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Dapagliflozin (type 1 diabetes mellitus) –

Addendum to Commission A19-37[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
CI	confidence interval
DKA	diabetic ketoacidoses
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
PT	preferred term
SAE	severe adverse event
SOC	system organ class

1 Background

On 9 September 2019, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-37 (Dapagliflozin – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") presented the studies DEPICT 1 and DEPICT 2 for the benefit assessment of dapagliflozin in patients with type 1 diabetes mellitus. Both studies are relevant in the present therapeutic indication and were included in the benefit assessment of dapagliflozin. However, in the company's dossier, data or usable data were missing for several outcomes. Moreover, the company presented analyses only for part of the outcomes for the DEPICT 1 study under the exclusion of incorrectly randomized patients.

With its comments [3], the company submitted an unusable data package to the G-BA. After the oral hearing [4], the company again subsequently submitted analyses [5]. The G-BA commissioned IQWiG to assess these analyses subsequently submitted after the oral hearing.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

2.1 Data subsequently submitted

The data subsequently submitted after the oral hearing comprised the following data relevant for the assessment:

- for both studies, DEPICT 1 and DEPICT 2, analyses on the outcomes
  - symptomatic confirmed hypoglycaemia (plasma glucose ≤ 54 mg/dL)
  - severe hypoglycaemia
  - diabetic ketoacidoses (DKAs): possible and definite DKAs after assessment by an adjudication committee
  - severe adverse events (SAEs) (listing according to system organ class [SOC] and preferred term [PT])
- for DEPICT 1, analyses on side effects under the exclusion of 14 incorrectly randomized patients in the dapagliflozin group (see dossier assessment A19-37 [1]), however, exclusive of the outcomes "urinary tract infection", "symptomatic confirmed hypoglycaemia (plasma glucose ≤ 70 mg/dL)" and "discontinuation due to adverse events (AEs)"

In its comments, the company moreover clarified a discrepancy on the outcome "discontinuation due to AEs" which had been described in dossier assessment A19-37 [1].

In summary, the company therewith subsequently submitted a large part of the data that had been missing in the dossier. For the DEPICT-1 study, analyses on the outcomes "urinary tract infection", "symptomatic confirmed hypoglycaemia (plasma glucose ≤ 70 mg/dL)" as well as "discontinuation due to AEs" are still missing, each under the exclusion of the 14 incorrectly randomized patients in the dapagliflozin group.

The following Section 2.2 shows the results on the data subsequently submitted. The potential influence of the missing analyses on the outcomes "urinary tract infection", "symptomatic confirmed hypoglycaemia (plasma glucose ≤ 70 mg/dL)" and "discontinuation due to AEs" were addressed by sensitivity analyses (assumption: none of the 14 incorrectly randomized patients experienced one of the indicated events).

2.2 Results

Table 1 shows the results on side effects under consideration of the data subsequently submitted by the company. Results on common SAEs can be found in Appendix A.

Table 1: Results (side effects) – RCT, direct comparison: dapagliflozin + insulin vs. placebo + insulin

