

Use of metformin and vildagliptin for treatment of type 2 diabetes in the elderly

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Background: The aim of this study was to describe the clinical (treatment adherence, metabolic control, hypoglycemia, and macrovascular complications) and economic (resource use and costs) consequences of using a combination of metformin + vildagliptin to treat type 2 diabetes in elderly patients seen in daily clinical practice.

Methods: We conducted a multicenter, retrospective, observational study that included patients aged ≥ 65 years treated with metformin who started a second oral antidiabetic therapy during the years 2008–2009. There were two groups of patients: a study group receiving metformin + vildagliptin and a reference group receiving metformin + other oral antidiabetics (sulfonylureas or glitazones). The main measures were comorbidity, compliance/persistence, metabolic control (glycosylated hemoglobin $< 7\%$), complications (hypoglycemic, macrovascular), and total costs. The patients were followed for 2 years.

Results: We recruited 987 patients (49.1% male) of mean age 74.2 years. There were 270 (27.4%) patients in the metformin + vildagliptin group and 717 (72.6%) in the reference group. Vildagliptin-treated patients had significantly ($P < 0.05$) improved compliance (68.3% versus 62.5%, respectively), persistence (61.5% versus 55.1%), and metabolic control (63.3% versus 57.6%). They also had lower rates of hypoglycemia (17.4% versus 42.8%) and cardiovascular events (4.4% versus 8.6%) and lower total costs (€2,544 versus €2,699, $P < 0.05$).

Conclusion: Patients treated with metformin and vildagliptin showed better adherence and metabolic control and lower rates of hypoglycemia, resulting in lower health care costs for the national health system.

Keywords: vildagliptin, diabetes, metabolic control, hypoglycemia, cardiovascular events, health costs

Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in developed countries.¹ Type 2 diabetes mellitus (T2DM) is one of the diseases with the greatest public health impact, not only due to its high frequency but also because of its acute and chronic complications, the high rate of associated morbidity and mortality, and the impact on quality of life, all of which result in high use of health care resources, especially in elderly patients.^{2,3} In Spain, the prevalence of T2DM is 8% in females and 12% in males, with fluctuations of 6%–12% in different studies.^{4,5}

The aim of drug treatment for T2DM is to achieve optimal metabolic control with maximum safety. Metformin is recommended as the first therapeutic choice together with dietary measures.^{6,7} When metabolic control is not achieved, addition of a second drug is recommended as combination therapy.^{8,9} The most frequent acute complication

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of diabetes is hypoglycemia, particularly in patients treated with insulin and/or sulfonylureas.^{6,9–11} Dipeptidyl peptidase-4 (DPP-4) inhibitors, such as vildagliptin, have an advantage over traditional secretagogues in that they significantly reduce hypoglycemia because their insulin secretion stimulating mechanism is glucose-dependent.^{7,12}

The available evidence in clinical practice in Spain regarding the clinical and economic effects in older patients on oral antidiabetics is limited or nonexistent. The aim of this study was to compare the clinical (compliance/persistence with treatment, metabolic control, hypoglycemia, and macrovascular complications) and economic (resource use and health care costs) implications of a combination of metformin + vildagliptin versus a combination of metformin + other oral antidiabetics in T2DM patients aged ≥ 65 years.

Materials and methods

Design and study population

In this observational, longitudinal, multicenter study, we reviewed the computerized medical records of outpatients and inpatients treated with metformin. The study population consisted of patients attending six primary care centers managed by Badalona Serveis Assistencials SA. Information on health resources was obtained from two reference hospitals.

Inclusion and exclusion criteria

The study included all patients who started a second antidiabetic treatment between January 1, 2008, and December 31, 2009, and fulfilled the following conditions: age ≥ 65 years; diagnosis of T2DM for at least 2 years before the start of the study; following the cardiovascular risk protocol/guidelines of the participating centers; participating in the chronic prescription program for obtaining medical prescriptions (with a register of the daily dose and interval of time and duration of each treatment administered); metformin monotherapy as the first treatment option; and availability for progress to be monitored during the 2-year study period. Subjects transferring from other municipalities or regions and patients receiving insulin were excluded. There were two study groups, ie, a study group treated with metformin + vildagliptin and a reference group treated with metformin + other oral antidiabetics.

