Published in final edited form as:

Endocr Pract. 2011 ; 17(5): 691–698. doi:10.4158/EP10405.OR.

SITAGLIPTIN COMPARED WITH THIAZOLIDINEDIONES AS A THIRD-LINE ORAL ANTIHYPERGLYCEMIC AGENT IN TYPE 2 DIABETES MELLITUS

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Abstract

Objective—To compare sitagliptin and thiazolidinediones as third-line oral antihyperglycemic agents among ethnic minority patients with poorly controlled type 2 diabetes mellitus.

Methods—In an open-label, single-arm design, we treated type 2 diabetic patients who had suboptimal diabetes control on maximum tolerated dosages of metformin plus sulfonylureas with the addition of sitagliptin, 100 mg daily, and compared their responses with findings from a historical control group of similar patients treated with rosiglitazone, 8 mg daily, or pioglitazone, 45 mg daily, as their third-line oral agent. Patients were assessed bimonthly, and those who achieved hemoglobin A_{1c} levels less than 7.5% at 4 months continued through 1 year of follow-up.

Results—One hundred eight patients were treated with sitagliptin, and 104 patients constituted the historical control group treated with rosiglitazone or pioglitazone. At baseline, sitagliptin- and thiazolidinedione-treated patients had identical hemoglobin A_{1c} levels (mean $\pm$ SD) ($9.4 \pm 1.8\%$ and $9.4 \pm 1.9\%$, respectively) and similar known diabetes duration (6.7 ± 5.0 years and 7.6 ± 5.8 years, respectively). Hemoglobin A_{1c} was reduced in both groups at 4 months ($P < .001$), but the reduction was greater with thiazolidinediones than with sitagliptin ($-2.0 \pm 1.7\%$ vs $-1.3 \pm 1.8\%$; $P = .006$), as was the proportion of patients achieving a hemoglobin A_{1c} level less than 7.5% (62% vs 46%; $P = .026$). Of all patients achieving a hemoglobin A_{1c} level less than 7.5% at 4 months, the same proportions in each group sustained their hemoglobin A_{1c} level less than 7.5% by 12 months (59% vs 58%). Sitagliptin was well tolerated.

Conclusions—Among ethnic minority patients with poorly controlled type 2 diabetes while taking maximum tolerated dosages of metformin and sulfonylureas, third-line add-on therapy with a thiazolidinedione controlled hyperglycemia more effectively than sitagliptin after 4 months.

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DISCLOSURE

The entire study was investigator initiated, and its concept, design, conduct, analyses, presentation, and manuscript preparation were all under the exclusive control of the authors at all times. Other than supplying sitagliptin, Merck & Co, Inc, had no involvement with the design, conduct, analyses, or manuscript preparation for this study. This study was registered with Clinicaltrials.gov (NCT00686634). The authors have no multiplicity of interest to disclose.

INTRODUCTION

Sitagliptin was the first dipeptidyl-peptidase 4 (DPP-4) inhibitor approved for use in the United States as mono-therapy or in combination with other oral agents for type 2 diabetes mellitus. Its novel mechanism of action, by inhibiting the degradation of endogenous glucagonlike peptide 1 (GLP-1), enhances the antihyperglycemic action of GLP-1 via promoting glucose-stimulated insulin release and inhibiting glucagon release (1). In well-designed clinical trials, sitagliptin has effectively lowered hemoglobin A_{1c} (HbA_{1c}) levels as monotherapy or in combination with other agents, including thiazolidinediones (TZDs) (see review by Dhillon [2]).

Both the American Diabetes Association and the American Association of Clinical Endocrinologists have published clinical practice guidelines for the use of oral agents in type 2 diabetes (3,4), but sitagliptin and TZDs are regarded differently within these 2 sets of recommendations. In contrast to placebo-controlled sitagliptin trials, there have been fewer head-to-head comparison trials between sitagliptin and other oral agents (2), including TZDs (5,6), and none have compared them directly as third-line oral agents. Thus, their comparative utility in this setting remains unclear. Also, no previous studies have examined sitagliptin's efficacy in a low-income, ethnic minority population that is disproportionately affected (7) by type 2 diabetes.

