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Changes in antidiabetic treatment in a Swiss population-based sample. The CoLaus study

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Changes in antidiabetic drug treatment in a Swiss population-based sample. The CoLaus study

Short running title: 5.5-year changes in antidiabetic drug treatment

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Abstract

Background and aims: Treatment of type 2 diabetes mellitus (T2DM) evolves with time, but little information is available regarding its determinants in the general population. We aimed to assess changes and determinants associated to antidiabetic treatment in a Swiss population-based sample.

Methods: Two hundred and ten participants with T2DM (136 men, mean±SD age 59.8±8.8 years). Antidiabetic drug treatment was assessed at baseline (2003-2006) and follow-up (2009-2012), and categorized into maintainers, changers and reducers/quitters.

Results: at baseline, 146 (69.5%) of the 210 participants received antidiabetic treatment. Of the 146 participants treated, 124 (84.9%) received oral antidiabetics alone, 8 (5.5%) insulin alone and 14 (9.6%) insulin and oral antidiabetics. During the 5.5 year follow-up, 108 (74.0%) patients maintained, 27 (18.5%) changed and 11 (7.5%) reduced or stopped treatment. Patients who changed therapy had higher baseline fasting plasma glucose (FPG) levels than the others (10.3±3.7 vs. 7.8±2.0 and 7.6±2.0 mmol/L for maintainers and reducers/quitters, respectively, $p<0.001$) and also lower levels of FPG<7.0 mmol/L (7.4%, vs. 39.8% and 45.5% for maintainers and reducers/quitters, respectively, $p=0.002$). At follow-up, patients who changed therapy had the highest prevalence of FPG decrease relative to baseline (55.6%, vs. 46.3% and 9.1% for maintainers and reducers/quitters, respectively, $p=0.025$).

Conclusion: during a 5.5 year follow-up less than one fifth of patients with T2DM had his/her drug treatment changed. Changes in antidiabetic treatment lead to an improvement of the unfavourable FPG status. The reasons and impact of quitting or reducing treatment should be further explored.

Keywords: Type 2 diabetes; antidiabetic drugs; treatment; epidemiology; trends

Introduction

Diabetes mellitus is a worldwide public health concern and its prevalence is continuously rising with the increase of obesity (1). In Switzerland, the prevalence of diabetes mellitus is estimated to 6.3% (2). Diabetes is also a major cause of reduced life expectancy and is associated with increased mortality and morbidity (3). As diabetes is a progressive disease, improvement of pharmaceutic treatment is therefore a public health challenge. International guidelines have described a panel of antidiabetic drugs and among them, metformin was defined as the first choice therapy for diabetes treatment since 2009 (4). Conforming to these recommendations, recent studies showed an increase of metformin therapy (5, 6). Apparition of new antidiabetic agents, such as DPP4 inhibitors, seemed to affect the pattern of antidiabetic drug prescription as their use has been increasing over time (7, 8). Despite that, management of diabetes seems to be suboptimal, highlighting the need to assess in the future prescribing pattern of antidiabetic drugs (9, 10). In Switzerland, a previous study described that one third of treated subjects reported not achieving optimal levels of glycaemia (11). Even though epidemiological data have shown that screening and prevalence of treated diabetes patients increased these last years, there is little knowledge concerning management of diabetes for the Swiss population (11). These findings suggest the need for further research to improve control of diabetes mellitus.

This study aimed to describe trends in antidiabetic drug use in a Swiss cohort and to identify factors associated with evolution of diabetes treatment.

Methodology

Sampling

The sampling procedure of the Colaus study has been reported previously (12). Colaus is a prospective study aimed to assess the prevalence and determinants of cardiovascular disease in a Swiss population-based sample. The target population was composed of the inhabitants aged 35 to 75 living of the city of Lausanne, in the Swiss canton of Vaud. The list of eligible participants was obtained from the Lausanne's population office. The baseline study started in July 2003 and ended in May 2006, and the first follow-up started in May 2009 and ended in August 2012. The same participants were examined at baseline and follow-up. More details are available at www.colaus.ch.

