, a statistically significantly larger increase in body weight over 2 years was measured in the group treated with pioglitazone/metformin compared with the group treated with gliclazide/metformin (mean group difference: 1.3 kg). In contrast, in the open-label comparison of pioglitazone/metformin vs. glimepiride/metformin, no statistically significant difference in increase in body weight was shown over a period of 6 months. A statistically significant increase in body weight was shown in patients treated with pioglitazone/metformin compared with those treated with vildagliptin/metformin. The mean group difference was 2.4 kg within one year. A statistically significant group difference was reported with optimized antidiabetic therapy including pioglitazone vs. therapy optimization without pioglitazone over a period of 34.5 months (in the pioglitazone group the weight/BMI increase was 4.4 kg and 5 kg/m² higher). In the comparison of pioglitazone vs. glimepiride with accompanying therapy optimization, a 1.3 kg greater weight increase was measured in the pioglitazone group over a period of 18 months. The difference between groups was statistically significant.

Rosiglitazone

Compared with placebo, there was a statistically significant increase in body weight over 6 months in the groups receiving 2-drug therapy with rosiglitazone/metformin or rosiglitazone/sulfonylurea, as well as in the group receiving 3-drug therapy with rosiglitazone/metformin/sulfonylurea. In the meta-analysis of the comparison between rosiglitazone/metformin vs. placebo/metformin, a dose-dependent mean group difference of 1.7 kg (4 mg rosiglitazone) and 3.3 kg (8 mg rosiglitazone) was shown. For rosiglitazone/sulfonylurea (4 to 8 mg rosiglitazone) the group difference was 2.6 kg; in the 3-drug therapy, it was 3 kg (4 mg rosiglitazone) and 5 kg (8 mg rosiglitazone).

The results of the 3-drug therapy with rosiglitazone/sulfonylurea/metformin were also confirmed in the 2 open-label studies. Compared with a 2-drug therapy including sulfonylurea/metformin, a mean group difference in BMI of 0.7 kg/m² over both 24 and 35

weeks was determined. When the 2-drug therapy with sulfonylurea/metformin also included physical exercise, the mean group difference was 1.1 kg/m².

The results were inconsistent in the active-controlled studies comparing rosiglitazone/metformin and sulfonylurea/metformin. Patients in the glibenclamide group put on statistically significantly more weight over a period of 24 weeks than those in the rosiglitazone group (Garber 2006); the group difference was 1.5 kg. In contrast, no statistically significant difference was measured between treatment groups in a 32-week study (Bakris 2006). At 24 weeks, no statistically significant difference was shown between the rosiglitazone and gliclazide group for BMI. In contrast, at 52 weeks the increase in body weight was statistically significantly higher with rosiglitazone compared with the sulfonylureas glibenclamide and gliclazide (on average 1.1 kg and 0.5 kg/m²) (AVM 100264).

In a 6-month study, a statistically significant group difference of 1.3 kg was shown for the 3-drug combination of rosiglitazone/metformin/sulfonylurea compared with the combination of insulin glargine/metformin/sulfonylurea. In this context, a larger weight increase was shown for rosiglitazone. In another study, no appropriate analysis was conducted, so an assessment was not possible. In the comparison with NPH insulin, no statistically significant difference in the BMI was shown between treatment groups in the 3-drug combination over 52 weeks.

Cardiac events

In the 2-drug therapy including pioglitazone and metformin (AD-4833/EC410), statistically significantly more cardiac adverse events were shown in a 2-year study than in the control group receiving gliclazide and metformin (7.9% vs. 3.8% of patients). The rate of patients who experienced serious cardiac adverse events was also higher in the pioglitazone group than in the gliclazide group (3.8% vs. 1.3%); this difference was statistically significant. Event rates for heart failure were low (1.6% of patients in the pioglitazone group and 0.6% in the gliclazide group); this difference was not statistically significant. In contrast, in a 6-month open-label study (Umpierrez 2006), no difference in the rate of (serious) cardiac events was shown in the comparison between pioglitazone vs. glimepiride (event rates were also low). For this outcome, the results of the longer double-blind study (AD-4833/EC410) with higher event rates are relevant to the assessment.