Outcome category Outcome Study	Dapagliflozin + insulin		Placebo + insulin		Dapagliflozin + insulin vs. placebo + insulin
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Side effects					
AEs (supplementary information)					
DEPICT 1	*145*	*109 (75.2)*	*154*	*115 (74.7)*	–
DEPICT 2	*127*	*105 (82.7)*	*135*	*102 (75.6)*	–
SAEs					
DEPICT 1	145	17 (11.7)	154	16 (10.4)	1.13 [0.59; 2.15]; 0.775[a]
DEPICT 2	127	13 (10.2)	135	9 (6.7)	1.54 [0.68; 3.47]; 0.302
Total[b]					1.27 [0.77; 2.11]; 0.345
Discontinuation due to AEs					
DEPICT 1 (sensitivity analysis[c)]	145	6 (4.1)	154	6 (3.9)	1.06 [0.35; 3.22]; 0.963[a]
DEPICT 2	127	11 (8.7)	135	7 (5.2)	1.67 [0.67; 4.18]; 0.272
Total[b] (sensitivity analysis[c])					1.39 [0.69; 2.80]; 0.358
Symptomatic confirmed hypoglycaemia (plasma glucose ≤ 54 mg/dL)					
DEPICT 1	145	108 (74.5)	154	109 (70.8)	1.05 [0.92; 1.21]; 0.473
DEPICT 2	127	104 (81.9)	135	102 (75.6)	1.08 [0.96; 1.23]; 0.211
Total[d]					1.07 [0.97; 1.17]; 0.175
Symptomatic confirmed hypoglycaemia (plasma glucose ≤ 70 mg/dL)					
DEPICT 1 (sensitivity analysis[c])	145	128 (88.3)	154	114 (74.0)	1.19 [1.07; 1.33]; 0.002[a]
DEPICT 2	127	112 (88.2)	135	110 (81.5)	1.08 [0.98; 1.20]; 0.131
Total[b] (sensitivity analysis[c])					1.14 [1.06; 1.23]; < 0.001
Severe hypoglycaemia[e]					
DEPICT 1	145	4 (2.8)	154	2 (1.3)	2.12 [0.40; 11.42]; 0.380
DEPICT 2	127	2 (1.6)	135	2 (1.5)	1.06 [0.15; 7.43]; 0.951
Total[d]					1.59 [0.45; 5.59]; 0.466

(continued)

Table 1: Results (side effects) – RCT, direct comparison: dapagliflozin + insulin vs. placebo + insulin (continued)

Outcome category Outcome Study	Dapagliflozin + insulin		Placebo + insulin		Dapagliflozin + insulin vs. placebo + insulin
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Side effects					
DKAs (possible)					
DEPICT 1	145	0 (0.0)	154	1 (0.6)	0.35 [0.01; 8.62]; 0.524
DEPICT 2	127	5 (3.9)	135	1 (0.7)	5.31 [0.63; 44.87]; 0.125
Total[d]					2.66 [0.52; 13.58]; 0.241
DKAs (definite)	No data				
DKAs (possible + definite)					
DEPICT 1	145	1 (0.7)	154	2 (1.3)	0.53 [0.05; 5.79]; 0.604
DEPICT 2	127	7 (5.5)	135	2 (1.5)	3.72 [0.79; 17.58]; 0.098
Total[d]					2.13 [0.65; 6.98]; 0.214
Genital infections[f]					
DEPICT 1	145	24 (16.6)	154	6 (3.9)	4.25 [1.79; 10.09]; 0.001
DEPICT 2	127	15 (11.8)	135	6 (4.4)	2.66 [1.06; 6.64]; 0.036
Total[d]					3.45 [1.85; 6.45]; < 0.001
Gastrointestinal disorders (SOC) (AE)					
DEPICT 1	145	25 (17.2)	154	16 (10.4)	1.66 [0.92; 2.98]; 0.090
DEPICT 2	127	38 (29.9)	135	21 (15.6)	1.92 [1.20; 3.09]; 0.007
Total[b]					1.81 [1.251; 2.62]; 0.002
Urinary tract infections[f]					
DEPICT 1 (sensitivity analysis[c])	145	16 (11.0)	154	10 (6.5)	1.70 [0.80; 3.62]; 0.178[a]
DEPICT 2	127	16 (12.6)	135	10 (7.4)	1.70 [0.80; 3.61]; 0.166
Total[b] (sensitivity analysis[c])					1.70 [1.00; 2.90]; 0.051

a: Institute's calculation: RR [95% CI] (asymptotic); unconditional exact test, (CSZ method according to [6]).
b: Institute's calculation, meta-analysis with fixed effect (Mantel/Haenszel).
c: Sensitivity analysis: assumption of 0 events for 14 incorrectly randomized patients in the dapagliflozin group (worst-case analysis).
d: Pooled analysis.
e: Symptomatic hypoglycaemia which was medically treated or treated with glucagon injections or intravenous glucose (independent of blood glucose measurement).
f: Recorded with the company's prespecified PT list.
AE: adverse event; CI: confidence interval; DKA: diabetic ketoacidosis; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