Measurement of diabetes and complications

Diagnosis of T2DM was made according to the International Classification of Primary Care¹³ and from the coding

of hospital and emergency room discharges using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Baseline data were obtained on microvascular complications, ie, diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, and diabetic vasculopathy. We also identified all cases of symptomatic hypoglycemia.

Macrovascular complications and cardiovascular events included: heart disease, including cardiac ischemia, acute myocardial infarction, and heart failure, as defined by the World Health Organization diagnostic criteria; cerebrovascular disease, including stroke (ischemic or hemorrhagic, according to the American Heart Association)⁷ and transient ischemic attack; all types of peripheral arterial disease; and renal disease (diabetic nephropathy or impaired renal function [serum creatinine >133 mmol in males or >124 mmol in females, or glomerular filtration rate <60 mL per minute]). Applications laboratory and test performance creatinine or glomerular filtration rate <60 mL per minute. Laboratory results are captured at all centers of the organization as part of integrated information systems. The cumulative incidence rate was defined as the proportion of healthy individuals who developed a complication (number of new cases).

Compliance and persistence with treatment and metabolic control

Information was collected on the following oral antidiabetics according to the Anatomical Therapeutic Chemical Classification System:¹⁴ metformin (A10BA*); insulin release stimulators, ie, sulfonylureas (A10BB*) and glinides (A10BX*); glitazones (A10BG*); and vildagliptin in monotherapy or in combination. We did not include patients receiving alpha-glucosidase inhibitors due to insufficient patient numbers. Compliance during the study period was calculated by dividing the total number of tablets dispensed by those recommended or prescribed. Treatment persistence was defined as the time, measured in months, without abandoning the initial treatment or with no change to another medication for at least 30 days after the initial prescription. Metabolic control was assessed by glycosylated hemoglobin (HbA_{1c}) levels $<7\%$.⁶

Sociodemographic and comorbidity variables

The general comorbidity summary variables used for each treated patient were: the Charlson comorbidity index,¹⁵ which is used as a proxy for health status, and the individual

causality index, obtained from Adjusted Clinical Groups, which is a patient classification system based on isoresource use.¹⁶ The Adjusted Clinical Groups application provides resource utilization bands, with each patient placed in one of five mutually exclusive categories, according to general morbidity: 1 (healthy or very low morbidity); 2 (low morbidity); 3 (moderate morbidity); 4 (high morbidity); and 5 (very high morbidity).

Resource use and cost model

Direct health care costs were defined as costs related to medical care. The unit costs used in the study are in 2011 €. The tariffs were obtained from the cost accounting system used at each center, except for medications (retail price), as follows: medical visit in primary health care, €23.19; medical visit in the emergency room, €117.53; hospitalization for one day, €320.90; specialist medical visit, €104.41; laboratory tests, €22.30; conventional radiology, €18.50; diagnostic/therapeutic tests, €37.12; and drug prescriptions (retail price includes value-added tax).

Statistical analysis

A descriptive univariate analysis was performed, expressing values as the mean, standard deviation, and 95% confidence interval (CI). The normality of the distribution of quantitative variables was verified using the Kolmogorov—Smirnov test. In the bivariate analysis, we used analysis of variance, the chi-square test, Pearson's chi-squared test, and the Mann-Whitney-Wilcoxon nonparametric test. A logistic regression analysis was performed to determine the variables associated with CVE (cardiovascular events [presence/absence]) using an enter procedure (Wald statistic). The comparison of costs was done according to the recommendations of Thompson and Barber¹⁷ using analysis of covariance, with sex, age, resource utilization band, Charlson comorbidity index, and time of evolution as covariates.