Data collected

Each participant underwent a personal inquiry, a self-reported questionnaire, a physical examination and a blood sample analysis. All participants were examined at the Lausanne university hospital (CHUV) after an overnight fasting. A unique interview of 60 minutes was organized through

which information such as social or educational status and physical activity were collected. The inquiry also focused on the personal medical history of the subject (i.e. personal history of diabetes) and the presence of cardiovascular risk factor like smoking, high blood pressure and dyslipidaemia. The same methodology was applied at baseline and follow-up.

Educational status was categorized into [primary or apprenticeship], secondary and university level. Participants were considered as physically active if they performed leisure-time physical activity at least twice per week. Smoking status was categorized into current, former and never. Marital status was categorized into living alone (i.e. single, divorced or widowed) and living in a couple (i.e. married or equivalent).

All drugs prescribed to the participants were collected. Antidiabetic treatment was categorized into insulin, biguanides, sulfonylureas, sulphonamides, antidiabetic combination therapy, alpha-glucosidase inhibitors, thiazolidinediones and DPP4 inhibitors. Three categories were defined based on the antidiabetic drug treatments reported at baseline and follow-up: maintainers (i.e. no change in antidiabetic treatment), changers (i.e. addition of a new drug to the initial antidiabetic treatment or shifting from an oral antidiabetic to insulin) and reducers (either no treatment or a lower drug regimen at follow-up).

Body weight was measured in kg to the nearest 100 g with a Seca® scale; body height was measured in meters to the nearest 5 mm using a Seca® height gauge. Body mass index (BMI) was calculated as weight/(height^2), and further categorized into normal (<25 Kg/m^2), overweight (≥25 and <30 Kg/m^2) and obesity (≥30 Kg/m^2). Waist size was measured in duplicate at mid-distance between the lowest rib and the iliac crest using a non-stretchable tape, and the average of the two measures was used. Abdominal obesity was defined as a waist ≥102 cm for men and ≥88 cm for women.

Clinical chemistry analyses were performed at the Clinical Laboratory of CHUV. Venous blood samples were collected after an overnight fasting. Blood tests were performed on fresh blood sample and additional samples were preserved at -80 °C for eventual analyses. All measurements were conducted in a Modular P apparatus (Roche Diagnostics, Switzerland). Glucose assessment was determined by glucose dehydrogenase with a maximum inter-assay CV of 2.1% and a maximum intra-assay CV of 1.0%. Insulin was assessed by a solid-phase, two-site chemiluminescent immunometric assay (Diagnostics Products Corporation, Los Angeles, USA) with a maximum intra-assay CV of 13.7%. Insulin resistance was assessed by the HOMA index according to Matthiews et al (13). Diabetes was defined as fasting blood glucose (FBG) ≥7 mmol/l or the presence of antidiabetic drug treatment. As no measurements of HbA1c were available, management of diabetes was based on FBG levels; adequate management was considered if FBG was <7.0 or <6.5 mmol/L as performed previously (2).

Inclusion and exclusion criteria

Only participants with T2DM at baseline and who were followed were included. Participants not treated for diabetes, reporting a diagnosis of type 1 diabetes or without follow-up were excluded.

Statistical analysis

Statistical analyses were performed using Stata v.14.1 (Stata Corp, College Station, TX, USA). Results were expressed as number of participants (percentage) for categorical variables and as average ± standard deviation for continuous variables. Between-group comparisons were performed using $\chi 2$ or Fisher's exact test for categorical variables and Student's t-test or analysis of variance (ANOVA) for continuous variables. Trends in antidiabetic treatment over time were analysed using Mc Nemar's test. Trends regarding continuous variables were assessed using Student's t-test for matched pairs. Statistical significance was defined as a two-side tests with $p<0.05$.