We have previously established the equivalence of rosiglitazone and pioglitazone as third-line oral agents in non-insulin-requiring type 2 diabetes within our institution's indigent population (8). We therefore compared the use of sitagliptin with the use of TZDs in our historical sample when sitagliptin was used as the third-line oral agent under an identical treatment algorithm.

PATIENTS AND METHODS

The Diabetes Specialty Clinic at the Martin Luther King, Jr. Multi-Service Ambulatory Care Clinic, located in south Los Angeles, California, serves a large, ethnic minority population (almost exclusively Hispanic and African American patients) of low-income, often indigent patients. The clinic operates according to a standard treatment protocol, patterned after the American Diabetes Association guidelines (3), that involves incremental therapy with metformin followed by sulfonylureas and then TZDs, each escalated to maximally tolerated dosages, followed by initiation of basal insulin if a HbA_{1c} target less than 7.5% is still not achieved (as described previously [8]). We use this HbA_{1c} threshold for starting insulin because evidence not only indicates just a slight increase in the development or progression of retinopathy and/or nephropathy when HbA_{1c} levels are between 7% and 7.5% (9–13), but starting insulin imposes a significant lifestyle change (eg, the need for self-injections and monitoring, greater hypoglycemia risk). Our current study followed this identical approach, but substituted sitagliptin in place of TZDs as the third-line oral agent. Early use of basal insulin is not preferred in our population because the deep, cultural myths regarding insulin that our patients typically harbor, and the counseling that would be needed to gain their acceptance of insulin would unnecessarily delay intensification of their therapy at the earlier stages of disease when oral agents might still suffice.

Patients

We enrolled type 2 diabetic adults (aged 18 to 75 years) with HbA_{1c} levels greater than 7.0% despite at least 3 months of therapy with maximally tolerated dosages of metformin and maximum dosages of a sulfonylurea (glipizide, glyburide, or glimepiride). Patients were excluded if they had any current or previous long-term use of insulin (1 week other than for gestational diabetes or hospitalizations); any known contraindications to sitagliptin, concurrent use of digoxin, or evidence of renal insufficiency; symptomatic polyuria, polydipsia, or a fasting plasma glucose ≥ 300 mg/dL; active hemolytic anemia or any hemoglobinopathies that may have rendered HbA_{1c} measurements unreliable; pregnancy or lactation; or any clinical or laboratory evidence of systemic disorders that would interfere with the safe use of sitagliptin or the proper interpretation of data. Use of reliable contraception was required of all premenopausal female patients, and pregnancy tests were performed bimonthly throughout the study.

Study Structure

Because of some legal issues between Los Angeles County and Charles R. Drew University of Medicine and Science, Los Angeles County would not allow research to be performed in the Martin Luther King, Jr. Multi-Service Ambulatory Care Clinic. This precluded comparing TZDs and sitagliptin as third-line oral antihyperglycemic agents in an appropriate randomized controlled trial. Therefore, the effect of sitagliptin as a third-line antihyperglycemic agent was evaluated prospectively and compared with our published experience with TZDs (8). While this design is not ideal, in the intervening years since our previous publication, there have been no changes in the oral agents available on our clinic's diabetes drug formulary or the clinic's treatment algorithms that govern the sequential use of different oral agent classes, so the TZD-treated control patients were cared for in the exact same fashion as the current patients receiving sitagliptin. There have also been no changes to the clinic personnel who oversee clinical decisions, or the demographic or socioeconomic characteristics of the patient population served by the clinic over this time span. Therefore, our published experience using TZDs and our current observations using sitagliptin are comparable.

The Institutional Review Board of Charles R. Drew University of Medicine and Science insisted on informed consent of the patients receiving sitagliptin because of our intent to publish the results. The study protocol was reviewed and approved by the institutional review board, and informed consent was obtained from all patients at the university.

Procedures

Qualifying patients were assessed at baseline and then treated with open-label sitagliptin, 100 mg once daily, along with continuation of concurrent metformin and/or sulfonylureas at constant dosages and reinforcement of dietary and lifestyle principles. Patients were reassessed after 1 and 2 months, and thereafter at 2-month intervals for a total of 1 year. At each bimonthly visit, weight, body mass index, HbA_{1c}, fasting plasma glucose, hypoglycemic or other adverse events, and regimen adherence (pill counts) were assessed, along with ongoing reinforcement of dietary, lifestyle, and medication adherence. Down-titration of the sulfonylurea dosage was permitted if necessary to avoid recurrent,

symptomatic hypoglycemic episodes that could not be alleviated with dietary or lifestyle modifications alone. To facilitate pill counts, all unused tablets were collected in exchange for a new 90-day supply of sitagliptin at each bimonthly visit.

