BMJ Open Diabetes Research & Care

PERS&O (PERsistent Sitagliptin treatment & Outcomes): observational retrospective study on cardiovascular risk evolution in patients with type 2 diabetes on persistent sitagliptin treatment

Giulia Buonaiuto,[1] Valentina De Mori,[1] Alessandra Braus,[2] Annalisa Balini,[1] Denise Berzi,[1] Rita Carpinteri,[1] Franco Forloni,[1] Giancarla Meregalli,[1] Gian Luca Ronco,[3] Antonio C Bossi[1]

To cite: Buonaiuto G, De Mori V, Braus A, *et al*. PERS&O (PERsistent Sitagliptin treatment & Outcomes): observational retrospective study on cardiovascular risk evolution in patients with type 2 diabetes on persistent sitagliptin treatment. *BMJ Open Diabetes Research and Care* 2016;**4**:e000216. doi:10.1136/bmjdrc-2016-000216

Received 20 February 2016
Revised 15 May 2016
Accepted 31 May 2016

[1]Endocrine Unit, Diabetes Regional Center, Treviglio, Italy
[2]Pharmacy Unit, ASST Bergamo Ovest (Bg), Treviglio, Italy
[3]Emmonos, IT HealthCare Senior Consultant, Como, Italy

Correspondence to
Dr Antonio C Bossi;
antonio_bossi@asst-bgovest.it

ABSTRACT

Objectives: The UK Prospective Diabetes Study (UKPDS) Risk Engine (RE) provides the best risk estimates available for people with type 2 diabetes (T2D), so it was applied to patients on persistent sitagliptin treatment.

Design: A 'real-world' retrospective, observational, single-center study.

Setting: The study was performed in a general hospital in Northern Italy in order: (1) to validate UKPDS RE in a cohort of Italian participants with T2D without prespecified diabetes duration, with/without cardiovascular (CV) disease, treated with sitagliptin; (2) to confirm CV risk gender difference; (3) to evaluate the effect on metabolic control and on CV risk evolution obtained by 'add-on' persistent sitagliptin treatment.

Participants: Sitagliptin 100 mg once a day was taken by 462 participants with T2D: 170 of them (males: 106; age: 63.6±8.8; T2D duration: 11.58±7.33; females: 64; age: 65.6±7.95; T2D duration 13.5±7.9) were treated for 48 months with the same dosage.

Interventions: An analysis of normality was performed both for continuous, and for groups variables on UKPDS RE percentage values, defining the requirement of a base $\log_{10}$ transformation to normalize risk factor values for analysis validation.

Results: The evaluation of CV risk evolution by gender (t-test) confirmed the expected statistical difference ($p<0.0001$). Sitagliptin obtained significant results after 12 months, and at the end of the observation, both on metabolic control (expressed by glycated hemoglobin) and on UKPDS RE. Analysis of variance test revealed a significant effect on CV risk after 12 months ($p=0.003$), and after 48 months ($p=0.04$). A bivariate correlation analysis revealed a correlation index ($r=0.2$ between the two variables ($p<0.05$).

Conclusions: These 'real-world' data obtained applying UKPDS RE may reflect patients' and clinicians' interest in realizing individual CV risk, and its evolution. Sitagliptin-persistent treatment for a medium–long period obtained an improvement on metabolic control, as well as a reduction on CV risk.

Key messages

- The UK Prospective Diabetes Study (UKPDS) Risk Engine (RE) validation in Italian patients with type 2 diabetes (T2D) confirms the broaden use of the algorithm.
- UKPDS RE appears reliable in newly diagnosed patients with T2D, as well as in participants with non-prespecified diabetes duration, in the presence (or not) of previous cardiovascular (CV) disease.
- UKPDS RE confirmed the expected CV risk gender difference in this single-center Italian cohort of participants with T2D.
- 'Real-world' data obtained applying UKPDS RE may reflect patients' and clinician's interest in realizing individual CV risk, and its evolution.

INTRODUCTION

Sitagliptin was the 'first in class' dipeptidyl peptidase (DPP)-4 inhibitor (DPP4i) for the treatment of type 2 diabetes (T2D): it was approved for clinical use in 2006 and has been commercially available in Italy since 2008. Thereafter, several other DPP4i drugs (also named 'gliptins') have been introduced into clinical practice (vildagliptin, saxagliptin, linagliptin, alogliptin):[1] they are all oral agents that have to be taken once or twice a day. By inhibition of the DPP-4 enzymes, they prevent the inactivation of the incretin hormones: glucagon-like peptide-1 (GLP-1), produced by L-cells of the distal small intestine