Ethical statement

The institutional ethics committee of the University of Lausanne (Commission d'Ethique de la recherche Clinique www.cer-vd.ch) approved the baseline study (reference 16/03, decisions of 13th January and 10th February 2003). The approval was renewed for the follow-up study (reference 33/09, decision of 23rd February 2009). All participants gave their signed informed consent before entering the study.

Results

Of the initial 6733 participants, 6405 (95.1%) were excluded because they had no diagnosis of diabetes, and 11 (0.2%) because of a diagnosis of type 1 diabetes, leaving 317 participants with T2DM. Of these, a further 107 (1.6%) were excluded because of lack of follow-up (**Figure 1**). The characteristics of the participants with T2DM according to presence or absence of follow-up are summarized in **supplementary table 1**. Excluded participants had a higher frequency of personal history of hypertension, while no significant differences were found for the rest of variables.

Trends in antidiabetic treatment

Of the 210 participants with T2DM, 146 (69.5%) received antidiabetic treatment: 124 (84.9%) received oral antidiabetics alone, 8 (5.5%) insulin alone and 14 (9.6%) insulin and oral antidiabetics. At follow-up, 9 (6.2%) participants were not treated, 91 (62.3%) received oral antidiabetics alone, 14 (9.6%) insulin alone and 32 (21.9%) insulin and oral antidiabetics. Of the 146 patients treated at baseline, 138 (94.5%) received oral antidiabetics, which decreased to 84.3% at follow-up ($p<0.001$). The distribution of the different oral antidiabetic drugs at baseline and follow-up among treated

participants is provided in **Figure 2**. Biguanides were the most prescribed antidiabetic drug, but their use decreased within the study period. The same trend was found for sulfonylureas, thiazolidinediones and alpha-glucosidase inhibitors, while the proportion of participants treated with DPP4 inhibitors increased. The prevalence of insulin treatment among participants treated at baseline increased from 15.1% to 31.5% ($p<0.001$).

Trends and determinants of change in antidiabetic treatment

During the 5.5 year follow-up, 108 (74.0%) patients maintained, 27 (18.5%) changed and 11 (7.5%) stopped or reduced treatment. The baseline characteristics of the participants according to antidiabetic drug changes are summarized in **Table 1**. Participants who subsequently changed their medication had higher fasting plasma levels and a lower prevalence of optimal glucose levels, while no differences were found for BMI, waist, insulin and HOMA levels.

The impact of antidiabetic drug changes on glucose markers is summarized in **Table 2**. Patients who reduced their treatment had an increase of FPG levels at follow-up, while participants who changed their treatment had a reduction of FPG levels. Conversely, the changes in FPG levels, glycemic control or anthropometry within each group were not statistically significant.

Discussion

To our knowledge, only one study (14) examined the association between change in medication and change in glycemic control. Our results suggest that most patients with T2DM are properly managed, and that changes in treatment lead to an improvement in glycemic status. Still, a small percentage of patients reduces or even stops the treatment, resulting in deleterious consequences on their glycemic status.

Trends in antidiabetic treatment

Biguanides were the most frequently prescribed antidiabetic drug, but the frequency decreased at follow-up; a similar trend was found for sulfonylureas, thiazolidinediones and alpha-glucosidase inhibitors. Conversely the proportion of participants treated with DPP4 inhibitors or insulin increased. These trends are in agreement with other studies (5, 7, 15) and indicate a change in therapy to account for the progression of diabetes or for a better control of the disease. For example, the number of participants taking both oral antidiabetics and insulin more than doubled (14 to 32) between baseline and follow-up, and participants who changed their treatment had a better evolution of their FPG levels than the other participants. Overall, our results indicate that oral antidiabetic drugs tend to be replaced or complemented by insulin as longer is diabetes' duration.