In the comparison between pioglitazone/metformin vs. vildagliptin/metformin, no difference in the rate of cardiac adverse events was shown. The rate of serious cardiac adverse events could not be determined, as adverse event reporting in the study was not on the system-organ-class level (according to the MedDRA system). Heart failure events classified as serious adverse events did not occur.

No statistically significant difference between treatment groups was found for the rate of (serious) cardiac events in the PROactive study (comparison of therapy optimization with pioglitazone vs. therapy optimization without pioglitazone). The same applied to the PERISCOPE study (comparison of therapy optimization with pioglitazone vs. therapy optimization with glimepiride). Regarding the adverse event "heart failure", the patients

receiving pioglitazone in the PROactive study showed a statistically significantly higher rate of serious and non-serious heart failure (5.7% vs. 4.1% of patients with at least one event and 6.4% vs. 4.3% of patients with at least one event, respectively). There was no statistically significant difference in the rate of fatal heart failure between the 2 treatment arms (1.0% vs. 0.8% of patients). In the PERISCOPE study, the same number of serious heart failure events occurred in both the pioglitazone and the glimepiride groups (5 events each).

An assessment was not possible for the other pioglitazone studies included, due to a lack of data or very low event rates.

Regarding (serious) cardiac adverse events, no statistically significant difference between treatment groups was found between patients receiving a combination therapy including rosiglitazone/metformin vs. those receiving a combination therapy including sulfonylurea/metformin (Bakris 2006 and AVM 100264). The numerically higher number of serious cardiac adverse events in patients treated with sulfonylurea/metformin in Bakris 2006 was not confirmed in the AVM 100264 study. The rate of heart failure events was too low in both studies to perform an assessment. As for all other rosiglitazone studies included, no data on (serious) cardiac events based on MedDRA coding (“cardiac disorders”) were available; no assessment could be performed for these studies.

Fractures

A statistically significantly higher number of fractures occurred in the PROactive study in women in the “therapy optimization with pioglitazone” arm than in those in the “therapy optimization without pioglitazone” arm (5.1% vs. 2.5% female patients with at least one event). An analysis of the fracture rate in men was not available. In the PERISCOPE study, fractures only occurred in the pioglitazone group and not in the glimepiride group (3.0% vs. 0% of patients with at least one event). The difference between groups was statistically significant.

Health-related quality of life

No differences in health-related quality of life (QoL) were shown in patients treated with pioglitazone and metformin vs. those treated with glimepiride and metformin over a period of 6 months. Health-related QoL was already classified as being relatively good in both groups at baseline.

In the comparison of treatment with rosiglitazone vs. insulin glargine (in each case combined with metformin and sulfonylurea), patients in the insulin glargine group had a worse health-related QoL at baseline. In the course of the 6-month study, patients in the insulin glargine group (who had lower baseline scores) achieved a higher increase in health-related QoL scores than those in the rosiglitazone group.

In summary, due to the open-label study design and the resulting high bias potential for subjective outcomes such as health-related QoL, as well as to the poor reporting of results in

the publications, no conclusions as to an advantage or disadvantage of one of the therapy options can be inferred.

Treatment satisfaction

No statistically significant difference in treatment satisfaction was found over a 52-week period for combination therapy with rosiglitazone and metformin vs. sulfonylurea/metformin (MD 0.04 [95% CI -1.01; 1.09]). There is thus no indication of an advantage or disadvantage of treatment with rosiglitazone/metformin as combination therapy vs. treatment with sulfonylurea/metformin.

Results from studies with unclear applicability

The results of studies showing unclarity regarding their applicability to patients treated within the framework of the drugs' approval did not lead to a change in the conclusion. In these studies, no relevant results were shown for late complications, mortality, hyperosmolar or ketoacidotic coma, and for symptoms related to chronic hyperglycaemia. In accordance with the benefit assessment, the conjoint assessment of long-term glucose lowering and hypoglycaemia showed an advantage for treatment with glitazones compared with sulfonylurea. Disadvantages for treatment with glitazones were also shown regarding the adverse event "oedema", and a greater increase in body weight was also measured.