and colon; and glucose-dependent insulinotropic polypeptide (GIP), derived from the duodenal, jejunal and ileal K-cells. GLP-1 was mainly found to be a potent antidiabetic hormone due to its ability to stimulate insulin secretion and inhibit glucagon secretion, consequently increasing glucose usage and diminishing hepatic glucose production. Through reduction in postprandial and fasting glucose, GLP-1 reduces glycated hemoglobin (HbA1c) with a low risk for hypoglycemia and no disturbance on body weight.[2] Some clinical trials have recently evaluated the cardiovascular (CV) safety of gliptins. SAVOR-TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)-Thrombolysis in Myocardial Infarction (TIMI)) randomly assigned 16 492 T2D who had a history of, or were at risk for, CV events to receive saxagliptin or placebo and followed them for a median of 2.1 years. Saxagliptin did not increase or decrease the rate of the primary end point (a composite of CV death, myocardial infarction (MI), or ischemic stroke), though the rate of hospitalization for heart failure (HF) rose (3.5% vs 2.8%; HR 1.27; 95% CI 1.07 to 1.51; p=0.007); nevertheless, mortality did not increase in patients with HF.[3] Moreover, the EXAMINE trial (Examination of Cardiovascular Outcomes with Alogliptin vs Standard of Care) was performed on 5380 patients with T2D and with an acute MI or unstable angina requiring hospitalization within the previous 15–90 days. They were randomly assigned to receive alogliptin or placebo in addition to existing antihyperglycemic and CV drug therapy, and were followed for up to 40 months (median 18 months). The rates of major adverse CV events did not increase with alogliptin as compared with placebo.[4] Subsequent meta-analysis, on the other hand, speculated about a potential 'class effect' of gliptins on HF incidence;[5] however, an Italian 'real-world' observation did not find any increased HF risk and also suggested a potential reduction for all-cause mortality in patients with T2D treated with DPP4i. At most, insulin-treated patients may present a higher risk for hospitalization and mortality.[6] Similarly, a large Italian observational study revealed a reduction in HF with DPP4i in comparison with sulfonylurea (SU) treatment.[7] We may also consider that the CV safety of gliptins was previously supported by a meta-analysis of more than 70 randomized controlled trials (RCTs; enrolling 41 959 patients with a mean follow-up of 44.1 weeks), suggesting that treatment with DPP4i reduces the risk of CV events (particularly MI) and all-cause mortality in patients with T2D.[8] Finally, in TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin), 14 671 patients with T2D with stable CV disease were assigned to add either sitagliptin or placebo to their existing therapy in order to evaluate a primary CV outcome (a composite of CV death, non-fatal MI, non-fatal stroke or hospitalization for unstable angina). After a median follow-up of 3.0 years, the authors concluded that adding sitagliptin to usual care did not appear to increase the risk of major adverse CV events.[9]

RESEARCH DESIGN AND METHODS

The aforementioned clinical trials have followed patients with T2D during time, analyzing the incidence of CV events in participants treated with DPP4i. However, it may be useful in a real-world setting to apply algorithms able to predict the chance for a 'single patient' to succumb to CV disease: CV disease is indeed a major cause of morbidity and decreased life expectancy in patients with T2D. Risk calculators based on equations from the Framingham Heart Study[10] tend to underestimate risks for participants with T2D, as this study included relatively few participants with diabetes. The UK Prospective Diabetes Study (UKPDS) is a source of information based on a cohort that originated from a trial of 5102 patients aged 25–65 with newly diagnosed T2D.[11 12] In 2001, UKPDS researchers proposed an algorithm to evaluate CV risk, with an equation that included both diabetes duration and glycemic control (expressed by means of HbA1c; UKPDS Risk Engine V.2.0: UKPDS RE).[13] The UKPDS RE Isis Innovation Ltd 2001 is available without charge to clinical and non-commercial organizations visiting the website: https://www.dtu.ox.ac.uk/riskengine/download.php.[14] As a matter of fact, International Diabetes Federation (IDF) guidelines consider UKPDS RE as the most reliable and predictable algorithm for patients with T2D.[15] The UKPDS RE may tend to overestimate CV risk in the Italian population, which is at a lower risk in comparison with British people.[16] Nevertheless, the UKPDS Outcomes Model satisfactorily predicted a set of actual incidences of mortality and complications in another Italian diabetes cohort up to a duration of ~12 years.[17] The performance of the model was best for patients with a recent history of disease (duration <6 years), because UKPDS patients were 'newly' diagnosed participants with T2D. Among the complications, the predicted cumulative incidences of MI and congestive HF were very close to those observed. Since 'real-world' data may reflect the patient and clinician's interest to understand individual CV risk and its evolution, the objectives of the present retrospective observational study may be summarized as follows:

1. UKPDS RE validation in Italian outpatients with T2D recruited from a single center, without age or diabetes duration prespecified, with or without previous CV disease, evaluating risk at baseline (prior to sitagliptin 'add-on' treatment) and during a medium–long follow-up period;
2. UKPDS RE estimate as referred to gender, in order to confirm CV risk difference;
3. Evaluation of the effects of persistent sitagliptin treatment both on metabolic control and on CV risk evolution during time.