The results show no additional added benefit for any of the outcomes and no greater harm from dapagliflozin versus the ACT in comparison with dossier assessment A19-37 [1]. Based on the

results of the sensitivity analyses, this also applies to the outcomes for which analyses under the exclusion of incorrectly randomized patients are missing. The individual results are as follows:

- As in dossier assessment A19-37, there is no statistically significant result for the outcome "SAE".
- There is no statistically significant result for the outcomes "symptomatic confirmed hypoglycaemia (plasma glucose ≤ 54 mg/dL)" "severe hypoglycaemia" and "DKAs (possible + definite)". The dossier contained no results on these outcomes.
- As in dossier assessment A19-37, greater harm from dapagliflozin in comparison with the ACT was shown for each of the outcomes "genital infections" and "gastrointestinal disorders". Also as in dossier assessment A19-37, the extent of greater harm was considerable for both outcomes (lower limit of the 95% confidence interval (CI) for the relative risk > 1.25).
- The result under the inclusion of the incorrectly randomized patients for the outcomes "discontinuation due to AEs" and "urinary tract infections" (see dossier assessment A19-37) is not statistically significant. The sensitivity analyses in the present addendum show no statistically significant result either.
- There was a statistically significant result for the outcome "symptomatic confirmed hypoglycaemia (plasma glucose ≤ 70 mg/dL)" under the inclusion of the incorrectly randomized patients; however, the effect was no more than marginal (see dossier assessment A19-37). The sensitivity analysis in the present addendum also shows a statistically significant result with an effect that was no more than marginal (lower limit of the 95% CI for the relative risk < 1.11).
- In comparison with dossier assessment A19-37, the results on AEs and SAEs at SOC and PT level showed no notable differences between the treatment groups for any further specific AE.

However, the subsequently submitted data permit a better overall assessment of the added benefit, because the data in the dossier are no longer incomplete with regard to content. The following Section 2.3 describes the resulting consequences for the extent of added benefit.

2.3 Extent of added benefit

The following Table 2 shows the positive and negative effects from the assessment of dapagliflozin + insulin in comparison with placebo + insulin on the basis of dossier assessment A19-37 and the present addendum.

Table 2: Positive and negative effects from the assessment of dapagliflozin + insulin in comparison with placebo + insulin

Positive effects	**Negative effects**
Serious/severe symptoms/late complications HbA1c-value[a]: indication of an added benefit – extent "non-quantifiable"	Non-serious/non-severe side effects ▪ Genital infections: proof of greater harm – extent: "considerable" ▪ Gastrointestinal disorders: proof of greater harm – extent: "considerable"
a: Sufficiently valid surrogate for microvascular late complications. HbA1c: haemoglobin A1c	

In contrast to dossier assessment A19-37, the presently available data are no longer incomplete with regard to content. The overall consideration of the positive and negative effects thus results in an indication of minor added benefit of dapagliflozin over the ACT.

However, this result is restricted to patients whose insufficient glycaemic control is not associated with severe hypoglycaemic episodes. This is due to the fact that patients who had been hospitalized because of hypoglycaemic episodes or severe hypoglycaemic episodes in the month before start of the study were excluded from the studies DEPICT 1 and DEPICT 2 conducted by the company and is supported by the results of these studies, in which the frequency of symptomatic hypoglycaemic episodes was statistically significantly higher under dapagliflozin. The studies DEPICT1 and DEPICT 2 do not permit a derivation of the conclusion that the risk of hypoglycaemic episodes is similar or even lower under dapagliflozin + insulin than under insulin alone for patients whose insufficient glycaemic control is associated with severe hypoglycaemic episodes. Moreover, it cannot be concluded that additional administration of dapagliflozin results in a similar difference in blood-glucose lowering as treatment with insulin alone in these patients, because the occurrence of severe hypoglycaemic episodes might present a restricting factor also for the combination with dapagliflozin. For patients whose insufficient glycaemic control is “associated” with severe hypoglycaemic episodes, the added benefit of dapagliflozin in comparison with the ACT is not proven due to the lack of data.