Results

Of the 10,477 subjects aged ≥ 65 years assigned to and attending the study centers regularly, 9,876 sought attention and 1,899 were diagnosed with T2DM (prevalence 19.2%; 95% CI 17.4–21.0). Of these, 700 patients were excluded for the following reasons: 151 received no drug treatment, 63 received other drug therapies, 40 discontinued treatment, treatment was modified in 299 during follow-up, 103 were lost to follow-up, and 44 were lost for unknown reasons and/or other causes. The percentage distribution of patients excluded was similar in the two study groups.

Therefore, 987 patients receiving combination therapy were included in the study: 27.4% ($n=270$) in the study group were treated with vildagliptin and 72.6% ($n=717$) in the reference group were treated with sulfonylureas (82.5%) or glitazones (17.5%). Table 1 shows the baseline characteristics of patients included by treatment group. The overall mean age was 74.2 ± 6.2 years and 49.1% were male. Mean age and general comorbidity was similar between the study group and the reference group (73.6 years versus 74.4 years and 5.7 diagnoses versus 5.8 diagnoses, respectively).

Vildagliptin-treated patients showed better compliance (68.3% versus 62.5%, $P=0.002$) and persistence (61.5% versus 55.1%, $P=0.031$) with therapy (Table 2). There was an acceptable correlation between degree of compliance and months of treatment persistence ($r=0.541$, $P<0.001$). Metabolic control ($HbA_{1c} < 7\%$) of T2DM at the end of follow-up was better in vildagliptin-treated patients (63.3% versus 57.6% respectively, $P=0.022$). In the logistic model, vildagliptin-treated patients showed better therapeutic compliance (odds ratio 1.2, 95% CI 1.1–1.4, $P=0.013$), treatment persistence (odds ratio 1.1, 95% CI 1.0–1.2, $P=0.032$), and metabolic control (odds ratio 1.4, 95% CI 1.2–1.6, $P=0.038$).

Vildagliptin-treated patients had fewer medical visits in primary care (24.1 versus 31.2, $P<0.001$) and hospital (1.9 versus 2.5, $P=0.018$) than patients in the reference group. The gross and adjusted (covariates) cost models for the two groups during a follow-up of 2 years is shown in Table 3. The total cost for care of diabetic patients was 2.6 million Euros, of which 88.9% was spent on primary care and 11.1% was spent on specialized care. The gross mean unit costs for vildagliptin-treated patients were lower than those of the reference group (€2,518 versus €2,685, respectively, $P=0.041$). The corrected costs (analysis of covariance) were €2,544 (95% CI 2,385–2,703) in the vildagliptin-treated group and €2,699 (95% CI €2,602–2,796) in the reference group ($P=0.044$). Health costs were moderately correlated with age ($r=0.335$) and overall comorbidity (resource utilization band; $r=0.341$, $P<0.05$).

Seventy-four patients experienced CVE (7.5%, 95% CI 6.3–8.7). Vildagliptin-treated patients had a lower rate of CVE than the reference group (4.4% versus 8.6%, $P=0.025$) and a lower proportion of new cases of ischemic heart disease (0.7% versus 2.1%, $P=0.043$), cerebrovascular accident (2.2% versus 4.3%, $P=0.042$), and renal failure (1.5% versus 2.2%, $P=0.138$). The overall percentage of patients with hypoglycemia was 35.9%. Vildagliptin-treated patients had a lower rate of hypoglycemia (17.4% versus 42.8%, $P<0.001$).