Patients suffering from a not well-controlled T2D (HbA1c>7.5%=58 mmol/mol) with usual antihyperglycemic drugs were retrospectively recruited by consulting our local Health Electronic Recording (HER) system (MyStarConnect, METEDA, Italy). Patients who had

previously taken a DPP4i or a GLP-1 receptor agonist, or those whose estimated glomerular filtration rate was <30 mL/min/1.73 m^2 of body-surface area at baseline were excluded. PERS&O (PERsistent Sitagliptin treatment & Outcomes) was approved by the Bergamo Ethical Committee. Anthropometric and clinical values before sitagliptin 'add-on', in agreement with an Italian Drug Agency (AIFA) recommendation, were recorded as 'baseline' conditions; data of patients who maintained sitagliptin therapy were registered after 12 and 48 months. At the same time interval, the CV risk of these patients was calculated applying UKPDS RE as previously reported.[14] Sitagliptin was taken by 462 participants with T2D; changes in therapy during the 48 months of follow-up were recorded. The validation process allowed us to consider 170 of them (males: 106; age: 63.6±8.8; T2D duration: 11.58±7.33; females: 64; age: 65.6±7.95; T2D duration 13.5±7.9) who had been treated with sitagliptin for 48 months: 145 patients with 100 mg, 25 participants with 50 mg once a day. After 48 months, metformin was increased for five patients and reduced for one participant; SU dosage was reduced for three patients, but intensified for two participants; one patient reduced the dosage of pioglitazone. All patients were managed by endocrinologists of our hospital team, performing visits every 6 months (earlier if complications occurred). Table 1 summarizes the clinical parameters and UKPDS RE values. At baseline, 28.56% of males and 7.81% of females were smokers; 44.36% of males and 40.62% of females suffered from hypertension. Total cholesterol at baseline was 185.47 ±38.49 mg/dL; after 48 months, it was reduced at 172.11 ±37.34 mg/dL. Low-density lipoprotein cholesterol at baseline was 103.06±32.34 mg/dL; after 48 months, it was reduced at 90.24±24.08 mg/dL. At baseline, 36 patients were treated with diuretics or antialdosteronic drugs; 36 were on β-blockers and 29 were on calcium-channel antagonists; 63 were on treatment with ACE inhibitors (ACE-I) and 38 with angiotensin receptor blockers (ARB); 82 patients were treated with statins and 8 with fibrates. After 48 months, 44 were on diuretics or antialdosteronic drugs (+8 vs baseline); 43 were on β-blockers (+8 vs baseline) and 35 were on calcium-channel antagonists (+6 vs baseline); 70 were treated with ACE-I (+7 vs baseline), while 48 were on ARB (+10 vs baseline); 101 were treated with statins (+19 vs baseline) and 9 with fibrates (+1 vs baseline).

Statistical analyses: Descriptive and normality tests were routinely performed on the data set. The cases were also clustered with reference to standard clinical indicators in order to be more compliant with practitioners' experience. Data mining techniques were applied to the data set in order to obtain meaningful information for statistical analyses. We focused on the identification of therapeutic models, with an emphasis of frequencies and their percentage variation during the 48 months follow-up. A correlation analysis was performed to verify the hypothesis of preservation or improvement of the

Table 1 Clinical data of patients with T2D on sitagliptin-persistent treatment, at baseline, after 12 months, and after 48 months of follow–up

	Mean value		95% CI				Median value		SD		Shapiro-Wilk significance	
			Lower limit		Upper limit							
	M (N=106)	F (N=64)	M (N=106)	F (N=64)	M (N=106)	F (N=64)	M (N=106)	F (N=64)	M (N=106)	F (N=64)	M (N=106)	F (N=64)
Age (years)	63.60	65.61	61.91	63.62	65.30	67.60	64.50	66.00	8.80	7.95	0.469	0.742
T2D duration (years)	11.58	13.58	10.17	11.60	13.00	15.55	10.00	13.50	7.33	7.90	0.000	0.000
BMI at baseline	29.88	30.47	28.94	29.16	30.81	31.77	29.25	29.80	4.86	5.24	0.000	0.015
FPG at baseline	172.98	165.78	165.78	157.21	180.18	174.36	168.00	169.00	37.37	34.33	0.230	0.015
HbA1c (%) at baseline	8.37	8.22	8.21	8.07	8.54	8.38	8.40	8.20	0.87	0.63	0.234	0.112
HbA1c (%) after 12 months	7.31	7.41	7.14	7.24	7.49	7.59	7.30	7.50	0.91	0.69	0.000	0.205
HbA1c (%) after 48 months	7.33	7.32	7.19	7.15	7.48	7.48	7.40	7.20	0.75	0.65	0.319	0.215
UKPDS (log_{10}) at baseline	1.36	1.14	1.31	1.08	1.40	1.20	1.38	1.15	0.24	0.23	0.250	0.425
UKPDS (log_{10}) after 12 months	1.30	1.12	1.25	1.05	1.35	1.18	1.32	1.15	0.25	0.25	0.082	0.317
UKPDS (log_{10}) after 48 months	1.33	1.12	1.28	1.07	1.38	1.18	1.35	1.13	0.25	0.23	0.194	0.843