2.1 Summary

The following Table 3 shows the result of the benefit assessment of dapagliflozin under consideration of dossier assessment A19-37 and the present addendum.

Table 3: Dapagliflozin – probability and extent of added benefit

Therapeutic indication	**ACT**	**Probability and extent of added benefit[a]**
Type 1 diabetes mellitus as an adjunct to insulin in patients with BMI ≥ 27 kg/m^2, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy	Human insulin or insulin analogues (insulin detemir, insulin glargine, insulin aspart, insulin glulisine, insulin lispro)[b]	Patients whose insufficient glycaemic control is not connected with severe hypoglycaemic episodes: **Indication of minor added benefit** Patients whose insufficient glycaemic control is connected with severe hypoglycaemic episodes: Added benefit not proven
a: Changes in comparison with dossier assessment A19-37 are printed in **bold**. a: The unchanged continuation of an inadequate therapy of type 1 diabetes mellitus, if there is still the option of optimizing insulin therapy, does not correspond to an ACT. The approvals and SPCs of the drugs of the ACT have to be considered. ACT: appropriate comparator therapy; BMI: body mass index; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics		

The G-BA decides on the added benefit.

3 References

The reference list contains citations provided by the company in which bibliographical information may be missing.

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Appendix A – Common AEs

The following tables present events for SOCs and PTs according to Medical Dictionary for Regulatory Activities (MedDRA) for the overall rates of "SAEs", each on the basis of the following criteria:

- for all events irrespective of the severity grade: events that occurred in at least 10 patients and in at least 1% of the patients in one study arm

SAEs corresponding to the above criteria did not occur in DEPICT 1.

Table 4: Common SAEs – RCT, direct comparison: dapagliflozin + insulin vs. placebo + insulin in the study DEPICT 2

SOC[a]	**Patients with event n (%)**	
	Dapagliflozin + insulin N = 127	**Placebo + insulin N = 135**
Metabolism and nutrition disorders	7 (5.5)	4 (3.0)

c: MedDRA version 20.1.
MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: severe advere event; SOC: System Organ Class; vs.: versus