Trends and determinants of change in antidiabetic treatment

Approximately three quarters of the participants treated for diabetes maintained their treatment, 18.5% changed and a 7.5% reduced or quit. The percentage of reducers was considerably lower compared to a prospective study conducted in 2002-2008 in Taiwan among 12,123 newly diagnosed patients with type 2 diabetes (12% decreasing adherence and 20.6% non-adherents) (16) and also to a study conducted in 1989-1997 in the US (13% of quitters) (15). Possible explanations include a relatively old age of our participants, as it has been shown that older people are more compliant to treatment (16, 17), and a higher motivation or health consciousness among included participants.

Participants who changed their antidiabetic treatment had a worse glycemic status at baseline; conversely, their FPG levels tended to decrease and the proportion of participants with FPG <6.5 more than tripled between baseline and follow-up. Our results are in agreement with a previous study (14) and indicate that adapting antidiabetic treatment can lead to an improvement in glycemic status and reduction in diabetes-related complications.

Participants who either stopped or reduced antidiabetic treatment had relatively adequate FPG levels and almost half had FPG <6.5 mmol/L at baseline. Conversely, their status was much worse at follow-up, with an average increase in FPG levels of 1.9 mmol/L and less than one third achieving FPG levels <6.5 mmol/L. Our findings are in agreement with a previous study (14) where a reduction in treatment adherence was associated with an increase in HbA1c levels. Several studies have shown that significant weight loss is associated with an improvement of glycemic status (18, 19), but this could not be the reason for decreasing or quitting in this study, as participants who decreased or quit had the same trend regarding weight and BMI than the others. Our results show that decreasing or even quitting antidiabetic treatment considerably impacts glycemic status, with a higher likelihood to develop complications and to have higher health costs (20). Thus, the need of a sustained and lifetime treatment among diabetic patients should be stressed.

Strengths and limitations

To our knowledge, this is one of the very few studies that assessed the impact of changes in antidiabetic treatment on T2DM status using a population-based sample of diabetic patients. Our results thus correspond to real life practice and not to a specific setting such as a hospital-based study.

Our study also has some limitations. First, sample size was small compared to other studies (10, 16), leading to a low statistical power to detect significant trends regarding FPG status within each group. Still, the trends were in agreement with the literature (14) and also with what would have been

expected from a pathophysiological perspective. Second, we did not collect HbA_1c levels, which precluded adequate assessment of diabetes control. Still, we used commonly accepted glycemic thresholds (21-23) to define diabetes management. Third, only participants who accepted follow-up could be included, and it has been suggested that nonparticipants differ from participants regarding several socio-demographic and health behavior characteristics. Still, the same study also suggested that correlations between variables appeared to be insensitive to sampling bias (24). Finally, we collected neither adherence nor the dosage of antidiabetic drugs, and it is possible that some participants categorized as maintainers actually changed their adherence or dosage, and it would be of interest that further studies focus on this issue.

Conclusion

During a 5.5 year follow-up, less than one fifth of patients with T2DM had his/her drug treatment changed. Changes in antidiabetic treatment lead to an improvement of the unfavorable FPG status, while reducing or quitting antidiabetic treatment considerably worsened FPG status.

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Statement of authorship

VS and PMV made most of the statistical analyses and wrote the article; GW revised the article for important intellectual content. PMV had primary responsibility for final content.

Conflict of interest statement

The authors report no conflict of interest.

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Tables

Table 1: baseline characteristics of participants associated with 5.5-year changes in antidiabetic drug treatment, CoLaus study, Lausanne, Switzerland.