BMI, body mass index; F, females; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; M, males; T2D, type 2 diabetes; UKPDS, the UK Prospective Diabetes Study.

patient's clinical status during the follow-up period based on the therapeutic schema in use. In addition, multivariate linear regression analysis and bivariate correlation analysis were applied to UKPDS normalized values. Intermediate analyses were performed to grant the conformance to analysis constraints assuring the validity and integrity of the analysis themselves. The confounding factors were properly taken into account in multivariate models (analysis of variance, ANOVA). The primary outcome was to verify the hypothesis that the therapeutic model adopted has created a significant effect on metabolic control through HbA1c values and the CV risk factor expressed by the UKPDS index. The null hypothesis assumes that there has been no significance. The sample size calculation was obtained, depending on the type of statistical analysis that it was intended to apply, assuming α=0.05 (type I error)—β=0.20 (type II error)—f (U)=0.30 (effect size) and 80% power to test the hypothesis with 170 valid cases (N=170). Assuming, also on the basis of previous experiences,[18–20] the eventuality of dropping out incomplete data that were collected during the follow-up period for a maximum of 55% cases, we have established retrieving from the HER in use in the ward at least 400 cases that meet the assumed selection criteria. Finally, in order to minimize the ratio between the value of the research and its cost,[21 22] we have considered it appropriate to manage a sample size coherent to the total costs of the study. The statistical analysis was performed using SPSS V.20—IBM Corp.

RESULTS

An analysis of normality was performed both for continuous, and for groups variables on UKPDS RE percentage values, defining the requirement of a base $\log_{10}$ transformation to normalize risk factor values for analysis validation. An analysis of the evaluation of CV risk evolution by gender (t-test) confirmed the expected statistical difference (p<0.0001), as shown in table 2. Sitagliptin obtained significant results after 12 months, and at the end of the observation (48 months), on metabolic control (expressed by HbA1c) and on UKPDS RE. After having verified that sitagliptin treatment was able to determine a significant effect on HbA1c values (a not significant effect was considered as null hypothesis), a univariate analysis among antihyperglycemic therapy plans was performed: ANOVA test revealed a significant effect of sitagliptin on HbA1c levels after 12 months, as well as after 48 months (table 3). Variance analysis did not reveal any significant difference among groups (p>0.05) during the whole follow-up time. Sitagliptin also exerted a significant effect on CV risk both after 12 months (p=0.003) and after 48 months (p=0.04; table 4). A bivariate correlation analysis revealed a correlation index (r)=0.2 p<0.05 among the two variables.

CONCLUSIONS

TECOS[9] enrolled patients with T2D with established CV diseases who were at least 50 years old, with HbA1c level from 6.5% to 8.0%. However, during daily outpatients' clinic activity, AIFA recommended potential 'add-on' therapy with sitagliptin if the HbA1c value was from 7.5% to 9.0%, with no limits regarding age or previous CV disease. Therefore, it should be interesting to consider a 'real-world' sitagliptin treatment in patients with T2D without prespecified limitation pertaining to vital statistics, nor atherosclerotic disease, adding CV risk evaluation by means of UKPDS RE. We recognize that the historical nature of the British cohort makes it difficult to generalize, because of its exclusion of people over 65, and we underline the mean age of participants with T2D recruited in PERS&O (males: >63; females: >65 years; no gender statistical difference). Furthermore, the UKPDS cohort excluded those with various comorbidities, such as established heart disease, non-fatal and fatal coronary heart disease (CHD), non-fatal and fatal stroke. Nevertheless, the UKPDS RE provides risk estimation for various ethnic groups, for any given duration of T2D based on current age, sex, ethnicity, smoking status, presence or absence of atrial fibrillation and levels of HbA1c, systolic blood pressure, total cholesterol, and high-density lipoprotein cholesterol. We were aware of some limitations when applying UKPDS RE to our Italian population, but we were supported by our 'normality' analysis: abnormal risk estimates would have led to inconsistent data. Moreover, another Italian paper encouraged our observation.[17] In their paper, Pagano and colleagues used data from the Casale Monferrato

Table 2 CHD at baseline and after 48 months, and evaluation of CV risk evolution (evaluated by UKPDS RE) by gender (t-test) at baseline, after 12 months, and after 48 months

	Males Mean (SD)	Females Mean (SD)	Effect size	Mean difference and 95% CI	p Value
CHD at baseline	21/106 (19.81%)	4/64 (6.25%)			
CHD after 48 months	27/106 (25.47%)	5/64 (7.81%)			
UKPDS at baseline	1.36 (0.24)	1.14 (0.23)	0.91	0.22 (0.14 to 0.29)	<0.0001
UKPDS after 12 months	1.30 (0.25)	1.12 (0.25)	0.73	0.19 (0.11 to 0.26)	<0.0001
UKPDS after 48 months	1.33 (0.25)	1.12 (0.23)	0.85	0.21 (0.13 to 0.28)	<0.0001

CHD, coronary heart disease; CV, cardiovascular; UKPDS RE, the UK Prospective Diabetes Study Risk Engine.