Appendix B – Meta-analyses

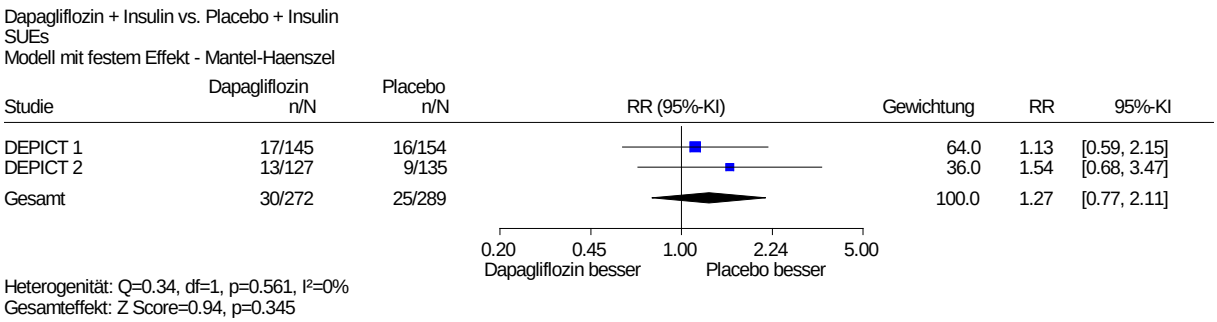


Figure 1: Meta-analysis (fixed effect model according to Mantel-Haenzsel); SAE

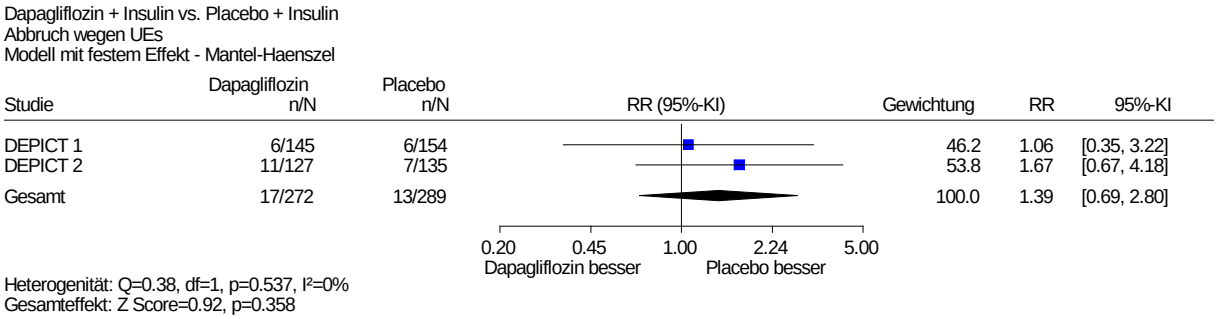


Figure 2: Meta-analysis (fixed-effect model according to Mantel-Haenszel); discontinuation due to AEs

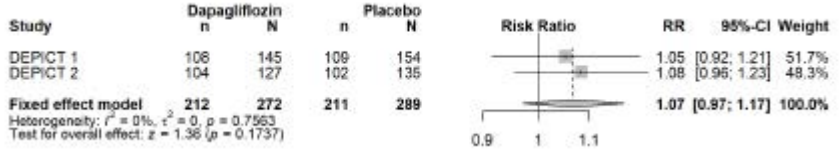


Figure 3: Meta-analysis (fixed-effect model according to Mantel-Haenszel); symptomatic confirmed hypoglycaemia (plasma glucose ≤ 54 mg/dL)

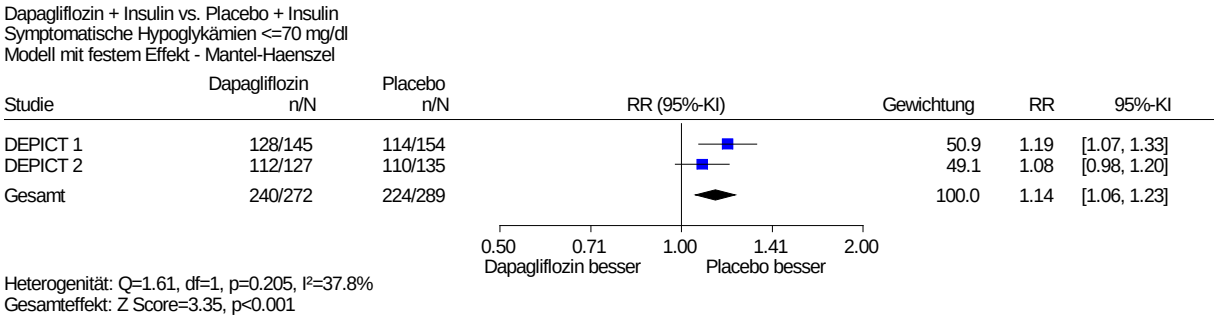


Figure 4: Meta-analysis (fixed effect model according to Mantel-Haenzsel); symptomatic confirmed hypoglycaemia (plasma glucose ≤ 70 mg/dL)

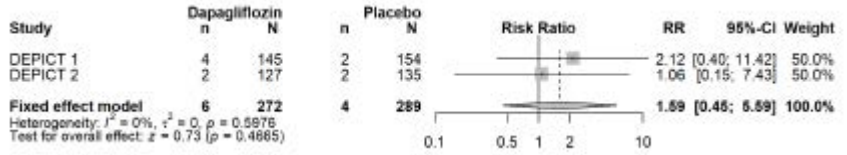


Figure 5: Meta-analysis (fixed effect model according to Mantel-Haenzsel); severe hypoglycaemic episodes