	Maintainers	Changers	Reducers	P-value
Number of participants (%)	108 (74.0)	27 (18.5)	11 (7.5)	
Male gender (%)	78 (72.2)	23 (85.2)	8 (72.7)	0.386
Age (years)	63.0 ± 6.8	59.4 ± 7.6	61.0 ± 10.4	0.063
Educational level (%)				0.312
University	9 (8.3)	5 (18.5)	1 (9.1)	
Secondary	23 (21.3)	7 (25.9)	4 (36.4)	
Primary+apprenticeship	76 (70.4)	15 (55.6)	6 (54.6)	
Marital status (%)				0.247
Living alone	33 (30.6)	10 (38.5)	6 (54.6)	
Living in couple	75 (69.4)	16 (61.5)	5 (45.5)	
Smoking status (%)				0.352
Never	33 (30.6)	6 (22.2)	3 (27.3)	
Former	57 (52.8)	13 (48.2)	4 (36.4)	
Current	18 (16.7)	8 (29.6)	4 (36.4)	
Physically active (%)	40 (37)	11 (40.7)	3 (27.3)	0.767
Body mass index (kg/m^2)	30.9 ± 5.2	30.0 ± 4.8	27.4 ± 4.0	0.082
BMI categories (%)				0.110
Normal	13 (12.0)	3 (11.1)	4 (36.4)	
Overweight	33 (30.6)	12 (44.4)	4 (36.4)	

Obese	62 (57.4)	12 (44.4)	3 (27.3)	
Waist circumference (cm)	107.1 ± 15.4	104.7 ± 12.3	98.8 ± 12.2	0.180
Abdominal obesity (%)	79 (73.2)	16 (59.3)	5 (45.5)	0.081
History of				
Hypertension	75 (69.4)	16 (59.3)	5 (45.5)	0.209
Dyslipidemia	64 (59.3)	14 (51.9)	6 (54.6)	0.774
Fasting plasma glucose (mmol/L)	7.8 ± 2.0	10.3 ± 3.7	7.6 ± 2.0	<0.001
Fasting plasma levels (%)				
<7.0 mmol/L	43 (39.8)	2 (7.4)	5 (45.5)	0.002
<6.5 mmol/L	26 (24.1)	2 (7.4)	5 (45.5)	0.022
Insulin (µIU/mL)	15.3 ± 10.7	14.5 ± 12.4	13.9 ± 10.7	0.483 §
HOMA	5.4 ± 4.3	6.5 ± 6.0	5.0 ± 4.1	0.461 §

BMI, body mass index; FPG, fasting plasma glucose. Results are expressed as number of patients (column percentage) or as average ±standard deviation. Bivariate analysis performed using Fisher's exact test for categorical data and analysis of variance or Kruskal-Wallis test (§) for continuous data.

Table 2: characteristics of participants of follow-up associated with 5.5-year changes in antidiabetic drug treatment, CoLaus study, Lausanne, Switzerland.

	Maintainers	Changers	Reducers	P-value
Number of participants	107	27	11	
Glucose and insulin				
Fasting plasma glucose (mmol/L)	8.0 ± 2.8	9.6 ± 3.7	9.4 ± 5.2	0.057
Fasting plasma levels (%)				
<7.0 mmol/L (%)	39 (36.5)	7 (25.9)	4 (36.4)	0.600
<6.5 mmol/L (%)	25 (23.4)	5 (18.5)	3 (27.3)	0.788
Difference to baseline (mmol/L)	0.3 ± 2.7	-0.8 ± 4.3	1.9 ± 4.1	0.045 §
Reduction in FPG (%)	50 (46.3)	15 (55.6)	1 (9.1)	0.025
Insulin (µIU/mL)	23.8 ± 81.8	35.4 ± 69.5	51.5 ± 131.4	0.502 §
HOMA	9.5 ± 39.3	14.6 ± 24.2	22.1 ± 58.6	0.355 §
Anthropometry (N)	**105**	**25**	**10**	
Weight (kg)	89.1 ± 18.3	89.5 ± 14.2	79.2 ± 18.6	0.225
Difference to baseline (kg)	0.13 ± 6.0	-0.08 ± 7.12	0.57 ± 6.44	0.904 §
Increased weight (%)	51 (48.6)	10 (40.0)	4 (40.0)	0.727
Body mass index (kg/m^2)	31.1 ± 5.4	29.7 ± 5.1	27.5 ± 5.2	0.093
Difference to baseline (kg/m^2)	0.29 ± 2.05	0.03 ± 2.26	0.48 ± 2.26	0.801 §

FPG, fasting plasma glucose. Results are expressed as number of patients (column percentage) or as average ±standard deviation. Bivariate analysis performed using Fisher's exact test for categorical data and analysis of variance or Kruskal-Wallis test (§) for continuous data.