Using the HbA_{1c} threshold of less than 7.5% as an index of treatment success, we substituted pioglitazone, 45 mg daily, for sitagliptin as a rescue therapy in patients who did not meet this criterion (sitagliptin “failures”), and then continued to follow their HbA_{1c} levels for at least 4 months while on pioglitazone. Patients who achieved a HbA_{1c} level less than 7.5% after 4 months on sitagliptin were permitted to continue on sitagliptin for the remainder of the study as long as their HbA_{1c} level remained less than 7.5%. Patients were withdrawn if they were nonadherent to scheduled follow-up.

Because of administrative restrictions imposed in our clinic environment that made the rigorous conduct of a properly blinded, randomized trial impossible, we were forced to apply the single-arm strategy with historical comparison presented here. All clinical assessments were made using standardized methods, and all laboratory assays were performed by the Martin Luther King, Jr. Multi-Service Ambulatory Care Clinic clinical chemistry laboratory. HbA_{1c} assays used a high-performance liquid chromatography method that conforms to the Diabetes Control and Complications Trial (DCCT)-aligned method. Merck & Co, Inc (Whitehouse Station, New Jersey), provided a dedicated supply of sitagliptin hydrochloride (100-mg tablets) for this study.

Outcomes

Our primary outcomes were the change from baseline in HbA_{1c} in each group and the between-group difference. Secondary outcomes included the proportions of patients who achieved a HbA_{1c} level less than 7.5% at 4 months and the proportions of patients with HbA_{1c} levels less than 7.5% at 4 months who successfully sustained their HbA_{1c} level less than 7.5% at 1 year. We also tested for any association between known diabetes duration and the HbA_{1c} reduction from baseline to 4 months, adjusted for baseline HbA_{1c}, for either group or all patients combined. As safety measures, we examined the occurrence of any symptomatic hypoglycemia, weight changes, or other adverse events with sitagliptin. Because patients who did not maintain their HbA_{1c} level less than 7.5% were switched to pioglitazone rescue therapy, we also analyzed the proportion of patients who did not maintain control on sitagliptin who achieved a HbA_{1c} level less than 7.5% after 4 months of pioglitazone rescue therapy.

Statistical Methods

Baseline comparisons between groups were made using analysis of variance for continuous variables and the chi-square test for categorical variables. The changes in HbA_{1c} from baseline and the comparison of HbA_{1c} changes between groups were made using the paired Student *t* test and analysis of variance, respectively. Proportions of patients were compared using chi-square tests, associations with known diabetes duration were analyzed using linear regression adjusting for baseline HbA_{1c}, and changes in weight and sitagliptin adherence over time were compared using analysis of variance. For missing data points, the last available HbA_{1c} level was carried forward for patients who had a rise in HbA_{1c} at 2 months

and were switched to an alternative therapy before 4 months and for patients who maintained a HbA_{1c} level less than 7.5% through 10 months of follow-up, but did not attend their final 12-month visit. Based on our previously published mean HbA_{1c} level among non-insulin-treated patients (8), we determined that at least 100 sitagliptin-treated patients were required to detect noninferiority as compared with TZDs (defined as a HbA_{1c} difference <0.5%) at the 5% 2-tailed significance level with 80% power, allowing for an estimated 30% dropout rate.

RESULTS

Recruitment began in December 2007, and the last patient completed the study in March 2010. A total of 108 patients who met the study's entry criteria were prescribed sitagliptin, 100 mg once daily. The flow of all patients over the course of the study is shown in Figure 1. The baseline characteristics of patients prescribed sitagliptin and TZDs (Table 1) were comparable for all measures except that the percentage of patients treated concurrently with metformin was higher for the sitagliptin group. This is because in our previous publication, metformin was withheld or discontinued if the serum creatinine concentration was 1.5 mg/dL or higher in men or 1.4 mg/dL or higher in women, whereas in the current study, with routine estimated glomerular filtration rate reporting, the more stringent criterion was used (an estimated glomerular filtration rate less than 30 mL/min to exclude metformin). Of the 108 sitagliptin-treated patients, 6 were nonadherent to their medication regimen and/or follow-up within the first 2 months, and they did not provide a HbA_{1c} measurement at 4 months. Of the remaining 102 sitagliptin-treated patients, 11 were switched to alternative therapy before 4 months because of a paradoxical rise in HbA_{1c}; their last available HbA_{1c} value while on sitagliptin was carried forward to 4 months.