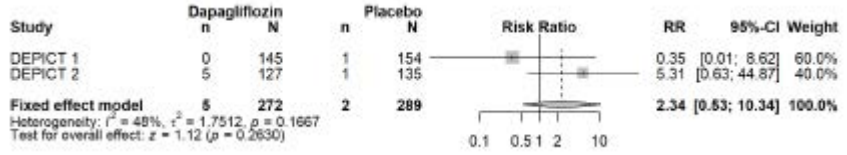


Figure 6: Meta-analysis (fixed effect model according to Mantel-Haenzsel); possible DKAs

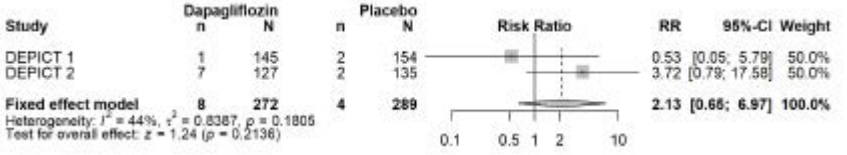


Figure 7: Meta-analysis (fixed-effect model according to Mantel-Haenszel); possible + definite DKAs

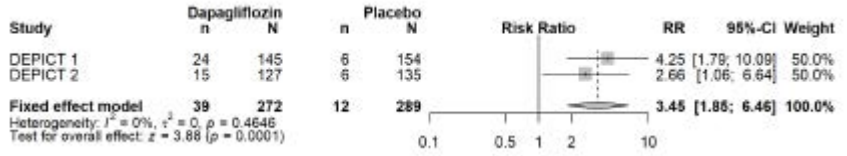


Figure 8: Meta-analysis (fixed effect model according to Mantel-Haenzsel); genital infections

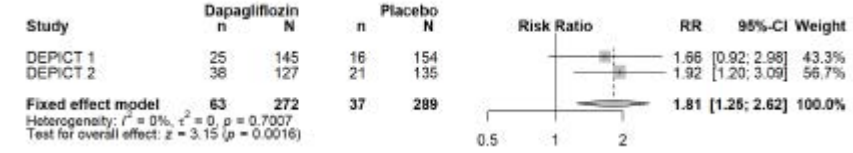
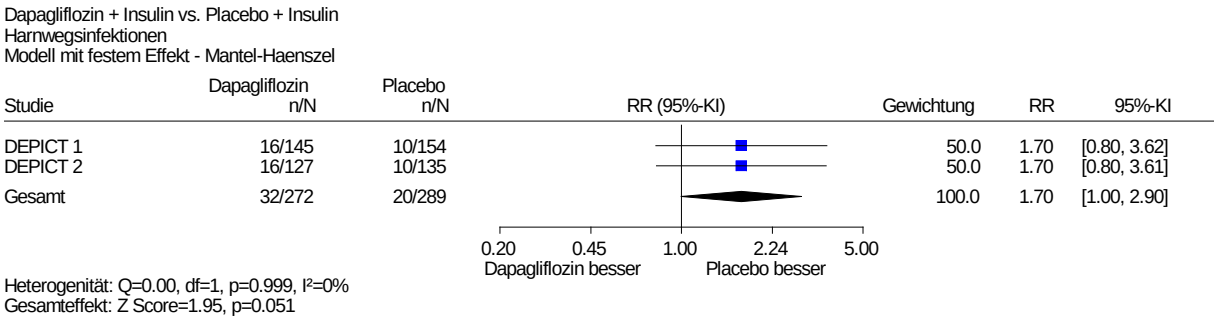


Figure 9: Meta-analysis (fixed effect model according to Mantel-Haenzsel); gastrointestinal disorders



Harnwegsinfektion: urinary tract infection; Modell mit festem Effekt: fixed-effect model; Studie: study; Gewichtung: weighting; Gesamt: total; Besser: better; 95%-KI: 95 %-KI; Heterogenität: heterogeneity; Gesamteffekt: overall effect

Figure 10: Meta-analysis (fixed effect model according to Mantel-Haenzsel); urinary tract infections