Table 3 HbA1c evolution (at baseline, after 12 months, and after 48 months) in relation to various antihyperglycemic plans

Adopted therapeutic plan	HbA1c at baseline				HbA1c after 12 months				HbA1c after 48 months			
	N	Mean (SD)	F (df)	p Value	N	Mean (SD)	F (df)	p Value	N	Mean (SD)	F (df)	p Value
DPP4i (sitagliptin alone)	8	7.85 (1.28)	2.63 (7.162)	0.014	4	6.15 (0.74)	4.36 (7.162)	<0.0001	5	6.44 (0.61)	6.09 (7.162)	<0.0001
DPP4i+metformin	70	8.25 (0.72)			72	7.10 (0.74)			74	7.05 (0.69)		
DPP4i+metformin+SU	75	8.46 (0.72)			75	7.66 (0.81)			75	7.63 (0.61)		
DPP4i+metformin+SU+other	1	9.20 (0.00)			2	7.70 (1.41)			1	7.70 (0.00)		
DPP4i+metformin+other	4	8.70 (0.55)			4	7.43 (0.36)			4	8.08 (0.17)		
DPP4i+SU	6	8.42 (0.93)			7	7.49 (0.76)			6	6.98 (0.63)		
DPP4i+SU+other	1	8.60 (0.00)			1	7.60 (0.00)			1	7.90 (0.00)		
DPP4i+other	5	7.26 (0.97)			5	7.00 (0.91)			4	7.37 (0.23)		

DPP4i, dipeptidyl peptidase-4 inhibitor (sitagliptin); HbA1c, glycated hemoglobin; other, other oral antihyperglycemic agents, or insulin therapy; SU, sulfonylureas.

Survey, a cohort enrolled in 1988 and surveyed in 1991 (n=1967), to assess the prevalence of CV risk factors. In 2000, a new survey included all the members of the original cohort who were still alive (n=860) and, in addition, all individuals identified with a new diagnosis of T2D since 1993 (n=2389). They compared the mortality predicted by the model for the 1991 survey over the subsequent 17-year period with the observed risk. The UKPDS Outcomes Model satisfactorily predicted a set of actual incidences of mortality and complications in this Italian diabetes cohort up to a duration of ~12 years. On the one hand, the UKPDS RE now provides the best risk estimates available for people with newly diagnosed T2D. On the other hand, the mean T2D duration was >11 years in the PERS&O study, and it is known that the risk of diabetic complications increases with duration of disease. In detail, diabetes duration was longer in females than in males (years: 13.58±7.33 vs 11.58±7.9; p<0.0001). So, the UKPDS RE, as with all risk calculators, should tend to underestimate the actual risk for any individual with long-standing T2D or for people who have had unrecognized diabetes for many years. Additionally, females were more frequently overweight or obese than men (body mass index: 30.47±5.24 vs 29.88±4.86; p<0.15). Nevertheless, our data confirmed CV gender difference (p<0.0001) during the entire observational period (tables 1 and 2). Similarly, in a cohort of CV disease-free Italian participants with T2D (6032 women and 5612 men), a Diabetes And Informatics (DAI) study reported an age-standardized incidence rate (per 1000 person-years) of first CHD event greater in men (28.8%; 95% CI 5.4% to 32.2%) than in women (23.3%; CI 20.2% to 26.4%). Major CHD (MI, coronary artery bypass grafting, and percutaneous transluminal coronary angioplasty) was less frequent in women than in men, with a sex ratio of 0.5.[23] HbA1c was satisfactorily reduced among all the adopted therapeutic plans of our study after sitagliptin 'add-on', since the very first year of treatment (p<0.001), with no difference among groups over time (table 3). Anyway, patients who fail to respond to DPP4i should be at increased CV risk or should suffer from most severe diabetes, requiring multiple drugs: we were not allowed to support any hypothesis based on our data. Sitagliptin obtained a major HbA1c reduction in the 'real world' if compared with what predictable by an intriguing recent 'nomogram' proposed to estimate the HbA1c response to different DPP4i drugs in T2D.[24] Even if most literature reports an improvement in HbA1c of 0.5–0.9% with sitagliptin,[25 26] PERS&O's patients presented a larger HbA1c reduction. A possible explanation may be that we studied patients on persistent sitagliptin therapy, excluding treatment failure or patients with DPP4i intolerance. Furthermore, greater reductions in HbA1c were seen in participants with higher baseline levels.[27] ANOVA evaluation between therapeutic plans and UKPDS RE values showed a significant effect on CV risk since the first year of treatment modification, with no difference among