Table 2 shows the changes in glycemic control among all patients who had paired HbA_{1c} levels at baseline and 4 months. Both groups improved their HbA_{1c}, but the TZD group had a significantly greater decrement ($P = .006$) (Fig. 2). Also, a larger percentage of patients achieved a HbA_{1c} level less than 7.5% at 4 months taking TZDs than those taking sitagliptin ($P = .026$). In linear regression analyses adjusting for baseline HbA_{1c} levels, known diabetes duration was not an independent predictor of the HbA_{1c} response at 4 months for either group or for all patients combined.

Of the 47 sitagliptin-treated patients who achieved a HbA_{1c} level less than 7.5% at 4 months, 3 were lost to follow-up before the next visit at 6 months and were thus excluded from further analyses. Of the remaining 44 sitagliptin-treated patients, 26 (59%) sustained their HbA_{1c} level less than 7.5% through 12 months, while the remaining 18 patients (41%) had a HbA_{1c} measurement rise to 7.5% or higher on or before 12 months. In comparison, 37 of 64 TZD-treated patients (58%) sustained their HbA_{1c} level less than 7.5% through 12 months ($P = .895$ between groups, Table 2).

For sitagliptin safety, we found no significant weight changes over time among all sitagliptin-treated patients who provided paired HbA_{1c} measures between baseline (84.9 ± 21.8 kg) and 4 months (86.0 ± 22.8 kg; $P = .717$), as well as between 4 and 12 months (85.8 ± 24.3 kg at 12 months; $P = .963$ compared with 4 months). Sitagliptin adherence ranged

between 95% and 100% throughout the study (nonsignificant changes over time). Three patients each reported 1 episode of mild hypoglycemia; 2 of these episodes were confirmed with blood glucose readings (62 and 51 mg/dL) and were attributed to dietary inconsistencies. Reinforcement of dietary education prevented further recurrences. The third patient reported night sweats, but did not provide confirmatory blood glucose readings; his glipizide dosage was reduced empirically, which also prevented further recurrences. There were no reports of severe hypoglycemia (defined as requiring the assistance of another person). Adverse events included only constipation in 1 patient and toothaches in 2 other patients.

Fifty-five sitagliptin-treated patients who did not achieve a HbA_{1c} level less than 7.5% (sitagliptin “failures”) received pioglitazone, 45 mg daily, as rescue therapy and had a follow-up HbA_{1c} measurement. At the time of treatment failure, the mean HbA_{1c} value was $9.1 \pm 1.5\%$, which dropped to $8.4 \pm 1.4\%$ after a mean of 124 ± 34 days (~4 months) on pioglitazone; 15 of these 55 patients who had sitagliptin failure (27%) achieved a HbA_{1c} level less than 7.5% on pioglitazone rescue therapy. In linear regression analyses adjusting for the HbA_{1c} level at the time of sitagliptin failure, known diabetes duration did not correlate significantly with the HbA_{1c} response after approximately 4 months of follow-up.