Figure legends

Figure 1: detailed sampling procedure, CoLaus study, Lausanne, Switzerland.

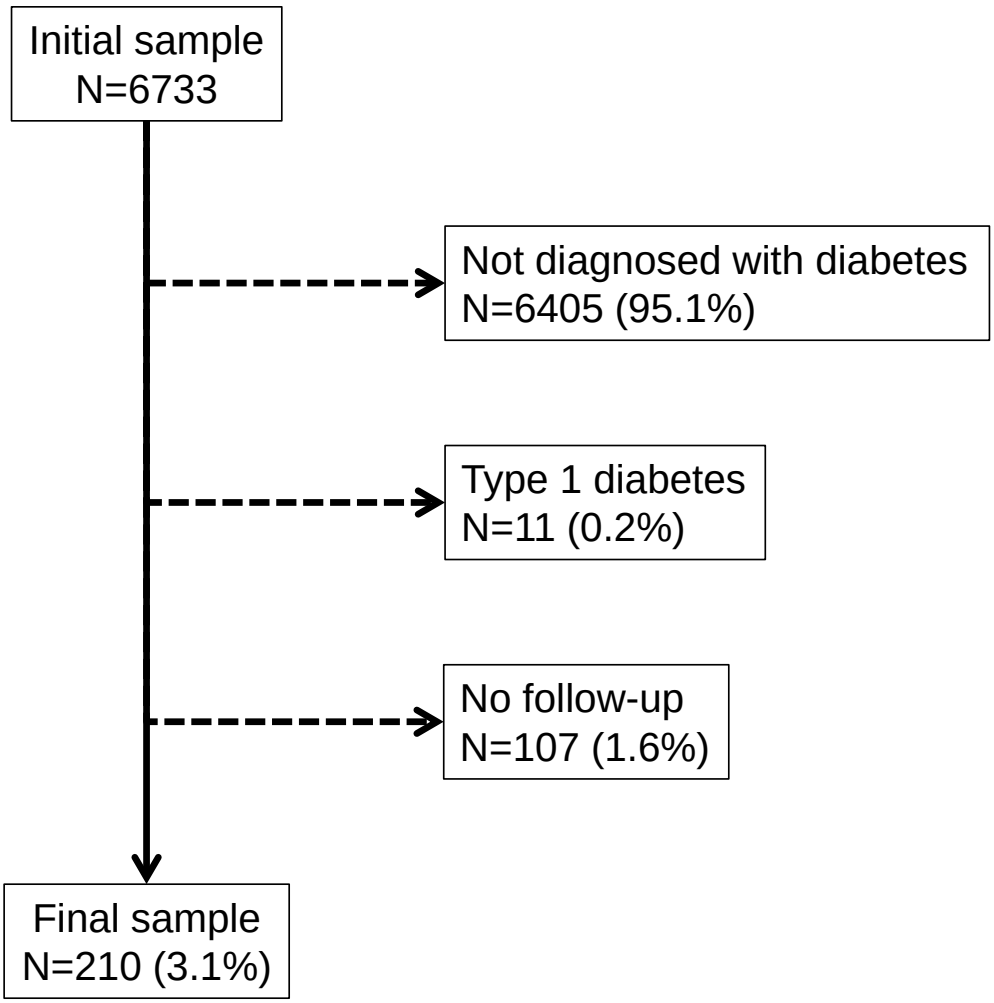
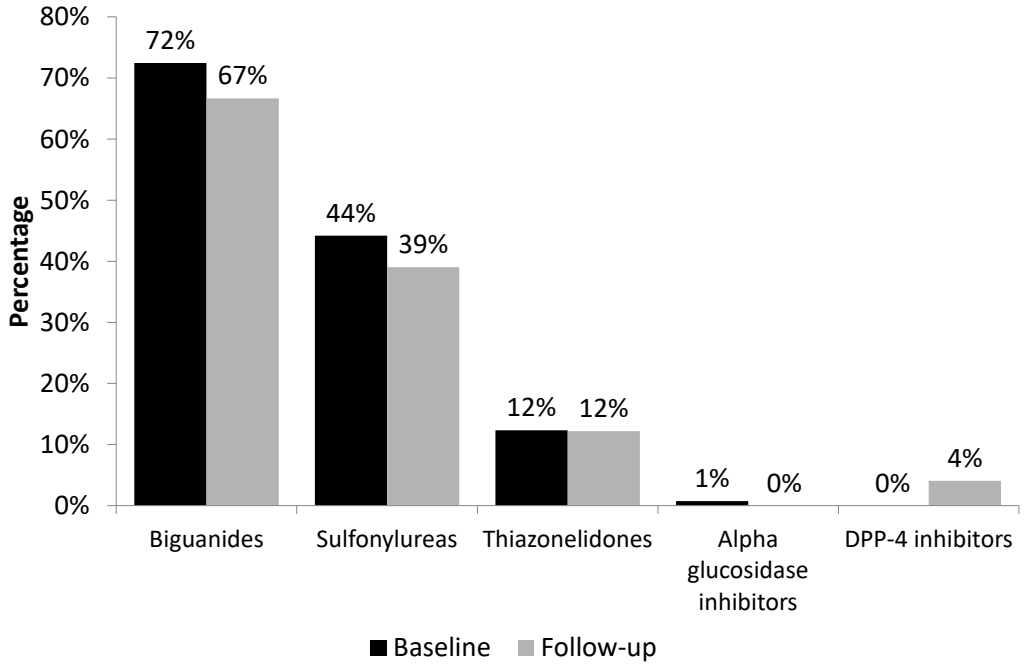