Table 4 UKPDS RE values at baseline, after 12 months, and after 48 months in relation to various antihyperglycemic plans

	UKPDS RE at baseline			UKPDS RE after 12 months			UKPDS RE after 48 months		
Adopted therapeutic plan	N	Mean (SD)	p Value	N	Mean (SD)	p Value	N	Mean (SD)	p Value
DPP4i (sitagliptin alone)	8	1.28 (0.30)	0.14	4	1.16 (0.17)	0.003	5	1.13 (0.23)	0.04
DPP4i+metformin	70	1.21 (0.26)		72	1.15 (0.27)		74	1.20 (0.25)	
DPP4i+metformin+SU	75	1.31 (0.25)		75	1.28 (0.25)		75	1.27 (0.26)	
DPP4i+metformin+SU+other	1	1.28 (0.00)		2	1.11 (0.28)		1	1.25 (0.00)	
DPP4i+metformin+other	4	1.46 (0.28)		4	1.44 (0.24)		4	1.40 (0.35)	
DPP4i+SU	6	1.46 (0.13)		7	1.48 (0.17)		6	1.53 (0.19)	
DPP4i+SU+other	1	1.23 (0.00)		1	1.18 (0.00)		1	1.23 (0.00)	
DPP4i+other	5	1.34 (0.33)		5	1.36 (0.31)		4	1.52 (0.07)	

DPP4i, dipeptidyl peptidase-4 inhibitor (sitagliptin); other, other oral antihyperglycemic agents, or insulin therapy; SU, sulfonylureas; UKPDS RE, the UK Prospective Diabetes Study Risk Engine.

groups during the observational period (table 4), while a bivariate correlation analysis was able to demonstrate a correlation index (r)=0.2 between the two variables ($p<0.05$). By the way, this is a single-center observational study with comprehensible limitations: first of all, the retrospective design, as well as the small number of participants with 48 months of follow-up, and the absence of a competing treatment in comparison with sitagliptin. Furthermore, the evolution in therapeutic plans during time may play a crucial role in determining the reduction of CV risk. However, it must be taken into consideration that healtcare arranged by a single center is certainty of a standardized approach to T2D, while multicenter studies should introduce potential bias in the therapeutic decision process. PERS&O aim was not the evaluation of Major Adverse Cardiovascular Event (MACE) incidence during time, but the application of UKPDS RE in people with T2D coming from a peculiar region in Northern Italy. Treatment with DPP4i, according to a recent meta-analysis,[8] was seen to reduce the risk of CV events and all-cause mortality in patients with T2D. The reduction in the incidence of MI was greater than what was predicted on the basis of conventional risk factors, suggesting a role for other mechanisms. Potentially, DPP4i efficacy on mean amplitude of glycemic excursions (MAGE), on oxidative stress, and on systemic inflammatory markers in patients with T2D should be a protective CV mechanism. MAGE diminishment is associated with reduction of oxidative stress and markers of systemic inflammation.[28] In a very recent observation in Japanese patients with T2D, sitagliptin showed superior antihyperglycemic effects compared with voglibose, but both agents demonstrated unique pleiotropic effects that lead to reduced CV risk in Japanese people with T2D.[29] So, CV risk evolution, and metabolic control obtained with DPP4i treatment, should be focused on RCT, as well as on 'postmarketing' studies and on 'real-world' experience: routine practice requires complex interactions between clinical knowledge, medical expertise, guidelines pertinence, and personal judgment. Such a requirement is common in various fields: chronic obstructive pneumopathies,[30] arterial hypertension,[31] chemotherapy for oncological patients.[32] Diabetes management, as well, requires facts able to translate RCT results, and guidelines recommendations, into daily activity.[33] For instance, a very recent 'real-world' study provides some welcome reassurances regarding the HF risk of DPP4i.[34] However, to impart actual real-world data, such observational studies should ideally strive to evaluate the full spectrum of users of these drugs.[35] Other algorithms were developed to identify patients at high risks of macrovascular complications, such as QStroke (proposed to identify patients at high risk of ischemic stroke), which includes diabetes type in the prediction formula.[36] A validated risk prediction equation was recently proposed in order to quantify the absolute risks of blindness and lower limb amputation over 10 years in men and women with type 1 diabetes (T1D) and T2D;[37] in addition, a novel method was published by the same authors to quantify the predictable risk of HF among people with T1D or T2D for further assessment and proactive treatment.[38] The research for, and the proposal of, prediction algorithms are quite understandable because patients need good quality information on how likely they are to develop complications and the expected risks and benefits from interventions to reduce the risk. This is even more admissible for participants suffering from diabetes, because some microangiopathic or macroangiopathic complications may impair their quality of life or reduce their life expectancy. On the basis of our findings, we would propose applying UKPDS RE to every patient with T2D at every follow-up visit, in order to understand the evolution of her/his personal CV risk. More accurate and individualized information on the risk of complications (and complications' evolution) may help patients to make more aware decisions about the risk–benefit ratio of the treatment options reflecting their own values and choices. Better information on the absolute risk of individual complications could also prompt a more intensive treatment of modifiable risk factors.[37]