Table I Baseline characteristics of the study population

Study groups	Metformin + OA	Metformin + vildagliptin	Total	P-value
Patients, n (%)	n=717	n=270	n=987	
Sociodemographics				
Mean age, years	74.4 (6.2)	73.6 (6.1)	74.2 (6.2)	0.077
Sex (male)	50.5%	45.6%	49.1%	0.167
General comorbidity				
Mean diagnoses	5.8 (2.5)	5.7 (2.3)	5.8 (2.5)	0.488
Mean Charlson comorbidity index	1 (0.4)	1.1 (0.5)	1.1 (0.4)	0.296
Mean RUB	3 (0.6)	3 (0.5)	3 (0.6)	0.574
RUB-1	0.7%	0.1%	0.5%	
RUB-2	12.2%	10.1%	11.6%	
RUB-3	73.1%	81.4%	75.4%	
RUB-4	12.4%	7.2%	11.0%	
RUB-5	1.6%	1.2%	1.5%	0.066
Comorbidities				
Hypertension	76.3%	73.7%	75.6%	0.399
Dyslipidemia	61.2%	63.3%	61.8%	0.544
Obesity	23.2%	23.3%	23.2%	0.952
Active smoker	14.2%	15.2%	14.5%	0.703
Alcoholism	2.5%	2.6%	2.5%	0.942
Ischemic heart disease	16.3%	14.8%	15.9%	0.565
Cerebrovascular accident	19.8%	18.9%	19.6%	0.746
Cardiovascular event	31.2%	28.1%	30.4%	0.346
Organ failure	20.2%	21.9%	20.7%	0.573
Bronchial asthma	5.6%	3.3%	5.0%	0.148
COPD	7.7%	10.0%	8.3%	0.237
Neuropathies	1.5%	0.4%	1.2%	0.137
Dementia (all types)	5.2%	4.8%	5.1%	0.825
Depressive syndrome	18.8%	22.6%	19.9%	0.186
Malignant neoplasm	13.5%	11.9%	13.1%	0.486
Relationship with diabetes				
Time since diagnosis, years	17.4 (7.3)	20 (5.2)	18.1 (6.9)	0.002
Diabetic retinopathy	28.2%	32.0%	29.0%	0.346
Diabetic neuropathy	13.5%	13.7%	13.5%	0.870
Diabetic nephropathy	12.1%	12.2%	12.1%	0.899
Change in glomerular filtration	26.0%	25.6%	25.9%	0.853

Note: Values expressed as the percentage or mean (standard deviation).

Abbreviations: RUB, resource utilization band; COPD, chronic obstructive pulmonary disease; OA, oral antidiabetics, including sulfonylureas and glitazones.

In the logistic regression model, CVEs were associated with noncompliance with therapy (odds ratio 1.1, CI 1.0–1.3), metabolic control of T2DM (odds ratio 1.2, 95% CI 1.1–1.4), male sex (odds ratio 1.4, 95% CI 1.2–1.8), and age (odds ratio 1.1, 95% CI 1.0–1.2, $P < 0.05$). Overall, 0.8% of patients required hospitalizations, 3.5% were treated in the emergency department, and 44.6% were treated in primary care.

A subanalysis found no significant differences between patients treated with sulfonylureas and those treated with glitazones or between patients older and younger than 75 years. The proportions were maintained for all the variables analyzed.

Discussion

Our results show that elderly patients treated with a combination of metformin + vildagliptin had a lower rate of

hypoglycemia and lower health costs than a reference group of patients receiving metformin and other oral antidiabetics. Scientific societies recommend addition of a DPP-4 inhibitor (gliptin) to metformin as an alternative to sulfonylureas, a glitazone, a glinide, or an α -glucosidase inhibitor for the treatment of patients with T2DM who do not achieve metabolic control.¹⁸ This proportionality in treatment was maintained in this study. There remain uncertainties in the treatment of elderly patients with T2DM which have not been addressed in clinical trials.^{18,19}

There are few published studies of compliance and persistence with oral antidiabetics and comparisons are difficult because of the different methodologies used; however, they show a compliance rate of 40%–80%.^{6–7,19,20} A recent study by Marquez et al²¹ found that one quarter of diabetic patients did

Table 2 Compliance, persistence, and metabolic control according to the study groups