Figure 2: distribution of the different antidiabetic drugs at baseline and follow-up among treated participants, CoLaus study, Lausanne, Switzerland.



Supplementary information

Supplementary table 1: characteristics of participants treated for type 2 diabetes mellitus, according to follow-up status.

	Excluded (n=107)	Included (n=210)	P-value
Male gender (%)	64 (59.8)	136 (64.8)	0.388
Age (years)	60.3 ± 10.1	59.8 ± 8.8	0.679
Educational level (%)			0.460
University	10 (9.4)	28 (13.3)	
Secondary	20 (18.9)	45 (21.4)	
Primary+apprenticeship	76 (71.7)	137 (65.2)	
Marital status (%)			0.363
Living alone	41 (38.7)	70 (33.5)	
Living in couple	65 (61.3)	139 (66.5)	
Smoking status (%)			0.636
Never	34 (32.1)	65 (31)	
Former	42 (39.6)	94 (44.8)	
Current	30 (28.3)	51 (24.3)	
Physically active (%)	43 (40.2)	80 (38.1)	0.718
Body mass index (kg/m^2)	30.6 ± 6.2	30.1 ± 5.7	0.518
BMI categories (%)			
Normal	19 (17.8)	38 (18.1)	
Overweight	33 (30.8)	70 (33.3)	
Obese	55 (51.4)	102 (48.6)	

Waist circumference (cm)	103.0 ± 16.6	103.3 ± 16.3	0.880
Abdominal obesity (%)	67 (62.6)	135 (64.3)	0.770
History of			
Hypertension	84 (78.5)	127 (60.5)	0.001
Dyslipidemia	58 (54.2)	117 (55.7)	0.798

BMI, body mass index. Results are expressed as number of patients (column percentage) or as average ±standard deviation. Bivariate analysis performed using chi-square for categorical data and student's t-test for continuous data.