Possible clinical implications: These 'real-world' data obtained by applying UKPDS RE to patients with T2D in persistent DPP4i therapy for a medium–long period

confirmed that sitagliptin obtained an improvement on metabolic control, as well as a reduction on CV risk, but larger and longer studies are mandatory to verify sitagliptin 'durability'. UKPDS RE validation in this single-centre cohort of Italian patients with T2D proved the forcefulness of the algorithm, and confirmed the expected CV risk gender difference both at baseline and at final observation. UKPDS RE appeared reliable in newly diagnosed patients with T2D, as well as in participants without prespecified diabetes duration, with or without previous CV disease. Finally, data obtained by applying UKPDS RE may reflect patients' and clinicians' interest in realizing individual CV risk and its evolution.

Contributors ACB, GB, and AB designed the protocol and the methods. GLR carried out the statistical analyses. All authors contributed to data collection and drafting of the article and approved the final version of the manuscript.

Funding This study was funded by the Treviglio Hospital Health Management.

Competing interests ACB received consultancy fees, attended advisory boards, or held lectures for the following pharmaceutical companies producing devices and/or antidiabetic drugs: Lilly Italia SpA, Novo Nordisk Italia SpA, Johnson and Johnson Italia SpA, Boehringer Ingelheim Italia SpA, and Artsana Italia SpA. GLR received consultancy fees from MSD Italia Srl.

Patient consent Obtained.

Ethics approval Bergamo Ethic Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Preliminary reports of the study have been presented (as poster presentations) at the 26th SID Annual Meeting (Rimini, Italy, 4–7 May 2016). A more complete report has been submitted to the 52nd EASD Annual Meeting (Munich, Germany, 12–16 September 2016).