DISCUSSION

Both of the head-to-head comparison studies by Scott et al (5) and Rigby et al (6) found no differences between sitagliptin and rosiglitazone when used as second-line oral agents in terms of HbA_{1c} reduction or the proportion of patients achieving HbA_{1c} targets. In both studies, the magnitudes of HbA_{1c} reduction were less than in our study, probably because our baseline HbA_{1c} level was substantially higher. Ours is the first comparison study of sitagliptin vs TZDs as third-line oral agents and the first to demonstrate that their HbA_{1c} reduction may not be comparable. While Chapell et al (14) demonstrated that the apparent differential benefits between sitagliptin and TZDs across different studies are attributable to differences in baseline HbA_{1c} levels, this would not explain our findings since the patients in our study were all at the same point along a predefined, stepwise treatment algorithm and both their baseline HbA_{1c} levels and their known diabetes duration were very comparable, suggesting that they were at comparable stages in the natural history of their diabetes. However, what is striking is our patients’ extremely poor control at baseline, with their mean HbA_{1c} level of 9.4% being substantially higher than that of every other published sitagliptin trial, including the multiracial cohort of Raz et al (15). It is possible that at this level of hyperglycemia, an actual difference in efficacy between sitagliptin and TZDs may be unmasked. That would also explain why more than one-quarter of the patients who experienced sitagliptin failure in our study still responded to pioglitazone as a rescue therapy. The reason behind this difference may be related to the fact that obese and highly insulin-resistant patients would be expected to benefit more from a strong insulin sensitizer than to a drug that acts only through secretagogue and/or antilucagon effects. Alternatively, there may be pharmacogenetic differences in the relative efficacies of these agents that only pertain to Latino and African American ethnic groups, which have been less represented in most comparative sitagliptin trials to date.

Nevertheless, we did find that sitagliptin was very well tolerated, with no reports of upper respiratory infections. Medication adherence, verified through pill counts, remained high throughout the study, which testifies to sitagliptin's tolerability, especially for a population that is highly prone to medication nonadherence. TZDs, in contrast, are known to precipitate fluid retention and heart failure (16), reduce bone formation (17), and possibly cause debatable adverse cardiovascular effects (in the case of rosiglitazone) (18). They may also precipitate weight gain due to increased adiposity (19), which many patients find undesirable. None of these adverse effects have been associated with sitagliptin, which is weight neutral and generally well tolerated (20), as we observed over a full year of follow-up. Two TZD-treated control patients actually required less than the protocol-mandated maximum dosage of their sulfonylurea because they experienced hypoglycemia while taking their TZD. Although hypoglycemia might seem unlikely for patients with poor control, such as those in our study, 30% of the sitagliptin-treated patients actually achieved a HbA_{1c} level less than 7.0% after 4 months, thus making hypoglycemia more likely. However, even with all patients taking maximum dosages of sulfonylureas (except for 1 patient requiring down-titration), reports of symptomatic hypoglycemia among the sitagliptin-treated patients were rare throughout the entire study. Sitagliptin's cardiovascular effects and its long-term durability of benefit (21) still need to be better defined.

The most obvious limitation of our study is its single-arm design and use of historical controls, which was our only viable option because of administrative restrictions imposed on our ability to conduct proper, randomized trials within our clinic environment; this also made it impossible for us to conduct the study's follow-up visits out of our clinical research facility without further jeopardizing patient retention and follow-up. While this study design may introduce biases, our groups were still well matched for key factors that affect outcome, including demographic characteristics, baseline HbA_{1c}, body mass index, known diabetes duration, and concurrent medications. Although the frequency of metformin use differed between groups at baseline, this imbalance should have biased the HbA_{1c} reductions in favor of sitagliptin, not TZDs. Also, as an open-label study, we cannot rule out possible bias due to the unintended perception of a newer medication somehow being "better." However, such a bias would tend to favor sitagliptin rather than TZDs, and therefore also cannot account for the difference that we observed. In addition, the TZD-treated patients were studied at a time when TZDs were themselves considered relatively "new," an effect that would tend to offset any such bias. Thus, while our findings cannot be definitive, they do suggest that for patients with poor diabetes control, sitagliptin and TZDs may not have equivalent efficacies.

CONCLUSION

In summary, sitagliptin was less effective for glycemic control than TZDs when used for 4 months as a third-line oral antihyperglycemic agent added to metformin and sulfonylureas among ethnic minority patients with poorly controlled type 2 diabetes. However, among patients who met the treatment target and continued beyond 4 months, there was no difference in the ability of sitagliptin or TZDs to sustain HbA_{1c} below target by 12 months. Among patients whose HbA_{1c} level did not remain below target beyond 4 months with sitagliptin, approximately one-quarter still achieved target when switched to pioglitazone. Nevertheless, sitagliptin was well tolerated and did not precipitate any clinically significant

adverse effects. Our findings will help to clarify the relative utilities of sitagliptin and TZDs for the benefit of evidence-based clinical practice recommendations, especially as they may pertain to underrepresented minority groups.