Study groups	Metformin + OA	Metformin + vildagliptin	Total	P-value
Patients, n (%)	n=717	n=270	n=987	
Months on metformin	29 (14.2)	25.9 (12.1)	28.1 (13.7)	0.002
Metformin use > 1 year	76.3%	73.6%	75.7%	<0.001
Months of associated treatment				
Mean (SD)	19.3 (7.1)	21.2 (5.1)	20.0 (6.8)	<0.001
Median (P25–P75)	21.0 (10.0–23.0)	22.0 (17.0–24.0)	22.0 (13.0–23.0)	<0.001
Therapeutic compliance	62.5%	68.3%	64.1%	0.002
≥80%, high	49.1%	55.1%	51.4%	
50%–79%, medium	30.7%	29.1%	30.3%	
<50%, low	20.2%	15.8%	18.2%	<0.001
Treatment persistence	55.1%	61.5%	56.1%	0.031
Metabolic control				
Initial period	55.7%	58.8%	56.5%	0.360
Final period	57.6%	63.3%	59.4%	
Difference in percentages	1.9%	4.5%	2.9%	0.022

Notes: Values expressed as a percentage or mean (standard deviation); treatment persistence was defined as the time without abandonment of initial treatment or with no change to other medication for at least 30 days after the initial prescription; metabolic control was defined as glycosylated hemoglobin <7%.

Abbreviations: OA, oral antidiabetics, includes sulfonylureas and glitazones; SD, standard deviation; P, percentile.

not comply with their treatment. A review by Cramer et al²² of 39 studies found that the rate of persistence at 12 months was 63% and compliance with oral antidiabetics was 58%, and this was similar for all therapeutic classes analyzed. Jermendy et al²³ studied patients receiving combination therapy with metformin and sulfonylureas and found a persistence of 56%

at one year. This could be due to a random event (individual variability) or to the presence of unidentified confounding variables. However, one plausible explanation could be a better tolerability and safety profile, in particular because of significantly lower rates of hypoglycemia.^{6,8} Although more studies comparing the use of combination therapy are

Table 3 Model of gross and adjusted costs according to study group (mean unit cost in Euros) in the 2 year study period

Study groups	Metformin + OA	Metformin + vildagliptin	Total	P-value
Patients, n (%)	n=717	n=270	n=987	
Gross costs model				
Primary care costs	2,374.6 (1,277.4)	2,272 (1,098.7)	2,346.5 (1,231.4)	0.244
Medical visits	723.5 (365.7)	557.9 (335.4)	678.2 (365.1)	<0.001
Laboratory tests	70.1 (40.3)	51.2 (31.6)	64.9 (39)	<0.001
Conventional radiology	18.5 (22.5)	20.6 (24)	19.1 (22.9)	0.189
Complementary tests	17.4 (28.4)	17.3 (25.7)	17.4 (27.7)	0.950
Drug costs (total)	1,545.1 (1,087.4)	1,625 (946.4)	1,566.9 (1,050.8)	0.287
Metformin	598.9 (342.2)	430.2 (385.1)	552.8 (457.5)	0.031
OA versus vildagliptin	655.2 (539.2)	992.5 (888.7)	747.5 (659.4)	0.012
Other drugs	291.1 (194.1)	202.3 (155.3)	266.7 (177.3)	0.597
Specialized care costs	310.3 (442.6)	245.4 (287.8)	292.6 (407)	0.026
Days of hospitalization	17.9 (184.9)	8.3 (64.4)	15.3 (161.2)	0.405
Medical visits	261 (379.6)	201.9 (251.3)	244.8 (350.1)	0.018
Emergency room visits	31.5 (64)	35.3 (71.2)	32.5 (66.1)	0.422
Health costs	2,684.9 (1,456.5)	2,517.5 (1,173.2)	2,639.1 (1,386.2)	0.041
Adjusted costs model*			Difference	
Primary care costs	2,383.7	2,294.5	–89.2	0.290
95% CI	2,297.6–2,469.8	2,153.3–2,435.7		
Specialized care costs	315.3	249.5	–65.9	0.028
95% CI	284.8–345.9	199.3–299.6		
Health costs	2,699.1	2,544.0	–155.1	0.044
95% CI	2,602.2–2,795.9	2,385.1–2,702.8		

Notes: Values expressed as the mean (standard deviation). *Analysis of covariance model, the contrasts are based on comparisons of linearly independent pairs among the estimated marginal means.