REFERENCES

1. Deacon CF, Holst JJ. Dipeptidyl peptidase-4 inhibitors for the treatment of type 2 diabetes: comparison, efficacy and safety. *Expert Opin Pharmacother* 2013;14:2047–58.
2. Ahrén B. Dipeptidyl peptidase-4 inhibitors: clinical data and clinical implications. *Diabetes Care* 2007;30:1344–50.
3. Scirica BM, Bhatt DL, Braunwald E, *et al*, SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013;369:1317–26.
4. Zannad F, Cannon CP, Cushman WC, *et al*, EXAMINE Investigators. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicenter, randomised, double-blind trial. *Lancet* 2015;385:2067–76.
5. Monami M, Dicembrini I, Mannucci E. Dipeptidyl peptidase-4 inhibitors and heart failure: a meta-analysis of randomized clinical trials. *Nutr Metab Cardiovasc Dis* 2014;24:689–97.
6. Giorda CB, Picariello R, Tartaglino B, *et al*. Hospitalisation for heart failure and mortality associated with dipeptidyl peptidase 4 (DPP-4) inhibitor use in an unselected population of subjects with type 2 diabetes: a nested case–control study. *BMJ Open* 2015;5:e007959.
7. Fadini GP, Avogaro A, Degli Esposti L, *et al*, OsMed Health-DB Network. Risk of hospitalization for heart failure in patients with type 2 diabetes newly treated with DPP-4 inhibitors or other oral glucose-lowering medications: a retrospective registry study on 127,555 patients from the Nationwide OsMed Health-DB Database. *Eur Heart J* 2015;36:2454–62.
8. Monami M, Ahrén B, Dicembrini I, *et al*. Dipeptidyl peptidase-4 inhibitors and cardiovascular risk: a metaanalysis of randomized clinical trials. *Diabetes Obes Metab* 2013;15:112–20.
9. Green JB, Bethel MA, Armstrong PW, *et al*, TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2015;373:232–42.
10. Anderson KM, Odell PM, Wilson PW, *et al*. Cardiovascular disease risk profiles. *Am Heart J* 1991;121:293–8.
11. [No authors listed]. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:837–53.
12. Adler AI, Stratton IM, Neil HA, *et al*. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ* 2000;321:412–19.
13. Stevens RJ, Kothari V, Adler AI, *et al*, United Kingdom Prospective Diabetes Study (UKPDS) Group. The UKPDS risk engine: a model for the risk of coronary heart disease in type II diabetes (UKPDS 56). *Clin Sci (Lond)* 2001;101:671–9.
14. https://www.dtu.ox.ac.uk/riskengine/download.php (accessed 15 May 2016).
15. International Diabetes Federation. Global guidelines for type 2 diabetes. http://www.idf.org/node/1283 (accessed 15 May 2016).
16. Janssen F, Kunst AE, Netherlands Epidemiology and Demography Compression of Morbidity research group. Cohort patterns in mortality trends among the elderly in seven European countries, 1950–1999. *Int J Epidemiol* 2005;34:1149–59.
17. Pagano E, Gray A, Rosato R, *et al*. Prediction of mortality and macrovascular complications in type 2 diabetes: validation of the UKPDS Outcomes Model in the Casale Monferrato Survey, Italy. *Diabetologia* 2013;56:1726–34.
18. Sacket DL, Richardson WS, Rosenberg W. *Evidence-based medicine: how to practice and teach EBM*. New York: Churchill Livingstone, 1997.
19. Diggle PJ. Testing for random dropouts in repeated measurement data. *Biometrics* 1989;45:1255–8.
20. Kristman V, Manno M, Côté P. Loss to follow-up in cohort studies: how much is too much? *Eur J Epidemiol* 2004;19:751–60.
21. Bacchetti P. Current sample size conventions: flaws, harms, and alternatives. *BMC Med* 2010;8:17.
22. Bacchetti P, Wolf LE, Segal MR, *et al*. Ethics and sample size. *Am J Epidemiol* 2005;161:105–10.
23. Avogaro A, Giorda C, Maggini M, *et al*, Diabetes and Informatics Study Group, Association of Clinical Diabetologists, Istituto Superiore di Sanità. Incidence of coronary heart disease in type 2 diabetic men and women: impact of microvascular complications, treatment, and geographic location. *Diabetes Care* 2007;30:1241–7.
24. Esposito K, Chiodini P, Maiorino MI, *et al*. A nomogram to estimate the HbA1c response to different DPP-4 inhibitors in type 2 diabetes: a systematic review and metaanalysis of 98 trials with 24 163 patients. *BMJ Open* 2015;5:e005892.
25. Aschner P, Kipnes MS, Lunceford JK, *et al*. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care* 2006;29:2632–7.
26. Raz I, Hanefeld M, Xu L, *et al*. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus. *Diabetologia* 2006;49:2564–71.
27. Deacon CF. Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review. *Diabetes Obes Metab* 2011;13:7–18.
28. Rizzo MR, Barbieri M, Marfella R, *et al*. Reduction of oxidative stress and inflammation by blunting daily acute glucose fluctuations in patients with type 2 diabetes: role of dipeptidyl peptidase-IV inhibition. *Diabetes Care* 2012;35:2076–82.
29. Matsushima Y, Takeshita Y, Kita Y, *et al*. Pleiotropic effects of sitagliptin versus voglibose in patients with type 2 diabetes inadequately controlled via diet and/or a single oral antihyperglycemic agent: a multicenter, randomized trial. *BMJ Open Diabetes Res Care* 2016;4:e000190.
30. Price D, Brusselle G, Roche N, *et al*. Real-world research and its importance in respiratory medicine. *Breathe (Sheff)* 2015;11:27–38.
31. Laken MA, Dawson R, Engelman O, *et al*. Comparative effectiveness research in the "real" world: lessons learned in a study of treatment-resistant hypertension. *J Am Soc Hypertens* 2013;7:95–101.
32. Fujita K, Sasaki Y. Optimization of cancer chemotherapy on the basis of pharmacokinetics and pharmacodynamics: from patients enrolled in clinical trials to those in the 'real world'. *Drug Metab Pharmacokinet* 2014;29:20–8.

33. Johnson M, Jones R, Freeman C, *et al*. Can diabetes prevention programmes be translated effectively into real-world settings and still deliver improved outcomes? A synthesis of evidence. *Diabet Med* 2013;30:3–15.
34. Fu AZ, Johnston SS, Ghannam A, *et al*. Association between hospitalization for heart failure and dipeptidyl peptidase 4 inhibitors in patients with type 2 diabetes: an observational study. *Diabetes Care* 2016;39:726–34.
35. Filion KB, Suissa S. DPP-4 inhibitors and heart failure: some reassurance, some uncertainty. *Diabetes Care* 2016;39:735–7.
36. Hippisley-Cox J, Coupland C, Brindle P. Derivation and validation of QStroke score for predicting risk of ischaemic stroke in primary care and comparison with other risk scores: a prospective open cohort study. *BMJ* 2013;346:f2573
37. Hippisley-Cox J, Coupland C. Development and validation of risk prediction equations to estimate future risk of blindness and lower limb amputation in patients with diabetes: cohort study. *BMJ* 2015;351:h5441.
38. Hippisley-Cox J, Coupland C. Development and validation of risk prediction equations to estimate future risk of heart failure in patients with diabetes: a prospective cohort study. *BMJ Open* 2015;5:e008503.