Acknowledgments

We are grateful to the following individuals for their assistance: Liberata Ramos, NP, for assistance with the conduct of the study and Peter Tom, PharmD, for pharmacy support. We also acknowledge Merck & Co, Inc, for providing the supply of sitagliptin used in this study. Dr. Hsia and Dr. Davidson were funded by research grants from the National Institutes of Health (NCRR: Center for Clinical Research Excellence [CCRE]: U54 RR14616) and the American Diabetes Association (Dr. Hsia: 1-09-CR-28; Dr. Davidson: 1-09-CR-15) during the conduct of this study. Dr. Shaheen is funded by a research grant from the National Institutes of Health (NCRR: Accelerating Excellence in Translational Science [AXIS]: U54 RR026138-01). The opinions expressed in this article are those of the authors and do not necessarily represent those of Merck & Co, Inc. These data were previously presented at the 12th Research Centers in Minority Institutions International Symposium on Health Disparities in Nashville, Tennessee, December 9, 2010.

Abbreviations

Dipeptidyl-peptidase 4	DPP-4
glucagonlike peptide 1	GLP-1
hemoglobin A_{1c}	HbA _{1c}
TZD	thiazolidinedione

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Fig. 1.

Flowchart of all sitagliptin-treated patients. ^aIncluded 11 patients with last observation at 2 months carried forward (hemoglobin A_{1c} paradoxically increased and patients were given alternative therapy). ^bIncluded 2 patients with last observation at 10 months carried forward (hemoglobin A_{1c} level sustained at less than 7.5%, but they did not attend the 12-month visit).

Fig. 2. Hemoglobin A_{1c} (HbA_{1c}) responses at 4 months for sitagliptin- and thiazolidinedione (TZD)-treated patients. Dotted line indicates the hemoglobin A_{1c} threshold of 7.5%. Solid dashes indicate the mean HbA_{1c} levels for each group at baseline and 4 months.

Table 1

Baseline Characteristics of Type 2 Diabetic Study Population

Characteristics	Sitagliptin (n = 108)	Thiazolidinediones (n = 104 [48 taking rosiglitazone and 56 taking pioglitazone])	P value ^a
Age, mean (SD), y	50.7 (9.8)	52.5 (10.8)	.215
Female, No. (%)	68 (63)	63 (61)	.721
Ethnicity, No. (%)			.110
Hispanic	91 (84)	82 (79)	
African American	17 (16)	18 (17)	
Other	0 (0)	4 (4)	
Known diabetes duration, mean (SD), y	6.7 (5.0)	7.6 (5.8)	.226
Patients taking sulfonylureas, No. (%)	108 (100)	104 (100)	>.99
Patients taking metformin, No. (%)	107 (99)	92 (88)	.001
Body mass index, mean (SD), kg/m ²	32.7 (8.3)	32.2 (7.3)	.656
Hemoglobin A _{1c} , mean (SD), %	9.4 (1.8)	9.4 (1.9)	.952

^a P values are for analysis of variance for continuous variables or chi-square test for categorical variables.

Table 2Hemoglobin A_{1c} Outcomes in Type 2 Diabetic Patients Taking Sitagliptin or a Thiazolidinedione

Hemoglobin A _{1c}	Sitagliptin (n = 102)	Thiazolidinedione (n = 104)	<i>P</i> value ^a
Hemoglobin A _{1c} , mean (SD), %			
Baseline	9.4 (1.8)	9.4 (1.9)	.952
4 Months	8.0 (1.8)	7.4 (1.3)	.007
Change	-1.3 (1.8) ^b	-2.0 (1.7) ^b	.006
Patients with hemoglobin A _{1c} <7.5%, No. (%)			
Baseline	9 (8.8)	11 (10.6)	.671
4 Months	47 (46.1) ^c	64 (61.5) ^c	.026
Patients sustaining hemoglobin A _{1c} <7.5% by 12 months, No. (%)	26/44 (59.1)	37/64 (57.8)	.895

^a *P* value is for between-group differences by analysis of variance for hemoglobin A_{1c} or chi-square test for proportions.^b *P* < .001 for the change from baseline (determined by the paired Student *t* test).^c *P* < .001 for the change from baseline (determined by the chi-square test).