The ADOPT study was the largest (4360 patients included in 3 arms) and longest (median: 4 years) off-label study. In this study, fractures occurred statistically significantly more often in women in the rosiglitazone group compared with those in the metformin or sulfonylurea monotherapy group (9.3% vs. 5.1% [metformin] and 3.5% [glibenclamide] patients with at least one event). With regard to cardiovascular diseases, no advantage of rosiglitazone vs. metformin was shown in the ADOPT study. In the comparison with glibenclamide, a higher rate of serious cardiovascular diseases (incl. heart failure) was even shown in the rosiglitazone group (3.4% vs. 1.8% of patients with at least one event). However, the evidential value of this result is limited, as the observation and treatment period of patients in the glibenclamide group was shorter. However, in a meta-analysis (incl. ADOPT) of serious adverse events, a higher event rate was shown in patients receiving rosiglitazone monotherapy than in those receiving sulfonylurea monotherapy (RD 0.03 [0.01; 0.05]).

In older patients (≥ 60 years) receiving combination therapy with rosiglitazone/sulfonylurea (RESULT study), the rate of hospital admissions and emergency department (ED) visits was reduced over a period of 2 years compared with patients receiving sulfonylurea monotherapy (hospital admissions: 0.37 vs. 0.76 mean event rate per 1000 patient days; ED visits: 0.59 vs. 1.47 mean event rate per 1000 patient days). In addition, patients showed greater treatment satisfaction (MD 2.76 [95% CI: 1.28; 4.24]). Oedema occurred more frequently in the rosiglitazone group (23% vs. 9% of patients with at least one event). In this study it was allowed to increase the sulfonylurea dose to a maximum dose in both groups.

If the sulfonylurea dose was increased only in patients receiving monotherapy and the dose in the rosiglitazone-sulfonylurea combination group remained constant, the overall rate of adverse events was statistically significantly higher with rosiglitazone in three 6-month studies (RR 1.18 [1.08; 1.29]). In 2 studies, study discontinuations due to an adverse event were also increased with rosiglitazone (RR 1.74 [95% CI: 1.09; 2.79]). Study discontinuations due to oedema occurred statistically significantly more often in patients receiving rosiglitazone (Peto OR 4.70 [95% CI: 1.17; 18.89]).

Conclusion

Regarding the patient-relevant outcomes **micro- and macrovascular late complications and mortality**, there is no proof of an additional benefit of treatment with glitazones compared with other therapy options. In the comparison between therapy optimization with pioglitazone vs. therapy optimization without pioglitazone in patients with a contraindication for metformin, an indication of an additional benefit of pioglitazone was provided by a lower risk for a composite outcome of all-cause mortality, non-fatal MI (excl. silent MI), and stroke. Moreover, in patients who had experienced a stroke in the past, an indication of an additional benefit of pioglitazone with regard to recurrence of a stroke was provided in those receiving therapy optimization with pioglitazone vs. those receiving therapy optimization without pioglitazone. In contrast, in respect of the occurrence of **serious and non-serious heart failure**, the findings provided an indication of greater harm caused by therapy optimization with pioglitazone vs. therapy optimization without pioglitazone.

Regarding the **outcomes blindness, need for dialysis, amputations, hospitals stays, hyperosmolar and ketoacidotic coma, and symptoms related to chronic hyperglycaemia**, there was no indication of a benefit, additional benefit or harm caused by treatment with glitazones.

With regard to the **conjoint assessment of hypoglycaemia and long-term glucose lowering**, proof of an additional benefit was provided for treatment with pioglitazone versus treatment with sulfonylurea, in each case as a 2-drug combination including metformin. This additional benefit was not shown for severe/serious hypoglycaemia.

In the assessment of long-term glucose lowering, an indication of an additional benefit of pioglitazone was provided for (severe) hypoglycaemia in the comparison between therapy optimization with pioglitazone vs. therapy optimization with the sulfonylurea glimepiride.

For patients treated with rosiglitazone, an indication of a benefit was provided for treatment with rosiglitazone/metformin vs. treatment with placebo/metformin or rosiglitazone/sulfonylurea vs. treatment with placebo/sulfonylurea (in patients with chronic kidney failure). However, this indication of a benefit is restricted by the fact that the advantage was only shown with regard to the HbA1c value and not the occurrence of hypoglycaemic events (i.e. better glucose lowering in patients receiving rosiglitazone, with comparable hypoglycaemia rates).