Abbreviations: OA, oral antidiabetics, includes sulfonylureas and glitazones; CI, confidence interval.

needed to reinforce the consistency of these results, it seems clear that the role of DPP-4 inhibitors (eg, vildagliptin) in the therapeutic armamentarium for T2DM is evolving rapidly, although long-term data evaluating their effect on metabolic control are lacking.^{24,25} The available evidence indicates that a direct association between compliance and control is beyond doubt.^{6,21,23}

Vildagliptin-treated patients had lower health care costs and used fewer health care resources. The few published studies available show that the higher the compliance and metabolic control in these patients, the lower the risk of hospitalization. A review by Breitscheidel et al²⁶ concluded that improving compliance may result in a reduction of total health care costs in T2DM. In seven studies, compliance was inversely associated with total health care costs, and costs were lower because of fewer days of hospitalization. However, the variability in the studies reviewed was high, making comparison of the results difficult. Overall, our results are consistent with those studies,²⁷ and again highlight the association between fewer episodes of hypoglycemia and less use of health care resources.^{28–30}

Our results show lower rates of CVE and renal failure in vildagliptin-treated patients. Various studies in patients with type 1 or type 2 diabetes mellitus^{6–8,19,20} have shown that good metabolic control, represented by lower HbA_{1c} values, leads to significant improvement in the incidence and evolution of microangiopathic complications, and that this benefit persists for years, even when metabolic control worsens. However, evolution of macrovascular complications does not seem so dependent on achieving an acceptable level of HbA_{1c} as on the type of treatment used and the presence or absence of hypoglycemia. Given the close relationship between certain microangiopathies (principally nephropathy) and CVE, it is logical to consider that good metabolic control would have a positive influence, but with a lower intensity than the control of other risk factors, such as dyslipidemia and hypertension.^{6,8,28} In our study, these results are surprising, given that there is no scientific evidence of this available to date from clinical trials. The cardiovascular benefit of vildagliptin could be interpreted as a random bias due to the study design.³¹

The possible limitations of this research include categorization of the disease, the potential bias of patient classification, selection of therapeutic groups, and operating costs, which depend on the computerized data systems available. Therefore, our study has the limitations inherent in observational retrospective studies, including under-reporting or possible variability of patients and professionals.

This type of design is not without bias (including factors not taken into account, such as the socioeconomic, cultural, or educational level, as well as pharmacological doses ingested or their therapeutic appropriateness) that should be minimized. The main limitation of the study is the selection bias arising from the physician being responsible for administering one or the other drug, for whatever reason, and the results should be interpreted with caution. Another limitation relates to the extent of hypoglycemia, given that we only identified episodes in which the patient required medical treatment and this was documented, so there may have been undiagnosed cases. Patients treated with vildagliptin had a lower rate of renal events during follow-up. The absence of data for single-treatment metformin or vildagliptin and is needed for comparison (monotherapy) and should also be interpreted as a limitation of the study. Further, glucagon-like peptide-1 levels and their correlation with glucose or insulin levels in our subjects are unclear. Another limitation of the study was not considered a confounding variable dosage of drugs.

Future research will be needed to include studies of cost effectiveness and collection of data from other health care organizations. Overall, our results are consistent with the recommendations of the Institute for Quality and Efficiency in Health Care.³² The measure of effectiveness (ie, economic evaluation) should be based on a set of health interventions, not just on the price of a drug. In conclusion, patients receiving vildagliptin in combination with metformin showed better compliance and metabolic control and lower rates of hypoglycemia than patients treated with metformin and other oral antidiabetics, resulting in lower health care costs for the national health system.

Author contributions

ASM conceived of and designed the manuscript. Data were collected by ASM and RNA. ASM performed the statistical analysis. Both authors participated in interpretation of the data, and in the drafting, revision, and approval of the final manuscript.

Disclosure

This study was funded by Novartis. ASM was paid by Novartis to develop the manuscript. The statistical analysis was performed by ASM and funded by Novartis. The other author reports no competing interests in this work. Novartis had no role in the study design, data collection or analysis, the decision to publish, or preparation of the manuscript.

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