Regarding the occurrence of (severe) hypoglycaemic events (with simultaneous assessment of glucose lowering), the comparison between rosiglitazone/metformin and sulfonylurea/metformin provided proof of an additional benefit of rosiglitazone.

An indication of an additional benefit of rosiglitazone was also provided with regard to nocturnal hypoglycaemia with a glucose level < 70 mg/dL (under consideration of long-term glucose lowering) in the comparison between rosiglitazone/sulfonylurea/metformin vs. insulin glargine/sulfonylurea/metformin.

Regarding the **overall adverse event rate**, no benefit, additional benefit, or harm of treatment with a glitazone was shown. Regarding **serious adverse events**, there was an indication of greater harm caused by treatment with pioglitazone/metformin compared with treatment with vildagliptin/metformin. Regarding **study discontinuations due to adverse events**, there was an indication of greater harm caused by rosiglitazone compared with insulin glargine (in each case combined with sulfonylurea and metformin).

Regarding the **overall oedema rate**, proof was provided of harm caused by rosiglitazone for the comparison rosiglitazone vs. placebo (in each case combined with metformin or metformin/sulfonylurea); for this outcome, proof of this harm in the 2-drug therapy was only provided for the 8 mg dose of rosiglitazone. In respect of the overall oedema rate, an indication was provided of greater harm caused by glitazone therapy for the following treatment options:

- a) pioglitazone/metformin vs. sulfonylurea/metformin;
- b) pioglitazone/human insulin vs. human insulin (refers only to peripheral oedema in patients with chronic kidney disease);
- c) therapy optimization with pioglitazone vs. therapy optimization without pioglitazone;
- d) therapy optimization with pioglitazone vs. therapy optimization with glimepiride (refers only to peripheral oedema);
- e) rosiglitazone/metformin vs. sulfonylurea/metformin; and
- f) rosiglitazone vs. insulin glargine (in each case with sulfonylurea and metformin).

In addition, in patients in the pioglitazone group, an indication was provided of an increased rate of **study discontinuations due to oedema** in the comparison of therapy optimization with pioglitazone vs. therapy optimization without pioglitazone.

Indications of a greater **increase in body weight/BMI** with pioglitazone or rosiglitazone could be inferred from the following comparisons:

- a) pioglitazone/sulfonylurea/metformin vs. placebo/sulfonylurea/metformin;
- b) pioglitazone/metformin vs. sulfonylurea/metformin;

- c) pioglitazone/metformin vs. vildagliptin/metformin;
- d) therapy optimization with pioglitazone vs. therapy optimization without pioglitazone;
- e) therapy optimization with pioglitazone vs. therapy optimization with glimepiride;
- f) rosiglitazone/metformin vs. placebo/metformin;
- g) rosiglitazone/sulfonylurea vs. placebo/sulfonylurea (in patients with chronic kidney failure);
- h) rosiglitazone/metformin/sulfonylurea vs. metformin/sulfonylurea (with/without placebo);
and
- i) rosiglitazone/metformin/sulfonylurea vs. insulin glargine/metformin/sulfonylurea.

Regarding **(serious) cardiac events**, an indication was provided of greater harm caused by pioglitazone/metformin vs. sulfonylurea/metformin.

Regarding **fractures**, in women an indication was provided of greater harm caused by a regimen of therapy optimization with pioglitazone vs. therapy optimization without pioglitazone. In addition, an indication was provided of a greater risk of fractures in patients receiving pioglitazone vs. those receiving glimepiride with an accompanying therapy optimization including metformin and/or insulin.

Closing comment

The long-term benefit and harm of glitazones compared with other glucose-lowering therapies within the framework of the drugs' approval has generally not been sufficiently investigated. Results on therapy optimization with pioglitazone vs. therapy optimization without pioglitazone are available from only one large long-term study, the PROactive study. However, further studies investigating this therapy regimen are also still necessary.

Key words: metformin, pioglitazone, rosiglitazone, sulfonylurea, diabetes type 2, systematic review